CLINICAL DISEASE ACTIVITY AND RADIOLOGICAL DAMAGE IN EARLY RHEUMATOID ARTHRITIS

DR KEERANUR SUBRAMANIAN JAYAKUMAR

Rheumatology Department
St Albans City Hospital
Waverly road
St Albans. AL3 5PN
Hertfordshire

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ABSTRACT

Disease progression in rheumatoid arthritis (RA) is assessed by standard clinical, radiological and functional measures. Clinical disease activity in RA is graded as no disease (remission), low, moderate and high disease, based on validated criteria. Radiological progression in RA is monitored by serial x-rays of hands and feet, and by quantification of structural damage, using various scoring methods. This proves to be a valuable outcome measure in RA studies.

RA patients with active disease usually develop progressive radiological damage. However, it has been shown that clinical disease activity may not correlate with radiological damage, particularly in early RA. Therefore, this thesis was mainly aimed to test the hypothesis that, 'radiological damage can progress despite clinical disease inactivity or remission' and to investigate possible underlying mechanisms including disease heterogeneity, treatment effect and scoring methodology. Disease progression, outcomes and prognostic factors were analysed in an inception cohort of early RA (Early Rheumatoid Arthritis Study/ERAS) for this thesis.

In this study of early RA patients, sustained remission was less frequent than remission at individual time points and baseline variables such as gender, duration of symptoms, disease activity (DAS) and health assessment questionnaire (HAQ) scores have shown predictive value for sustained remission. Structural damage on x-rays progressed despite clinical disease inactivity or remission in a subgroup of patients and disease heterogeneity was the most likely explanation for the disconnect between clinical disease activity and radiological damage in the ERAS cohort.

This study has also found that scoring methods as well as reading order of x-ray films could influence radiographic progression in early RA, particularly at individual level. Male sex, rheumatoid factor (RF) and radiographic damage at baseline showed prognostic value in predicting radiographic progression despite remission.

Study patients with persistent clinical disease inactivity have shown better radiological, surgical, functional, and other outcomes compared to relapsing-remitting or persistent disease activity. There was no significant difference in functional and other outcomes between patients in remission with x-ray progression and those in remission without x-ray progression.

Therefore, x-rays of hands and feet at regular intervals are valuable in determining true disease progression in early RA, even during clinical disease inactivity. Scoring methodology in itself could have an influence on the type of radiographic progression in RA studies. Sustained disease inactivity in RA is more favourable than relapsing-remitting disease.

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LIST OF ABBREVIATIONS

ACR	**American college of Rheumatology**
ANA	**Anti nuclear antibody**
APR	**Acute phase reactants**
ARA	**American Rheumatism association**
BMI	**Body mass index**
CDAI	**Clinical disease activity index**
COI	**Cost of illness**
CRP	**C-reactive protein**
CSF	**Colony stimulating factor**
CTX	**C-terminal telopeptide**
DAS	**Disease activity score**
DAS28	**Disease activity score with 28 joint count**
DMARDS	**Disease modifying anti rheumatic drugs**
EAC	**Early Arthritis Cohort**
EGA	**Evaluator global assessment**
EMS	**Early morning stiffness**
ERAS	**Early Rheumatoid Arthritis Study**
ESR	**Erythrocyte sedimentation rate**
EULAR	**European League against Rheumatism**
FBC	**Full blood count**
FG	**Functional grade**
GH	**Global health**
HAQ	**Health assessment questionnaire**
HLA	**Human leukocyte antigen**

HPA	**Hypothalamo-pituitary-adrenal**
HPG	**Hypothalamo-pituitary-gonadal**
ICAM	**Intercellular adhesion molecules**
IFN	**Interferon**
IGF	**Insulin like growth factor**
IL	**Interleukins**
ILAR	**International League of Associations for Rheumatology**
IP	**Interphalangeal**
JSN	**Joint space narrowing**
MCP	**Monocyte chemotactic protein**
MCP	**Matacarpophalangeal**
MHC	**Major histocompatibility complex**
MMP	**Matrix metalloproteinases**
MTP	**Metatarsophalangeal**
NTX	**N-terminal telopeptide**
ODF	**Osteoclast differentiation factor**
OMERACT	**Outcome Measures in Rheumatology Clinical Trials Conference**
OPG	**Osteoprotegerin**
PGA	**Physician global assessment**
PIP	**Proximal interphalangeal**
QoL	**Quality of life**
RA	**Rheumatoid arthritis**
RAI	**Ritchie articular index**
RANKL	**Receptor activator of nuclear factor κB ligand**
RF	**Rheumatoid factor**

SDAI	**Simplified disease activity index**
SE	**Shared epitope**
SDC	**Smallest detectable change**
SDD	**Smallest detectable difference**
SENS	**Simplified erosion narrowing scoring method**
SES	**Short erosion scale**
SJC	**Swollen joint count**
SRM	**Standardised response mean**
SvdH	**Sharp van der Heijde scoring method**
TGF	**Transforming growth factor**
TIMP	**Tissue inhibitors of metalloproteinases**
TJC	**Tender joint count**
TNF	**Tumour necrosis factor**
TRANCE	**TNF-related activation-induced cytokine**
US FDA	**United States Food and Drug Administration**
VAS	**Visual analogue scale**
VCAM-1	**Vascular cell adhesion molecule-1**
VEGF	**Vascular endothelial growth factor**
WHO	**World Health Organization**

CHAPTER 1: INTRODUCTION

1. INTRODUCTION

1.1 Rheumatoid arthritis

1.1.1 Background

Rheumatoid arthritis (RA) is a chronic systemic disease affecting joints as well as extra-articular structures and is the most common type of inflammatory arthritis worldwide. RA most commonly involves the small joints of hands and feet, often in a symmetrical distribution resulting in pain, stiffness and loss of function.

RA has a wide clinical spectrum ranging from mild joint symptoms to severe inflammation and damage to joints. RA is diagnosed on clinical, serological and radiological grounds. The American Rheumatism Association (ARA) first proposed classification criteria for RA in 1956 and then revised them in1958 (1;2).

Although, these criteria were widely used to diagnose RA for many years, they were heavily criticised for their lack of sensitivity and specificity. The ARA published revised classification criteria for RA in 1988, based on cross-sectional data from a large group of patients with rheumatoid and other types of inflammatory arthritis (3).

Table 1.1 1987 Revised ARA Classification Criteria for RA

Criterion		Definition
1	Morning stiffness	Morning stiffness in and around the joints lasting at least 60 minutes before maximal improvement
2	Arthritis of 3 or more joint areas	Arthritis of 3 or more joint areas at the same time with swelling involving proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle and metatarsophalangeal (MTP) joints
3	Arthritis of hand joints	At least one joint area swollen in PIP, MCP or wrist joints
4	Symmetrical arthritis	Simultaneous involvement of the same joint areas on both sides of the body
5	Rheumatoid nodules	Subcutaneous nodules over bony prominences or extensor surfaces or in periarticular regions
6	Rheumatoid factor	Presence of rheumatoid factor (RF) in the blood
7	Radiographic changes	Presence of erosions or juxta-articular osteoporosis on hands and feet x-rays

For classification purposes, RA is diagnosed if a patient satisfies 4 out of 7 criteria from the above table and criteria 1 to 4 must be present for at least 6 weeks. However, these criteria were based on data from patients with established disease and it is widely recognised that some of these features may be absent during early stages of the disease.

Disease course in RA can be unpredictable and in many cases, particularly in patients with active disease, it progresses to develop cartilage destruction, joint damage and deformity over a period of time (4-7). Clinical disease progression in RA is usually monitored by standard clinical, laboratory and functional indices, whereas serial x-rays of hands and feet assess structural damage (4-7).

It has been demonstrated that progression of structural damage on x-rays leads to more functional disability, increased requirement for orthopaedic surgery and negative impact on socioeconomic as well as other healthcare costs (8-12). Therefore, the ultimate goal of treatment in RA is to suppress disease activity as low as possible in order to induce and maintain clinical remission and to reduce joint damage and deformity and thus a more favourable long-term outcome.

1.1.2 Epidemiology

Prevalence of RA in the general population worldwide is estimated to be between 0.3 to 1.5 % using different types of classification criteria. Epidemiological data have shown that Native American populations such as Pima Indians have a high prevalence of RA and it is low in countries like China, Japan and Africa compared to Caucasians (13) . Although RA can occur at any age, its incidence increases with age and may vary depending upon the type of classification criteria used and demographics of the

population studied (14). The peak age of onset has risen to 50 years or more and is more common in women than men with a ratio of 3:1 (9;12;15)

1.1.3 Aetiology

RA is an autoimmune disease of unknown cause and interaction between genetic and environmental factors play an important role in the development of disease in susceptible individuals.

a) Genetic factors

Family and twin studies indicate that first degree relatives of patients with RA have an increased frequency of developing this disease, particularly if the patients had severe disease or were seropositive for rheumatoid factor (16). Identical twins have higher concordance rates of the disease compared to non-identical twins supporting genetic susceptibility (16;17). However, RA is a polygenic and genetically heterogeneous disease and non-inherited factors are also of great importance.

In RA, the causative role of different genes may vary between individual patients and various combinations of polymorphisms in a selection of different genes (genotype) may predispose to the clinical picture (phenotype). Some genes are responsible for severity of the disease rather than occurrence. Only few genes have been consistently associated with RA. The major histocompatibility complex (MHC) is a large genetic region on the short arm of chromosome 6, which has been consistently linked to RA. A large part of the MHC comprises human leukocyte antigen (HLA) genes, which encode individual's tissue type and are divided into class I (HLA-A, HLA-B, HLA-C) and class II (HLA-DR, HLA-DQ, HLA-DP) genes. The encoded proteins are crucial

in determining the individual's immune response to antigenic stimuli. HLA class II genes, in particular HLA-DR4 and HLA-DRβ1, have been strongly linked to RA. Particular HLA-DRβ1 molecules in RA share a sequence that influences the peptides that are bound and viewed by the immune system. This core amino acid sequence is named the 'shared epitope' and these epitopes have been linked with both predisposition to, and severity of RA (18-20). Other genes have also been implicated in the aetiology of RA, such as genes encoding tumour necrosis factor (TNF)-α and interleukins (IL).

b) Environmental factors

Population studies have shown that non-inherited factors such as environmental triggers, particularly smoking and infections play a major role in the aetiology of RA. Infectious agents, such as Epstein-Barr virus (EBV), Parvovirus B19, Mycobacterium tuberculosis, Escherichia coli and Proteus mirabilis have all been implicated as possible trigger factors for RA, but the results have been inconsistent (21-26).

Environmental agents are considered as triggers rather than as being directly involved in the disease process and complex interplay between genetic and environmental factors are probably important for the initiation of the disease process in susceptible hosts. Certain viruses and bacterial agents contain identical peptide sequence to autoantigen and infection with these microbial agents can induce an immune response that cross-reacts with the autoantigen, termed 'antigen mimicry'. Antigen mimicry is one hypothesis to explain induction of autoimmunity by environmental triggers. Another concept proposes that a local immune response to any environmental agents

may release pro-inflammatory cytokines to up regulate antigen-presenting capacity resulting in an immune mediated inflammatory cascade (27).

Hormonal factors may also play a possible role in the aetiology of the disease as suggested by increased female preponderance, high incidence during the pre-menopausal or post-partum period and protective effect of oral contraceptive pills presumably due to its progesterone content (28).

Diet and stress have also been considered to play a possible role in the disease expression (29;30). Vitamin D and its metabolites may have an inverse relationship with disease activity in inflammatory polyarthritis or RA, due to their immunomodulatory effects (31). Studies have shown that higher consumption of olive oil, oil-rich fish, fruit, vegetables and beta-cryptoxanthin may have a protective effect on the development of RA, whereas lower consumption of foods rich in antioxidants, could be associated with an increased risk of RA, but the results were inconclusive (32). Also, high intake of red meat and low intake of vitamin C might play a role in the development of inflammatory polyarthritis (33;34).

1.1.4 Normal joint

a) Normal synovium

The normal human body contains a number of synovial joints and each synovial joint is made up of two bones, linked by a fibrous capsule with a deeper synovium, which lines the joints except in the areas of articular cartilage. The normal synovium is characterised by lack of cellularity but it is a highly vascular connective tissue, bound by the fibrous joint capsule on one side and by the joint space on the other.

The synovial membrane has a thickness of one or a few cells and forms the surface layer of the synovial tissue. It comprises two layers, a superficial lining layer called intima and a deep sub-lining layer called sub-intima. The intima contains two major cell types on electron microscopy: type A synoviocytes, resembling macrophages, and type B synoviocytes with fibroblast characteristics. The intima does not have typical features of an epithelium and it lacks a basement membrane between synoviocytes. The matrix of the intima has abundant proteoglycans and glycosaminoglycans, particularly hyaluronic acid. The sub-intima is a vascular connective tissue stroma containing blood vessels, lymphatics and nerve endings within a matrix comprising varying proportions of lipid, collagen fibrils and more organized fibrous tissue.

b) Synovial fluid

The synovial membrane secretes this highly viscous and nourishing fluid with high concentration of hyaluronic acid, which acts as a lubricant and help to minimise joint damage. Other constituents of the synovial fluid include nutrients and solutes that diffuse from the blood vessels in the sub-intima. The exact mechanism of synovial fluid production is not known, but it appears that a balance of hydrostatic and osmotic forces regulates exchange of fluid between the circulation and the joint space.

c) Articular cartilage

Each articular surface is composed of hyaline cartilage, which strongly adheres to the underlying sub-chondral bone and the load bearing properties of the cartilage depend on the structure and matrix. The articular cartilage comprises chondrocytes embedded in a hydrated matrix composed of collagen, proteoglycans and other matrix proteins. The matrix contains more than 70 per cent water and chondrocytes occupy only 5-10

per cent of the normal cartilage by volume. However, chondrocytes are vital to maintain the integrity of the matrix as they synthesize collagen, proteoglycans and other components such as fibronectin (35).

Collagens are a family of secreted matrix proteins that contain elements of a unique triple-helical peptide structure, which accounts for their tensile strength. These fibrillar proteins, together with proteoglycans, account for the biomechanical properties of articular cartilage. There are 14 different types of collagen but are divided into three major groups based on the structure and properties of triple-helical peptides (36;37). The differences between collagens relate to either the length of the triple helix, the presence of non-collagenous units within the molecule that impart extra flexibility, or the addition of non-collagenous side chains such as carbohydrates. The most common collagen in the body is the type I fibrillar collagen, which is the main structural element in bone, ligaments and tendons, often occurring together with the type III collagen. The major collagen in articular cartilage is type II, constituting 80 to 90 per cent of the total content, with types IX and XI contributing most of the remainder.

Proteoglycans are large, negatively charged macromolecules comprising a polypeptide core with glycosaminoglycan side-chains. The major proteoglycan of articular cartilage is aggrecan, which contain abundant chondroitin sulphate and keratin sulphate side-chains. The main function of the aggrecans relates to their anionic and water-trapping properties, which provide deformability and compressibility. The superficial layer of articular cartilage has a high ratio of collagen to aggrecan compared to the deep layer close to the subchondral bone. Therefore, the

surface layers have high tensile strength and resilience whereas the deep layers have higher deformability and compressibility. Proteoglycans in the cartilage matrix have a steady turn over maintained by a constant slow rate of aggrecan degradation and loss and its replacement by new synthesis. The tissue content of aggrecan is maintained at a constant level by a co-ordinated turn over between degradation and biosynthesis.

The chondrocytes are responsible for controlling these events and appear to be sensitive to the aggrecan content of the matrix and some feedback mechanisms seem to co-regulate synthesis and degradation (38). Enzymes such as collagenase, gelatinase, stromelysin and aggrecanase mediate breakdown of collagen and the surrounding matrix. These enzymes are zinc-dependant matrix metalloproteinases (MMP) controlled by tissue inhibitors of metalloproteinases (TIMPs). In RA, release of pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α) reduce synthesis and increase catabolism of articular cartilage, resulting in rapid breakdown, as opposed to growth factors such as transforming growth factor-beta (TGF-β) and insulin-like growth factor-1 (IGF-1), which stimulate synthesis of cartilage components.

d) Subchondral bone

The basal layer of articular cartilage is calcified and is attached directly to subchondral bone. Major part of the bone matrix is composed of type I collagen and the remaining is made up of proteoglycans, glycoproteins, glycosaminoglycans such as hyaluronic acid, and proteins such as osteocalcin. Glycoproteins such as osteopontin, osteonectin and bone sialoproteins function as anchoring molecules, bridging matrix constituents to bone cells.

Bone contains three different cell types on histological sections: osteoblasts, multinucleated osteoclasts and osteocytes. Osteoblasts, derived from the mesenchymal stromal cell system, are critical for the synthesis of collagen and bone matrix as well as non-collagen proteins and they control bone mineralization. The factors that control bone formation are complex and not fully understood but they seem to largely work through osteoblasts. The other major cell type is osteoclasts, which are derived from precursors in the haemopoietic system and they break down bone via a combination of lysosomal enzymes and low pH. Calcitonin, and possibly oestrogens, exerts inhibitive effect on osteoclasts through specific receptors and the resorptive effects of thyroid and parathyroid hormones are probably mediated through the osteoclasts. The third cell type is osteocytes, which occupy lacunas within the mineralized bone and they probably have an important function in the detection of, and response to, mechanical forces within mineralized bone.

The activities of bone cells are influenced by cytokines, which are peptides produced by cells such as lymphocytes (lymphokines) or monocytes (monokines) that act as autocrine, paracrine, or endocrine mediators. Examples of such cytokines that have effects on bone include ILs, TNFs, interferons (IFN), IGF, TGF and colony stimulating factors (CSFs). These cytokines have anabolic or catabolic effects on the bone mediated through their multiple actions with synergism or antagonism on osteoblasts or osteoclasts. This constant process of bone formation and resorption i.e. bone remodelling is essential to maintain bone strength and to optimize load-bearing capacity and it also plays an important role in metabolic homeostasis, in particular calcium and magnesium.

Various mechanical forces and endocrine factors such as parathyroid hormone (PTH), thyroid hormone, vitamin D, calcitonin and sex hormone influences bone remodelling. Bone formation and resorption is carefully balanced in young adults to maintain bone mass but in the older people, particularly in postmenopausal women, breakdown exceeds synthesis, leading to osteoporosis. Bone resorption is also accelerated by drugs such as corticosteroids and by active inflammation.

1.1.5 Joint in RA

The most pronounced and fundamental pathology in RA is destruction of articular cartilage and subchondral bone by ectopic and hyperplastic synovium. The involvement of synovial joints in RA is both of the synovial fluid and membrane. Synovial fluid volumes and cellularity are increased with predominance of polymorphs. T lymphocytes and macrophages are also seen in large numbers along with dendritic cells, plasma cells and B-lymphocytes in the synovial fluid and membrane. The lining layer of the synovial membrane, which is normally two cells thick, become much thickened with increased numbers of both type A (macrophage-like) and type B (fibroblast-like) cells (39).

In RA, the synovium becomes highly vascular with increased number of new blood vessel formation termed ‘angiogenesis’. The junction between synovial tissue, cartilage, and the bare area of bone within the joint capsule is prone to develop erosions early in RA. The synoviocytes proliferate as the disease progresses and invade the adjoining articular cartilage, where the secretion of cytokines, and cartilage and bone-degrading enzymes, results in characteristic destructive changes of RA. The invading, hyperplastic synovium is called pannus and the zone of invasion is called

cartilage-pannus junction. Synovial membrane that lines the tendons and bursae also develop similar proliferative changes leading to destruction and deformity (39-41).

Rheumatoid synovium contains a number of pro and anti-inflammatory cytokines, which are mainly of T-cell and macrophage origin. Prominent pro-inflammatory cytokines are TNF-α, IL-1, IL-6, IL-8, IL-12, IL-15, IL-18 and interferon-gamma (IFN-γ), whereas the main anti-inflammatory cytokines are IL-4, IL-10, IL-11, IL-13, TGF-β, and cytokine neutralizing factors such as soluble TNF-α receptors and IL-1 receptor antagonist (IL-1ra). An imbalance between pro and anti-inflammatory cytokines may be the main pathogenic mechanism in RA as pro-inflammatory mediators, in particular TNF-α and IL-1, appears to play a major role in the immune mediated inflammatory cascade leading to various articular and systemic manifestations (39;42-44). Other pro-inflammatory factors present within the RA synovium include nitric oxide, prostaglandins, leukotrienes, and free oxygen radicals.

Rheumatoid synovium is characteristically highly vascular with angiogenesis and this is stimulated by various factors including hypoxia and soluble factors such as vascular endothelial growth factor (VEGF) and soluble vascular cell adhesion molecule-1 (VCAM-1), which stimulate endothelial cell growth. There are other adhesion molecules that are abundantly present on the vascular endothelium such as E-selectin and intercellular adhesion molecules (ICAMs). Their expression is stimulated by pro-inflammatory cytokines, particularly TNF-α and IL-1, resulting in the recruitment of inflammatory cells via specific receptors. Chemokines such as monocyte chemotactic protein-1 (MCP-1), IL-8 and MCP-2 are highly expressed in RA synovium and they stimulate progression of inflammatory cells into the joint (39;45;46).

Tissue hyperplasia and lymphocyte proliferation as a result of immune response is normally counteracted by programmed cell death or apoptosis to prevent over accumulation of cells. In rheumatoid joints, apoptosis is actively inhibited despite the presence of pro-apoptotic stimulants such as hypoxia and TNF-α in rheumatoid synovium. Impaired synoviocyte apoptosis may contribute to the pathogenesis of RA (39).

The exact mechanism of cartilage and bone destruction in RA is not understood, but may be related to a variety of destructive enzymes secreted by pannus. The important ones are MMPs, which include collagenases, stromelysins and gelatinases, and serine and cysteine proteases such as cathepsins. These enzymes destroy the articular cartilage by acting upon collagen and proteoglycan matrix but are normally controlled by physiological inhibitors such as TIMPs. An impaired regulatory mechanism between these destructive enzymes and their inhibitors may partly be responsible for the destructive nature of the disease (39;47-49).

Other destructive factors include the cytokines TNF-α and IL-1, which activate osteoclasts leading to bone resorption. Bone destruction may also be mediated by factors such as osteoclast differentiation factor (ODF) or TNF-related activation-induced cytokine (TRANCE) and receptor activator of nuclear factor κB ligand (RANKL). ODF interacts with membrane RANK that is present on osteoclast precursors, resulting in their differentiation and activation and subsequent bone destruction. The combination of TNF-α, IL-1 and ODF probably contributes to peri-articular as well as systemic osteoporosis in RA. There is also a soluble form of RANK called osteoprotegerin (OPG), which acts as a decoy receptor, inhibiting the effects of ODF on osteoclasts (39;50).

a) Extra-articular disease

Apart from joints, RA also affects many other structures in the body causing various extra-articular or systemic manifestations. Rheumatoid nodules are the most common and others include vasculitis, serositis, interstitial lung disease and Felty's syndrome. The precise mechanism of extra-articular disease in RA is unknown and one of the hypotheses is that rheumatoid factor (RF) activate macrophages expressing Fc-γ receptors, which then produce pro-inflammatory cytokines and chemokines, leading to further influx of inflammatory cells. RF also activate complement pathway resulting in immune complex deposition in the perivascular tissues leading to inflammation and vasculitis. Severe disease and extra-articular features may be associated with a double dose of the shared epitope, particularly in DR4/DR14 (51).

Neurological component may also possibly play a role in the pathogenesis of RA and is suggested by high levels of neuropeptides such as substance P, symmetry of the joints involved and sparing of paralysed limbs in patients with stroke. It has also been suggested that patients with RA have abnormalities in hypothalamo-pituitary-adrenal (HPA) and hypothalamo-pituitary-gonadal (HPG) axes, including a suppressed response to painful stimuli.

1.1.6 Impact of RA

RA, like many other chronic diseases, has a significant impact on patient's functional ability, job status and quality of life (QoL) and it represents a huge economic burden, not only for patients and their families, but also for the society as a whole (10;52-54).

a) Functional or work disability

RA affects patients' ability to perform day-to-day activities due to various reasons such as, pain, fatigue, stiffness, swelling, deformity and damage. As the disease progresses, a significant proportion of patients develop functional disability with increased requirement for aids, appliances, home adaptations and orthopaedic surgery (9;12;55). Therefore, patients with RA may experience a number of problems in relation to their work such as inability to continue working, not able to work in the same occupation or not able to work same number of hours. This is termed work disability and it is one of the most important outcomes in the RA studies (9;12;55). Previous studies have reported rate of work disability varying between 22% and 85% and the length of follow-up in those studies ranged from 1 year up to a maximum of 30 years (9;56;57).

b) Cost of RA

The overall costs and economic consequences of RA can be enormous with huge socioeconomic implications. Cost of illness (COI) due chronic, crippling disease like RA can be divided mainly into two components: direct costs and indirect costs. Direct costs relate to the treatment of RA, borne mainly by the health care sector, including hospitalizations, orthopaedic surgeries and social care. Indirect costs means costs incurred due to loss of productivity and there are two forms: morbidity and mortality costs. Morbidity costs include value of production losses due to work disability, whereas mortality costs are calculated as value of lost production due to disease related premature death.

It was estimated that the direct and indirect costs of RA in England was £1.265 billion in 1992, of which 48% was due to direct medical costs and 58% due to loss of productivity (58). Hospital costs were the largest direct expenditure in this study and the indirect costs were probably underestimated, as mortality costs were not included in the analysis. Other population-based COI studies have estimated a direct cost of £ 3680 to £3800 per RA patient per year and indirect costs were at least 3 times higher than direct costs in one study (59;60). Indirect medical costs appear to be the major financial burden as it can be as high as 85% of the total economic costs (61-63).

Some recent studies have also confirmed that the economic burden due to RA could be enormous. In a French study, it has been estimated that direct costs per patient was €1812 – €11,792 annually and indirect costs €1260 – €37,994 per annum. 75% of the direct costs were associated with in-patient care and 20% for medications. Physician visits accounted for 20% of the direct costs. However, indirect costs were more expensive and were responsible for 80% of the excess cost related to RA (64).

In another systematic review, the total average annual medical cost was estimated as ranging from $5720 (£3575) to $5822 (£3638). In this study, in-patient care constituted about 17 to 88% of total direct costs, whereas physician visits and medications accounted for 8 to 21% and 8 to 24% of total direct costs respectively (65).

In a primary care based inception cohort of early inflammatory polyarthritis (Norfolk Arthritis register/NOAR), mean 6-month total cost was estimated to be £2800/person, of which 14% was due to direct costs and the remainder was due to non-health service or indirect costs (66).

1.2) Early Rheumatoid Arthritis

Early RA was traditionally defined as disease duration of less than 5 years from onset of symptoms until 1990s. However, over the last two decades, disease duration of 24 months or less has been considered as early RA with much emphasis placed on the first 6 to 12 months. The concept of early RA and early arthritis clinics was introduced to make an early diagnosis and to plan timely interventions. This is because, observational studies have shown that significant percentages of patients had already developed erosive disease within the first 3 years of disease onset and they continued to progress strikingly, particularly if left untreated, with poor long-term outcomes (67-71).

Early RA patients with undiagnosed or untreated disease may develop persistent inflammation with progressive joint damage. It is essential to start treatment before patients develop irreversible damage or disability. Early intervention has been reported to reduce disease progression with better radiological and functional outcomes (72-75).

Longitudinal studies, involving a large number of early RA patients with prolonged follow-up are vital in providing key information on the nature of disease progression, prognosis and long-term outcomes. The advantages of these observational studies are that patients with mild or inactive disease are also included with less stringent exclusion criteria and patients are managed in a 'real life' setting, although high dropout rate may be a problem. On the other hand, clinical trials mainly recruit patients with active disease and have strict exclusion criteria with a limited follow-up period, but are more useful to assess treatment response.

1.3) Disease presentation and progression

The natural history of RA is not fully known, although a number of studies have examined the course of conventionally treated RA over time. The characteristic features of RA include joint inflammation, destruction, deformity and disability, with very variable disease presentation and subsequent course. The three main components of disease progression are clinical, radiological and functional.

1.3.1 Clinical

RA characteristically involves the small joints of hands and feet in a symmetrical distribution, although it can affect any joint and manifest in various extra-articular sites as well. The main symptoms include joint pain, tenderness, swelling, stiffness and deformity, which sometimes are associated with constitutional symptoms such as malaise, fever, fatigue and weight loss (76). The usual mode of disease onset is either acute (abrupt) or insidious (gradual), with the latter being more common and some patients may also have episodic (palindromic) presentation (76-78).

The pattern of joint involvement is usually polyarticular but it can also present with either oligoarticular (≤ 4 joints involved) or monoarticular involvement. In patients with recent-onset arthritis, other differential diagnoses such as, seronegative spondyloarthritides, connective tissue diseases, infections, post-viral and other types of inflammatory arthritis should be considered before making a definite diagnosis of ‘early RA’.

The natural course of RA can be unpredictable and usually patients tend to pursue one of the following clinical courses: 1. chronic and progressive; 2. relapsing and

remitting; and 3. non-recurrent or remission (6;70;76). The common course of disease process is chronic and progressive but it can vary or fluctuate depending upon the patients' and disease characteristics and treatment effect. The severity of clinical disease activity at a given time point or over a period of time is normally graded as, no disease (remission), low (mild) or minimal disease activity, moderate disease activity and high (severe) disease activity (79-81). Various criteria have been proposed and validated to assess the level of clinical disease activity using specific cut-off points and this helps to study the nature of disease progression, treatment response, prognosis and outcomes (79-85).

It has been suggested recently that the 'life cycle' of RA falls into four phases. Firstly, it is the period leading up to the onset of arthritis, and next period is the time during which disease persistence or remission is determined. Third phase is the evolution into a specific form of arthritis, and finally the outcome of arthritis (86). It was also suggested that the term 'early rheumatoid arthritis' is not appropriate and patients either have established RA or an undifferentiated inflammatory arthritis (86).

1.3.2 Radiological

In RA, persistent inflammation in the affected joints cause damage to the articular cartilage and surrounding bone, resulting in loss of joint space, joint destruction and deformity. Historically, plain film radiography has been used to detect these changes and a variety of abnormalities including osteoporosis, cysts, erosions, joint space narrowing (JSN), subluxation, ankylosis, malalignment and sclerosis can be identified. Erosions and joint space narrowing are more common during the early stages of the disease with further progression as the disease advances, whereas

subluxations, malalignment and ankylosis are more apparent in the later stages of the disease (87).

X-rays can be used to define structural damage at a given time point as well as damage progression over time. Early radiological changes of rheumatoid such as, erosions and JSN are more evident on the x-rays of hands, wrists and feet. A significant proportion of RA patients with early disease may have already developed erosions within 2 years of the disease onset and feet appear to develop erosions earlier than hands (88-91). Although erosions occur earlier and more frequently in the feet than in the hands, subsequent radiological damage progression seems to be fairly equal at both sites in patients with early RA (90;92). However, in a longitudinal study of patients with established RA, radiological damage was more evident in the wrists and feet initially and most of the subsequent progression occurred in the wrists, knees and MCP joints compared to the feet (93).

Joints may differ in their susceptibility to develop erosions and JSN. For example, PIP joints show more erosive changes than JSN, whereas the wrists show JSN and erosions to be equal. It has been suggested that it may be due to the tendency of the rheumatoid hands to flex, which makes it difficult to assess and similar problems may be experienced at the MTP joints due to dorsal subluxation. Erosions at the wrist tend to be less discrete and more often of a surface type leading to underestimation. Also, compressive forces transmitted through the wrist may further damage the cartilage and compress the porotic bone, resulting in sclerosis and making erosive changes less apparent (90). The rate of progression of JSN and erosions may be variable as some

patients showed erosions progressing faster than JSN (88;90), whereas others showed JSN exceeding erosions (92).

Ideally all synovial joints should be included to assess the radiographic progression, but this would be more time consuming and not practical. It has been shown that radiographic changes at the small joints of hands and feet correlate well with large joints, both for the extent of overall joint damage at a given time point and for the rate of progression over time (93-95). Therefore, x-rays of hands and feet have been used traditionally to assess radiological progression in RA (87;96;97).

The rate of radiographic progression in RA may be unpredictable, as individual patients will have variable progression dependent on disease severity, response to therapy and other factors. Some patients show more rapid progression during the early stages of the disease with slowing down in the later years (98), whereas others show constant linear rate of progression over time (7;68;99).

Different mathematical models of radiographic progression with time have also been proposed: 1) flat or non-progressive; 2) slow or moderate onset, but an increasing progression rate (linear); 3) moderate-to-fast onset and a stable progression rate (square-root type); 4) fast onset, but a later decreasing progression rate (first-order kinetics type); and 5) slow onset, then acceleration and later deceleration (sigmoid type) (100). Plant et al proposed 4 different models of radiographic progression in an 8 year outcome study of early RA patients: 1) flat or nonerosive; 2) linear; 3) lag; and 4) plateau (90). This study also showed that radiological progression was fast in the first 2 years of disease and thereafter it was highly variable.

Other imaging modalities such as, ultrasonography (US), magnetic resonance imaging (MRI) and computed tomography (CT) have also been used to study radiological damage at a given time point and progression over time (101;102). These newer techniques appear to be more sensitive in detecting erosions earlier than conventional radiography, and also correlate well with subsequent development of erosions on x-rays (101-104).

RA can also affect the cervical spine, which may lead to destructive changes close to the spinal column. Inflammation of the synovial membrane (synovitis) and pannus formation are seen in the odontoid-atlas joint, uncovertebral joint and facet joints in the cervical spine, ultimately leading to cervical spine instability, which can cause serious and life-threatening complications (76;105). X-rays of the cervical spine in flexion and extension views and MRI are commonly used to look for cervical spine involvement in RA and radiographically, atlantoaxial or C1-C2 subluxation is the common type of cervical spine instability in severe disease (76;105). There are other types of subluxations such as anterior and vertical subluxation.

1.3.3 Functional

RA can interfere with activities of daily living and cause significant impairment in physical function. Patients with active disease often develop progressive decline in their functional ability, which may be associated with increased rates of work disability and increased use of healthcare resources leading to high medical costs and poor socioeconomic outcomes (12;56;57;106;107).

Functional disability at the early stages of the disease appears to be mainly due to joint pain, swelling and stiffness secondary to active inflammation in the joints rather than structural damage, whereas at the later stages of the disease it correlates significantly with radiological damage (107;108).

Functional status of an individual is an important determinant of his or her employment and it is a good predictor of future work disability (56;57;109). It has been shown that patients with RA are more likely to lose their jobs due to their functional limitation and prevalence of work disability can be much higher in RA compared to the general population (56;110). Work disability is strongly influenced by the nature of work as manual workers are more likely to stop working and there are also other contributory factors such as, work autonomy, job characteristics and level of formal education (6;56). Age of disease onset, education, disease severity and disability are important predictors of employment outcome (56;111). Women, older age at disease onset ($\geq$ 60 years) and significant functional disability at disease presentation have been shown to be associated with worse functional outcomes (12;107;112).

A significant proportion of patients with RA develop substantial functional disability over time and the extent of disability is partly a function of disease duration at the time of assessment (6). Although patients show individual variation in the progression of their functional disability, several studies have shown that disability increases with disease duration at a fairly constant rate (107). It has also been shown that functional decline can be more rapid during the early (12;113) and late stages of the disease

(12;114). Sometimes patients show an initial improvement in their functional ability followed by a progressive functional decline (55;107;115).

In early RA, functional disability can be labile as it is mainly due to active inflammation in the joints rather than structural damage and so it can fluctuate in accordance with disease severity and can improve with effective treatment (107). Functional disability in patients with early RA may stabilise by 5 years and thereafter it often shows linear progression and strong correlation with radiological damage (107). Therefore, the ultimate goal of treatment in RA should be to control the inflammation as much as possible and to avoid structural damage in order to improve functional as well as socioeconomic outcomes.

1.4) Assessment of Disease Activity

In RA, measurement of disease activity at specific time points or at regular intervals helps to evaluate disease progression and it is vital to assess treatment response, outcomes and prognostic factors. Various methods have been introduced and validated to measure disease activity in RA over the last few decades. These methods have been designed and modified to evaluate three different but interrelated aspects of the disease progression: clinical, radiological and functional.

1.4.1 Assessment of clinical disease activity

Until 1980s, physicians used various terminologies such as active, inactive, mild, moderate or severe to describe the disease status based on their own observation and judgement without any consistency or standardization. Non-specific terms such as ‘entirely well’, ‘no arthritis’ and ‘symptom free’ had been used to define disease

inactivity state or remission (116). In 1981, the American Rheumatism Association (ARA) developed preliminary clinical criteria for remission (117) and both the original and modified versions of these criteria were used in several studies (116-118).

Preliminary ARA remission criteria

1. No joint pain
2. No fatigue
3. Early morning stiffness for <15 minutes
4. No joint swelling or tendon sheath swelling
5. No joint tenderness or pain on motion
6. Normal ESR of <30 in women and <20 in men

According to the above criteria, patients are classified as being in remission if they fulfil 5 out of 6 criteria at two time points i.e. on visits 0 and 2 months. This has been modified later by omitting fatigue and by making the assessment at one study point rather than two times, to make it more disease specific and more practical to use.

Modified ARA remission criteria

1. No joint pain
2. Early morning stiffness for <15 minutes
3. No joint swelling or tendon sheath swelling
4. No joint tenderness or pain on motion
5. Normal ESR of <30 in women and <20 in men

Using the modified ARA criteria, with the exclusion of fatigue, either 4 out of 5 or all 5 criteria have to be fulfilled to define remission (118).

Clinical remission criteria excluding patient reported joint pain, fatigue and morning stiffness from the preliminary ARA criteria have also been used (119).

Clinical remission criteria

1. No joint tenderness or pain on motion
2. No swollen joints
3. Normal ESR of <30 in women and <20 in men

Patients have to fulfil all the above 3 criteria at a given time point to qualify for remission using the clinical remission criteria. However, all the above criteria are based on categorical rather than continuous measures and so it is not useful to assess different levels of disease activity.

In the early 1990s, core sets of disease activity measures have been proposed by the American College of Rheumatology (ACR, formerly ARA), European League Against Rheumatism (EULAR) and World Health Organization (WHO) / International League of Associations for Rheumatology (ILR), to standardize disease activity assessments in the clinical trials involving RA patients (120-123). These measures included swollen joint count (SJC), tender joint count (TJC), patient assessment of pain, global assessment of disease activity by the patient (PGA) and by the evaluator (EGA) and acute phase reactants such as erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP). The core set also included structural damage on radiographs and functional status and these measures were identified on the basis of

available evidence, consensus by expert committees and most importantly because of their ability to predict outcome (123;124). These measures are also very useful and crucial to assess disease activity and treatment response in day-to-day clinical practice.

a) Swollen and tender joint counts

Joint involvement or inflammation in RA has traditionally been assessed using swollen (soft tissue swelling and effusion) and tender joint counts (tenderness on pressure or motion). Methods, to include deformed joints in the assessment have also been suggested but not used routinely (125;126). A number of different joint indices and counts have been developed over the years and they vary by the number of joints assessed or by the way several joints are aggregated to represent joint regions (124). Some of these methods weight joints by surface area (weighted joint counts), whereas others weight joints by severity of swelling and tenderness (graded joint counts) (124).

The joint indices that were introduced earlier involved extensive number of joint counts and grading of swelling and tenderness, which were time consuming and led to inter-observer disagreement (127-131). Ritchie et al, introduced a graded tender joint count, assessing 26 joint areas with grades ranging between 0 to 3 depending upon the severity of joint tenderness (130). Hart and colleagues modified this later to exclude grading by severity, which was the main reason for disagreement between observers (128). Further modifications of the joint indices and simplifications of the extensive joint counts were carried out by other groups over the years, reducing the number of

joints assessed (132-134). These simplified joint counts have been validated and are reliable and easy to use in clinical practice (135-137).

b) Pain

Pain is the main symptom for majority of patients with RA and it is usually measured on a 100-mm visual analogue scale (VAS), evaluating symptom for one week before the study point. Horizontal VAS is more commonly used than vertical scales and there are also other reliable methods of pain assessment such as, arthritis impact measurement scale (AIMS) and McGill pain questionnaire (124).

c) Global assessment of disease activity

Both patients and evaluators assess overall disease activity on a 100-mm VAS. Patient global assessment of disease activity (PGA) is a subjective measure and it is different from the patient assessment of global health (GH) as in the latter, all possible domains of health outcomes, including those that are directly or indirectly related to the disease process are included. On the other hand, evaluator global assessment of disease activity (EGA) is usually based on subjective and objective measures that is available to the evaluator (124).

d) Acute phase reactants

ESR and CRP are the most commonly used acute phase reactants (APRs) in RA to assess disease activity and progression. These inflammatory markers usually rise in direct proportion to the severity of disease activity and they correlate well with clinical and radiographic disease progression and also outcomes (138-140). There are

also other biomarkers of disease activity such as ILs, TNF-α, MMPs and RANKL, which are expensive and complex and so are mainly used as research tools.

e) Disease activity scores and indices

Using these disease activity measures individually to evaluate disease activity may not give reliable identification of disease activity as they assess different aspects of the disease and it may lead to methodological problems. Composite disease activity scores have been developed over the years to overcome these problems and these scores use special formulas integrating SJC, TJC, ESR or CRP and GH to measure overall disease activity (124).

Van der Heijde et al, introduced disease activity score (DAS) in 1990 with a view to help physicians grade the level of disease activity and to assess treatment response. The original DAS is based on Ritchie articular index (RAI) and 44-swollen joint count and it employs a complex formula, using square root and logarithmic transformation of variables and different weights for each variable (141;142). This was later modified to include the reduced 28-joint count, DAS28, which shows similar validity and reliability compared to DAS and has been widely used (84;136;137). Both DAS and DAS28 have been modified in several ways to exclude the assessment of GH (DAS-3 and DAS28-3) and to include CRP instead of ESR (DAS-CRP and DAS28-CRP) (124).

Formulae to calculate DAS with 4 or 3 variables and with ESR or CRP

DAS = $0.54 \times \sqrt{(\text{Ritchie})} + 0.065 \times \text{SJC44} + 0.33 \times \log_{nat}(\text{ESR}) + 0.0072 \times \text{GH}$

DAS-CRP = $0.54 \times \sqrt{(\text{Ritchie})} + 0.065 \times \text{SJC44} + 0.17 \times \log_{nat}(\text{CRP}+1) + 0.0072 \times \text{GH} + 0.45$

DAS-3 = $0.54 \times \sqrt{(\text{Ritchie})} + 0.065 \times \text{SJC44} + 0.33 \times \log_{nat}(\text{ESR}) + 0.224$

DAS-3 CRP = $0.54 \times \sqrt{(\text{Ritchie})} + 0.065 \times \text{SJC44} + 0.17 \times \log_{nat}(\text{CRP}+1) + 0.65$

Formulae to calculate DAS28 with 4 or 3 variables and with ESR or CRP

DAS28 = $0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.70 \times \log_{nat}(\text{ESR}) + 0.014 \times \text{GH}$

DAS28-CRP = $0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.36 \times \log_{nat}(\text{CRP}+1) + 0.014 \times \text{GH} + 0.96$

DAS28 -3 = $[0.56 \times \sqrt{(\text{TJC28})} + 0.28 \times \sqrt{(\text{SJC28})} + 0.70 \times \log_{nat}(\text{ESR})] \times 1.08 + 0.16$

DAS28 -3 CRP = [0.56 x √(TJC28) + 0.28 x √(SJC28) + 0.36 x $\log_{nat}$(CRP+1) x 1.10 + 1.15

Because of the complexities of the above formulae, which require calculator or computer program, simpler joint indices, based on ACR and EULAR core sets, have been developed. The advantages of these relatively newer indices are that they employ a linear sum of variables, which are untransformed and unweighted and they include PGA and EGA as well. One of them is the simplified disease activity index (SDAI), which is based on SJC, TJC, PGA, EGA and CRP and it has been used in several studies as well as routine clinical practice (85).

SDAI = SJC28 + TJC28 + PGA + EGA + CRP

The SDAI has been later modified by omitting CRP to help physicians calculate disease activity and make treatment decisions at the time of clinical assessment itself without having to wait for CRP, termed clinical disease activity index (CDAI) (82).

CDAI = SJC28 + TJC28 + PGA + EGA

f) Criteria to assess disease activity including remission

After the introduction of the composite disease activity indices, a number of criteria have been validated, based on DAS, DAS28, SDAI and CDAI, to assess different levels of disease activity including remission (79;81-83;85;143;144). EULAR has adapted disease activity criteria based on DAS and DAS28, which have been widely used in several studies (79;81-83;85;143;144).

EULAR criteria based on DAS

DAS < 1.60	-	remission
DAS ≥1.60 and ≤ 2.40	-	low disease activity
DAS >2.40 and ≤ 3.70	-	moderate disease activity
DAS> 3.70	-	high disease activity

EULAR criteria based on DAS 28

DAS 28 < 2.6	-	remission
DAS 28 ≥ 2.6 and ≤ 3.2	-	low disease activity
DAS 28 >3.2 and ≤ 5.1	-	moderate disease activity
DAS 28 > 5.1	-	high disease activity

SDAI criteria for disease activity

SDAI ≤ 3.3	-	remission
SDAI ≤ 11	-	low disease activity
SDAI ≤ 26	-	moderate disease activity
SDAI > 26	-	high disease activity

CDAI criteria for disease activity

CDAI ≤ 2.8	-	remission
CDAI ≤ 10	-	low disease activity
CDAI ≤ 22	-	moderate disease activity
CDAI > 22	-	high disease activity

The United States (US) Food and Drug Administration (FDA) has also proposed remission criteria, which is based on ACR remission criteria, but also takes into

account structural damage on x-rays and treatment status at the time of assessment. According to this, 5 out of 6 ACR remission criteria have to be fulfilled plus radiographic arrest for ≥ 6 months with no drug therapy (144).

g) Criteria to assess treatment response

Several criteria have been developed over the years to assess treatment response in RA and they are mainly used in clinical trials to measure treatment effect. As these criteria express improvement relative to a baseline, they are less useful in clinical practice (124).

In 1990, Paulus response criteria was developed, which required four out of six selected measures for improvement as follows: ≥ 20% improvement for morning stiffness, ESR, joint pain/tenderness score, joint swelling score, and two or more grades on a 5-grade scale for PGA and EGA (145).

The ACR response criteria, based on ACR core set variables, was introduced later in 1995 and it require 20% improvement (ACR20) in swollen and tender joint counts and three of the five remaining core set of variables such as joint pain, PGA, EGA, ESR or CRP and function (146). The ACR response criteria were expanded subsequently to include 50% improvement (ACR50) and 70% improvement (ACR70) in order to express significant improvement that are clinically meaningful.

The ACR numeric percentage (ACR-N) response criteria were a modification of the original ACR response criteria (147). It gives a quantitative measurement by grading a 0% to 100% improvement according to the smallest relative improvement in the

following three measures: SJC, TJC and median of the five remaining core set variables such as joint pain, PGA, EGA, ESR or CRP and function. These criteria, using a continuous scale, did not seem to discriminate reliably between drug treatments and so not used (124).

The US FDA response criteria include radiographic details and require patients to continue with drug therapy. According to this, patients are said to have major clinical response if they fulfil ACR70 response plus radiographic arrest for ≥ 6 months with continuing drug therapy. Complete clinical response is defined as, presence of 5 out of 6 ACR remission criteria plus radiographic arrest for ≥ 6 months with continuing drug therapy (144).

The EULAR response criteria are based on DAS and DAS28 scores. It categorize treatment response into no response, moderate response and good response according to the level of improvement in the DAS or DAS28 scores after treatment compared to baseline (79;81). The ACR20, 50 and 70 response criteria and the EULAR response criteria have been the most commonly used in the clinical trials. The EULAR response criteria have also been used in clinical practice since the introduction of biological agents to make decisions on either continuing or withdrawing biologic therapy depending upon the treatment response in a specified period of time.

1.4.2 Assessment of radiological progression

Conventional radiography has been traditionally used to assess structural damage in RA. X-rays of hands and feet and/or large joints have been used to define radiological damage at a given time point as well as progression of structural damage over a

period of time. The advantage of radiographic assessment of disease progression over other methods is that the damage seen on x-rays is largely irreversible and it represents the cumulative measure of disease activity and destructive process over time. The other major advantage is that apart from providing permanent records, radiographs can also be randomized and blinded for clinical investigations of new therapeutic agents in clinical trials (87;148).

It has been widely recognised that radiological damage on x-rays has to be quantified to define the disease status of the patient and more importantly to assess disease progression, treatment response and outcome (87;91;149). As there are no truly quantitative methods, semi-quantitative methods have been developed to translate the amount of structural damage on x-rays into a score value (149). There have been several studies and expert opinions including consensus statements about the scoring methodology, to answer some important questions such as, which abnormalities should be included, which joints should be scored, which views, which order the films should be read and which scoring system to use (150;151).

a) Radiographic abnormalities to be included

There are lot of abnormalities that can be seen on radiographs in patients with RA. These include soft tissue swelling, juxtaarticular and diffuse osteoporosis, erosions, subchondral cysts, joint space narrowing (JSN), subluxation and malalignment, and ankylosis. Erosions and, to a lesser extent, JSN are widely accepted to be included in the scoring methods as they give reliable and additive information on radiological progression (152-154). The relative weight given to erosion versus JSN varies between scoring methods and no consensus has yet been established (152).

Sometimes scoring these radiologic abnormalities can be made difficult by the presence of other features such as, severe subluxation or luxation and cyst formation.

b) Joints to be included

Although any synovial joints can be affected in RA, it is not feasible to include all joints in scoring radiological damage. Therefore, it was recognised that a representative group of joints should be selected to reflect changes in other joints. Hands (including wrists) and feet have been chosen to represent the overall radiological status of the disease as they are the most commonly involved joints in a majority of patients with RA. Also, erosions and JSN can be seen very early in the hands and feet especially the latter and it is easy to evaluate (87-91). It has been shown that radiographic damage on the hands and feet, correlate well with the large joints both at a specific time point for the extent of damage and over a period of time for progression (93-95).

The joints that are usually evaluated in the scoring methods include PIP joints, MCP joints, IP joints of thumbs, wrist joint as a whole or as individual joints, MTP joints and IP joints of the 1st toes (151). It has been shown that omitting joint areas that are technically difficult to read and not commonly affected from the assessment can still provide accurate information about the overall radiological abnormalities in patients with RA (154;155). Although RA is typically a symmetrical polyarthritis, radiological changes can appear asymmetrically and so both hands and feet should be included in the radiographic evaluation (151).

c) Standard views of radiographs

The technical quality of the radiographs is important for accurate assessment of structural damage, particularly in studies using radiographic outcome as a primary objective. Other factors such as, good positioning of the hands and feet and proper exposure of the film is also essential in obtaining accurate information.

Posteroanterior (PA) view of the hands and feet x-rays is the most commonly used technique, although other views such as, Norgaard view (a 45^0 supine view with straight finger) and Brewerton view (a tangential view with the MCP joints flexed at 65^0 and with a 15^0 volar beam) have been used without any significant advantage (156). Therefore, PA views are being widely used in the radiographic assessment of RA and exposure of the film is also vital in detecting subtle changes as tiny erosions may be missed on under or over-penetrated films.

d) Scoring order of the films

Serial x-rays of hands and feet help to monitor structural damage progression in RA and the films can be read in 3 different ways, 1. random order (single film at a time), 2. paired reading (films grouped together per patient and read without known sequence) and 3. chronological reading (serial x ray films read with known sequence) (151).

There are advantages and disadvantages for all these methods. Reading films randomly can introduce measurement error, as the reader will not be able to correct for variation in positioning of hands and films or for the quality of the films (157). It has been shown that paired reading is more precise than reading films randomly in assessing radiological progression (152;158;159).

The advantage of reading films in chronological order is its increased sensitivity to detect change compared to paired reading, although an overestimated progression of joint damage by the readers (expectation bias) can not be ruled out in reading films with known sequence. Also, with the paired or random reading, there is a possibility of introducing measurement error by limiting the information to the reader, that the signal is lost in the noise (signal-to-noise ratio). Reading films in chronological order also results in increased sensitivity of detecting radiological progression that is clinically meaningful (157;160;161).

e) Scoring methods

Several scoring methods have been developed and subsequently modified over the last few decades to quantify the radiographic damage in RA. Some of the very earlier scoring methods such as the Steinbrocker and the Kellgren methods assessed the worst affected joints and gave a global assessment with grading for the entire patient (162;163).

The scoring methods that were developed subsequently have been designed to assess individual joints and some of them scored erosions and JSN together with one overall score (global method), whereas others scored erosions and JSN individually with a separate score for each that are added together at the end to give a overall score (composite method).

In 1971, Sharp et al proposed a composite scoring method for the hands and wrists, which was later modified in 1985 and in these methods feet were not included. The modified Sharp method has been used in several studies and with this method the

erosion scores range from 0 to 170 and the JSN scores range from 0 to 144. Further modification of the Sharp method was proposed by Fries et al in 1986, which was more time consuming without any significant advantage and so not been used (98;152;154;164).

Genant et al, developed a composite scoring method in 1983 to include hands and feet and this method requires a standard reference set of radiographs for comparison. This method was later modified by the same group and this method is still being used but less commonly (165-167).

Kaye et al, combined the methods described by Sharp and Genant and introduced a new composite scoring method, which used the standard reference set of radiographs for comparison developed by Genant and included only hands and wrists (155;168). In this method, postoperative joint was taken into account and given a maximum score and joints that could not be evaluated were excluded from the total score.

In 1989, van der Heijde modified the Sharp method, described in 1985, and in this method (Sharp-van der Heijde/SvdH), feet were included. The SvdH method scores erosions and joint space narrowing separately and is expressed as erosion score, joint space narrowing score and total Sharp score (169).

Following joints are assessed in the SvdH method for erosions:

a. 10 MCP joints
b. 8 PIP joints
c. 2 IP joints of the thumbs
d. right and left 1st metacarpal bone
e. right and left radius and ulnar bones
f. right and left trapezium and trapezoid as one unit
g. right and left navicular bones
h. 10 MTP joints
i. 2 IP joints of the big toes

Erosions are scored 1 if they are discrete and 2 or 3 depending on the surface area of the joint involved. In the carpal bones it is sometimes very difficult to score erosions as the bone collapses completely and in this case the collapsed area is given a score according to the surface area involved and a complete collapse is scored as 5.

In each hand including the wrists, 16 joint areas are scored for erosions and a maximum erosion score for each joint is 5, whereas, in the feet 6 joint areas are scored for erosions in each foot with a maximum erosion score of 10 for each joint area, to increase weight of the feet joints in the total erosion score. Therefore, erosion score ranges from 0 to 160 in the hands and 0 to 120 in the feet with a total erosion score ranging from 0 to 280.

Following joints are assessed in the SvdH method for joint space narrowing:

a. 10 MCP joints
b. 8 PIP joints
c. right and left 3rd, 4th and 5th carpometacarpal joints
d. right and left multangular-navicular joints
e. right and left capitate-navicular-lunate joints
f. right and left radio carpal joints
g. 10 MTP joints
h. 2 IP joints of the big toes

Joint space narrowing is combined with score for (sub)luxation and is scored as:

0 = normal,

1 = focal or doubtful

2 = generalised but less than 50% of the original joint space,

3 = generalised and more than 50% of the original joint space or subluxation

4 = bony ankylosis or complete luxation

JSN is assessed in 15 joint areas in each hand including the wrists and in the feet 6 joint areas in each foot are scored. Therefore, JSN score in the hands ranges from 0 to 120 and in the feet it ranges from 0 to 48 with a total JSN score ranging between 0 and 168. Erosion score and JSN score are added together to give a total Sharp score, which ranges from 0 to 448 in the SvdH method. SvdH method has been used widely in several studies and is currently the most common method used in clinical trials.

In 1999, van der Heijde described simplified erosion, narrowing scoring method (SENS), which was essentially a simplification of the SvdH method (170). SENS assesses the same joints as the SvdH, but instead of grading, the number of joints with erosions and with JSN is simply summed in this method. In the erosion score, a joint is scored as 0 or 1 depending upon the absence or presence of erosions respectively and likewise, JSN score in each joint is scored as 0 or 1 depending upon the absence or presence of JSN. The score, both erosion and JSN, for each joint can therefore range from 0 to 2. Erosion is assessed in 32 joint areas in the hands and 12 in the feet, whereas JSN is evaluated in 30 joint areas in the hands and 12 in the feet. Therefore, erosion score ranges from 0 to 44 and JSN score ranges from 0 to 42 with a total score ranging from 0 to 86.

Larsen developed a global scoring method in 1974, based on a set of standard radiographs. In this method, both hands and feet were included and erosions and joint space narrowing were scored together. The original Larsen method was modified several times in the following years both by Larsen and by other groups (171-176). The number of joint areas assessed and the grading of radiographic abnormalities vary between the original and modified methods and so the total score range was also different between them. Scoring details of Larsen method, that was used in this thesis is described here (172).

Following joints are assessed in this modified Larsen method:

Proximal interphalangeal(PIP) joints of both hands	-	8
Interphalangeal(IP) joints of both thumbs	-	2
Metacarpophalangeal (MCP) joints of both hands	-	10
Both wrists (score multiplied by 5)	-	2
Metatarsophalangeal joints (MTP) of 2^{nd} -5^{th} toes on both sides	-	8
Interphalangeal (IP) joint of big toes on both sides	-	2

Grading of radiographic abnormalities in this modified Larsen method:

Grade 0: Normal finding

Grade 1: Soft tissue swelling, juxta-articular osteoporosis, possibly with slight narrowing of the joint space

Grade 2: Early but definite abnormality consisting of bone erosion and distinct narrowing of the joint space.

Grade 3: Medium destructive abnormality with marked narrowing of the joint space

Grade 4: Severe destructive abnormality. Only minor parts of the articular surfaces remain

Grade 5: Mutilating lesions

In this modified Larsen method, 20 joint areas in the hands and 10 joint areas in the feet are assessed with a maximum score of 5 for each joint area. The wrist is assessed as one unit and then multiplied by 5, which gives a maximum score of 25 for each wrist. Therefore, the total score in this method ranges from 0 to 200.

In 1998, Rau et al introduced a new scoring method, Ratingen score, which was derived from the Larsen score (177). There are also some unfamiliar scoring methods such as, the carpometacarpal ratio (C:MC), a quantitative measure of the wrist involvement, and the short erosion scale (SES), which was a modification of the Larsen method (178;179).

Although there are several scoring methods available to measure radiographic damage, Larsen and Sharp and their modifications, mainly SvdH, have been the most commonly used. Each of these scoring methods has their own advantages and disadvantages. The advantage of Larsen's score is that an experienced reader can perform it quickly whereas SvdH method is more time consuming (180). However, inclusion of soft tissue swelling in the Larsen's score may lead to a relatively high score at baseline, decreasing with response to treatment. This may reduce the total possible increased score due to progressive damage, contributing to low sensitivity to change (149). It has been shown that that SvdH method is better than others in relation to its sensitivity to detect a real change in x-ray progression over time (sensitivity to change) and in detecting changes that are clinically meaningful, termed minimal clinically important difference (MCID) i.e. smallest radiographic change that necessitates the physicians to alter their treatment (181-188).

Regarding evaluation of the radiographic data, there have been recommendations from the expert committees and the Outcome Measures in Rheumatology Clinical Trials Conference (OMERACT) about the standards and minimum requirements for reporting the radiographic results in clinical trials, which are described below.

f) Number of observers

It was recommended that in clinical trials a minimum of 2 observers should read the films and the average score of 2 observers should be used to express the analyses, to reduce measurement error, although it is expensive and time consuming. However, in epidemiologic studies and non-drug trials, one observer is acceptable provided intraobserver agreement is presented as a measure of the consistency of the results. Interobserver agreement of the single observer with another experienced reader or trainer should also be presented to ensure reliability of the results (189).

g) Reliability

The value of any scoring method depends on its reliability as shown by inter and intraobserver reproducibility and this is calculated using statistical tests. Pearson or Spearman correlation coefficients have been used for this but they are not the correct methods as they measure the strength of association and not of agreement. Intraclass correlation coefficient (ICC) and kappa statistics are the appropriate tests to measure inter and intraobserver agreement and a maximum score of 1.0 give perfect reliability (151;189).

Bland and Altman proposed another method, where the difference of the observers' scores (y axis) is plotted against the mean of the observers' scores (x axis). This method gives a graphical illustration of measurement error over the total range of scores and it will reveal whether there is a systematic difference between the 2 observers. The ideal situation would be for all points to be situated on or close to $y = 0$ (190;191). If only a single observer is used, readings from the same observer at different time points can be used for this method.

h) Sensitivity to change

The ability of a scoring method to detect a real change in radiographic progression over time is called sensitivity to change. In assessing longitudinal radiographic progression in RA, it is important to use a scoring method with high sensitivity to change and so better discriminative power. Methods such as standardised response mean (SRM) and smallest detectable difference (SDD) or change (SDC) have been used to assess the sensitivity to change of a particular scoring method and also to compare the discriminative power of different scoring methods (150;185;189;192).

SRM is calculated by dividing the mean of the difference between scores at two time points by the standard deviation (SD) of change score and a value above 0.80 is considered to have a high sensitivity to detect changes (150).

SDD or SDC is the difference or change that is greater than the measurement error and this can be derived from the intraobserver reproducibility if one observer is used or from reproducibility of the average scores if 2 observers' average scores were used (185;192).

SDD and SDC are calculated as follows:

$$SDD = \pm 1.96 \times SD_{difference} / \sqrt{k}$$

$$SDC = \pm 1.96 \times SD_{difference} / (\sqrt{2} \times \sqrt{k})$$

$SD_{difference}$ is the standard deviation of difference between two readings and k represents the number of readings or observers used for the actual analyses of a trial.

SRM and SDD and its relation to MCID have been used to compare different scoring methods like Larsen's and SvdH (183;184;187). The scoring method that has got high

SRM value is considered to be more powerful in assessing sensitivity to change. The lower the SDD value the higher the sensitivity of a scoring method in detecting radiographic progression that are considered clinically important (161;183;184;187;193).

i) Presentation of radiographic results

Erosions and joint space narrowing provide independent information as they represent different aspects of the biologic process underlying the development of structural damage. Therefore, if possible, erosion and JSN score should be presented as secondary endpoints for composite scoring methods like Sharp and SvdH (189).

The main purpose of scoring radiographic damage is to measure the change or progression between two study points and the results can be presented at group level as well as at individual level using appropriate statistical tools.

At group level, a change in mean or median score has been used to assess radiological damage and treatment response in studies involving large number of patients (161). However, in patients with extreme stages of radiological damage, a change in mean score ± SD may not indicate the specific stages of radiographic progression as the data is probably skewed (161). Median score with interquartile range (IQR) may be more useful to report radiologic progression in patients with different levels of disease activity and radiological damage (161). Therefore, both mean ± SD and median value with IQR have to be used to present radiographic data at group level (189).

At individual level, some studies have used arbitrary cut-off values (1-5 points/year) to measure the change or progression between two study points whereas others used the cut-off values based on SDD, which is a study or trial specific number (161;193). Although, SDD can be used to show progression above measurement error, there is a chance that patients with progression less than SDD may be missed. Therefore, percentage of patients with progression > 0.5 (for two readers) or > 0 (for single reader) should also be presented along with percentage of patients with progression > SDD (189). Also in early RA studies, it may be useful to know the number of patients with new erosions and the percentage of patients with a score of 0 at the study start and at the end (189).

Radiographic progression can also be presented as increase in absolute number or increase in percentage. One of the problems with these scoring methods, particularly in patients with a lot of structural damage at the start, is the 'ceiling effect' i.e. when a maximum joint score is reached in a joint, further joint damage can not be quantified (194). Scott and his colleagues proposed a method to reduce the ceiling effect, in which the progression is represented in relation to the radiographic score at the start and this is calculated as follows: absolute progression /(maximum score of the method-score at the start) x 100 % (195).

As each scoring method has a different score range, absolute numbers or mean ± SD and median with IQR do not provide exact information, if the scoring methods have to be directly compared. It has been suggested, that in order to make a direct comparison between two different scoring methods, the scores from each method can be linearly transformed from their original scale to a scale of 0 to 100. For example, to

transform SvdH (range 0-448) and Larsen scores (range 0-200) from their original scale to a scale of 0 to 100, the SvdH scores have to be multiplied by 0.2232 and the Larsen scores have to be multiplied by 0.5 (185). Another method called percentage or mean percentage of the maximum possible score has also been proposed to make direct comparisons between scoring methods and is calculated as follows: increase in absolute score / maximum score of the method x 100 % (189).

j) Radiographic remission

The FDA has included radiographic status of the disease in their strict remission criteria and according to this 5 out of 6 ACR remission criteria have to be fulfilled plus radiographic arrest (Larsen or SvdH method) for ≥ 6 months with no drug therapy (144). Some studies have reported on radiographic remission using different criteria such as, no extension of existing erosions and no development of new erosions between two time points (119) or no increase in radiographic score (Larsen) by > 1 point between the study points (196).

k) Radiographic healing

Interestingly, it has been reported that healing of radiographic damage or erosions can occur during sustained disease inactivity or remission in RA, as a result of treatment with DMARDS and/or biological agents (197). Radiographic healing has been described as a reparative process, which may be represented by various features, such as recortication, sclerosis, filling in, remodelling and restoration (197;198). Healing of erosions in patients with RA between two time points may result in decreased or negative radiographic scores at group or individual level. However, measurement

error should be considered and excluded before making a diagnosis of radiographic healing, particularly in clinical trials that investigate treatment effects (198).

Finally, in studies involving large number of patients with long-term follow-up, missing data may be an unavoidable problem. Methods such as 'last observation carried forward' (LOCF), mean substitution, and data imputation have been suggested to handle this but unfortunately no consensus has been reached to resolve this important issue (189).

1.4.3 Assessment of function

Functioning is an important aspect of overall health status and it strongly influences quality of life (QoL). Different types of instruments have been used over the years to evaluate health status and QoL. In general, they are classified as global measures (to measure overall QoL) and health related measures (health related QoL). The latter can be used either to compare different patient populations across different diseases (generic measures) or to evaluate problems associated with a particular disease (disease-specific measures) (124). The Medical Outcomes Study Short Form-36 (SF-36) is the most commonly used generic measure, which assesses both physical and mental aspects of QoL (199).

Functional assessment in patients with RA is a vital component in the evaluation of disease progression as it significantly correlates with disease activity, structural damage and long-term outcomes (12;56;57;107). Measures such as, Steinbrocker's functional grade (FG), patient self-reported questionnaires and quantitative objective instruments have traditionally been used to assess function.

In 1949, Steinbrocker et al introduced a grading method based on clinician's assessment of functional impairment according to a scale of I to IV, whereby FG III applies to patients mainly housebound and/or work disabled, and FG IV to mainly wheelchair or bed bound patients (163). This was later largely replaced by patient self-report questionnaires such as health assessment questionnaire (HAQ), which has been widely used in clinical trials and clinical practice to evaluate physical function. Steinbrocker's FG has been shown to correlate well with HAQ in relation to functional assessment in RA (8;200).

The HAQ or HAQ-disability index (HAQ-DI) is a 20-question instrument, which assess the degree of difficulty a patient has in accomplishing his or her tasks in eight functional categories such as dressing, rising, eating, walking, hygiene, reaching, gripping and usual day to day activities. For each question there is a four-level difficulty scale ranging from 0 to 3. The final score is the mean of the highest scores across eight categories and it ranges from 0 to 3, with higher levels indicating more disability (201;202). The HAQ has been modified several times subsequently to simplify it and to make it user friendly and also to include other domains such as depression and anxiety (203-205).

Previous studies have attempted to identify specific cut-off points for HAQ to define clinically meaningful response between two time points i.e. real improvement in HAQ that is noticeable by the patient after treatment, and in one study the cut-off point was found to be 0.25 (206;207). However, an improvement in HAQ depends upon the duration of disease as it assesses both reversible and irreversible components of

functional impairment. It has been shown that during the early stages of the disease (< 5 years duration), the HAQ score is mainly influenced by joint pain and swelling due to inflammation, which can improve with treatment (reversible), whereas in the late stages, the HAQ scores strongly correlate with structural damage (irreversible) and so the reversibility of HAQ in patients with established RA may not be as significant as in early RA (208).

The Arthritis Impact Measurement Scale (AIMS) is another form of patient self-reported functional questionnaire, which include assessment of depression and anxiety (209). There are longer and shorter versions of the AIMS, which have been used to evaluate function in patients with arthritis including RA (124).

Objective quantitative instruments have also been used to assess function and these include measures of grip strength and locomotion (210). Grip strength has been widely used to assess hand function and this is measured using a vigorimeter or a dynamometer, with readout indicating the pressure attained by squeezing a compressible rubber bulb (211). These instruments appear to be reliable and correlate with disease activity and also they have been shown to predict long-term outcomes (212).

1.5) Outcomes and prognostic factors

The natural (treated) course of RA varies greatly. At one end of the spectrum patients have mild disease, which remains stable for many years, whereas at the other end patients have severe disease with rapid progression. A significant proportion of patients do not follow such a consistent or predictable course and their disease progression may fluctuate with relapsing and remitting pattern.

Various factors have been shown to determine the disease onset, subsequent progression and outcomes in RA, but the results can be inconsistent and vary to a great extent among individual patients (153;213-219). Nonetheless, it is very important to learn the outcomes and prognostic factors in RA, both from the clinicians' and patients' perspective, as it not only helps in better understanding of the disease process but also in developing targeted management strategies to reduce the morbidity and mortality.

1.5.1 Outcomes

Outcomes in RA can either be due to the disease itself (disease specific) or due to the consequence of the disease (non-disease specific). Remission, radiographic damage and functional disability are examples for disease specific outcomes, whereas work disability, costs and mortality reflect non-disease specific outcomes. Other important disease specific outcomes include pain, global assessment of disease activity, joint swelling and tenderness, orthopaedic surgeries and adverse drug reactions (6).

1.5.2 Outcome measures

Studies have been reporting outcomes in RA cohorts for several decades. However, it was widely recognised that standard and validated measures have to be developed to measure or quantify outcomes in RA clinical trials. Therefore, outcome measures have been developed by the international associations such as ACR, ILAR and OMERACT to be used in clinical trials involving RA patients (121;220;221). Outcome measures are used to analyse different types of the disease specific outcomes and they can be broadly classified as clinical, radiological and functional.

a) Clinical

Clinical outcome measures include VAS for pain, DAS or DAS28 for joint tenderness (TJC) and joint swelling (SJC) and acute phase reactants (APRs) (121;124;220;221). ACR 20, 50 and 70 and EULAR response criteria are used to assess disease activity and treatment response using the standard clinical variables and APRs and so they have been widely used to measure clinical outcomes in RA studies (79;146).

b) Radiological

Structural damage seen on x-rays such as, erosions, JSN and deformities are considered as valuable radiographic outcomes in RA (87). The various scoring methods described in a previous section have been used as radiological outcome measures in most of the clinical trials, particularly in studies that analyse treatment effect and functional outcome (87;149;222).

c) Functional

Patient self report questionnaires have been the most commonly used tool to measure functional disability in RA, which sometimes include details on the use of aids and other appliances (124). Although several such questionnaires have been developed and modified over the years, HAQ is the most commonly used functional outcome measure in RA clinical trials as well as in routine clinical practice (124). Other measures that have been used to assess functional disability include Steinbrocker's FG I-IV and grip strength (12;124).

1.5.3 Prognostic factors

Prediction of disease progression and outcome in RA is crucial for optimal clinical management. Reliable prognostic factors would allow aggressive therapy to be targeted to patients at high risk early. However, the predictive value of many of the baseline variables can be inconsistent, particularly at the individual level. Observational studies and clinical trials have both reported on the power of various predictive factors for severity of RA, but the results have not been consistent because of differences in patient demographics, study design, methodology, treatment and choice of outcome measures.

Wolfe and Hawley analysed predictive factors for remission (ARA criteria) in a cohort of established RA and they have reported that female sex, disease onset before age 60 and early development of erosions were associated with decreased proportion of remission (116). Eberhardt and Fex have reported that the presence of rheumatoid factor (seropositivity) and presence of shared epitope were associated with reduced frequency of remission in their prospective study of early RA patients (118).

Several other studies have also analysed the predictive factors for remission and in general factors such as gender, age at disease onset, disease duration, TJC, RAI, SJC, DAS, morning stiffness, ESR, CRP, rheumatoid factor (RF), HAQ, baseline radiographic damage and type of treatment have all been shown to have some prognostic value, although the results have been inconsistent (223). Some of these factors are consistently reported for their prognostic value and they include female sex, RF, level of baseline disease activity and radiographic damage.

Prognosis for radiographic progression can only be studied reliably in a prospective study of early RA patients with regular clinical assessments and standardized laboratory and radiological measures at baseline and then at regular intervals.
Combe et al, studied the prognostic factors for radiographic damage and radiological progression in a prospective cohort of early RA patients who were followed up for 3 years (224). In this study, baseline variables such as RF positivity, HLA-DRB1, pain score and total Sharp score were predictive of radiologic damage at 3 years, whereas ESR, RF positivity, HLA-DRB1 and erosion score were predictive of radiographic progression.

Few other studies, which used radiographic damage as their primary outcome measure, have reported on various factors that are associated with worse radiological outcome and they include long disease duration, RF positivity, high ESR or CRP, and higher Sharp scores at baseline (225-229). Dixey et al studied radiographic progression over 3 years in a large sample of early RA patients from their Early Rheumatoid Arthritis Study (ERAS) (68). In their study baseline variables such as RF, shared epitope and rheumatoid nodules showed predictive value for development of

erosions at 3 years. They have also reported that certain variables at 1year follow-up had more powerful predictive value for radiographic damage (Larsen score), including RF positivity, high ESR, low haemoglobin (Hb) and high erosion score. Based on these studies, positive RF and high radiographic damage at baseline appear to be consistently associated with worst radiological outcome (68;224;226;228-230).

It is generally agreed that active disease and progressive structural damage are associated with functional disability and so it is logical to assume that bad prognostic factors for disease activity and radiological damage can be related to functional disability as well. There is only limited information on prediction of functional disability from prospective RA studies, which used functional outcome as the primary outcome measure. Some of the baseline variables have been shown to be associated with worse functional outcome and they include female sex, older age at disease onset and worse HAQ score (>1.0) (12). Other factors such as, poor grip strength, RF positivity and development of erosions within the first 2 years of disease presentation have also shown to be associated with poor functional outcome (8).

1.6) Clinical versus radiological disease activity

In RA, clinical and radiological disease activities are two important aspects of disease evolution, which affects subsequent disease progression and outcome.

1.6.1 Relationship between clinical and radiological disease activity

Local inflammation of the affected joints, manifesting as joint pain and swelling, generally represents the clinical disease activity in RA and is measured by various joint indices and acute phase reactants (APRs) (124). Persistent inflammation in the

affected joints leads to structural damage visualised as erosions, JSN and deformity on plain radiographs (161).

There is a close link between clinical and radiological disease activity in RA. How strong is this correlation when other factors are taken into account, for example disease heterogeneity and treatment effect? (107;231). Previous studies have shown that joint damage occurs early in the course of RA and about 60 to 70 % of early RA patients in these studies developed erosions within the first year or two of disease onset (87;90). As the disease progresses, most of the patients (> 90%) develop erosive disease and the disease duration has been shown to have a significant correlation with structural damage, assessed by Sharp or Larsen scores (90;107).

Several clinical trials, using various treatment strategies, have demonstrated that more the improvement in disease activity less is the joint damage (232-241). Also, time-integrated measures of disease activity such as, area under the curve (AUC) for DAS and ESR or CRP have been shown to correlate with radiological progression and treatments that control these measures more effectively lead to significant reduction in radiographic progression (138-140;242-244).

Welsing et al, however, argued that time-averaged estimates for disease activity do not reflect individual variability within patients (245). This group studied the longitudinal relationship between disease activity and radiological progression in two different early RA cohorts with a maximum follow-up of 9 years, by using a special regression technique called generalized estimating equations (GEE). They found that radiological progression was not linear in individual patients and fluctuations in

clinical disease activity (mean interval DAS and SD of the mean interval DAS) were directly related to changes in radiographic progression. Other studies have also showed similar results that radiographic progression may be highly variable at individual level, particularly in early RA, although it is approximately linear at group level (90;100).

The type of treatment may also have an influence on the link between clinical and radiological disease progression. In the COBRA trial, which studied the effect of DMARD combination therapy against monotherapy in patients with active RA, radiological progression was significantly reduced even in patients who did not respond clinically (ACR response criteria) to the combination therapy (246). However, it has been suggested that this paradox may be due to misinterpretation of the data as further detailed analyses of this cohort showed that time-integrated DAS was lower in the combination therapy group, even in non-responders, compared to monotherapy and this was not shown by the ACR response criteria as it was a measure of change only (245).

Other clinical trials have also shown that the radiographic progression may be reduced even in patients with no significant clinical improvement to anti-TNF therapy (247). It was suggested that it might be due to the inhibitory effect of anti-TNF on osteoclast induced bone resorption, independent of clinical disease activity, mediated via specific molecules such as RANKL and osteoprotegerin (248).

1.6.2 Radiological progression despite clinical disease inactivity

There is robust evidence that RA patients with active disease develop progressive structural damage compared to patients with low disease activity or remission (232;236;238;239). However, it has been shown that significant radiographic progression can occur even in patients with clinically inactive disease or remission (196;224;243;249-257). Several possible mechanisms or hypotheses have been suggested to explain this disconnect between clinical and radiological disease activity in patients with clinical remission and they are as follows:

1. Pathogenesis of joint inflammation and destruction may differ from each other in RA

Previous studies have shown that joint counts and acute phase reactants, reflecting synovial inflammation, continued to improve whilst radiological damage progressed (251;255;258). To explain this, it was suggested that the mechanisms, which are responsible for articular cartilage damage and synovial inflammation, may differ from each other (254). This hypothesis was supported by a study, which showed that synovial macrophages, but not lymphocytes, correlate with radiological progression, whereas both lymphocytic and non-lymphocytic populations correlate with measures of clinical disease activity (254;255).

It has been suggested that synovial macrophages and other non-lymphocytic populations such as fibroblasts along with various cytokines may lead to progressive radiological damage despite little evidence of synovial inflammation and this may not respond to treatment with conventional DMARDs. On the other hand, clinical and laboratory manifestations of synovial inflammation may reflect both lymphocytic and

non-lymphocytic populations in the synovium, which may respond to conventional therapy (254). This is supported by subsequent findings that biological therapies, targeting synovial macrophages and various proinflammatory cytokies as well as lymphocytic populations, have been shown to achieve better clinical response with retardation of radiographic progression compared to DMARDs (233;259-263).

2. Residual tender or swollen joint counts despite fulfilling DAS or DAS 28 remission criteria because of the weighting in the formulas

Assessment of disease activity using DAS involves comprehensive assessment of joints, which include 68 TJC and 44 SJC. On the other hand, using DAS28, disease activity (TJC and SJC) is assessed in 28 joints only omitting ankles and feet. Therefore, there is a possibility that patients classified as being in DAS28 remission may still have active inflammation in the ankles or feet (264-266).

Landewe et al compared DAS remission with DAS28 remission in patients with early RA who participated in the COBRA trial (266) . They have found that in patients who were in remission according to either DAS or DAS28, but not both, the discordance between those remission criteria was mainly (96%) due to patients fulfilling DAS28 remission but not DAS remission criteria. In this study, patients fulfilling DAS28 remission, but not DAS remission, had residual disease activity as indicated by high TJC and SJC (266). This was also supported by findings from other groups, who showed that DAS28 remission is less stringent, allowing for higher joint counts, compared to SDAI and CDAI based remission criteria (264;267).

3. Time lag between clinical disease activity and structural damage

Cumulative clinical disease activity could have been higher in the period prior to the point when DAS and structural damage on plain radiography are compared.

Matsuda et al studied the correlation between swollen joints, acute phase reactants, Larsen scores and number of erosive joints in early RA patients at 6 and 12 months (268). They have reported that there was certainly a time lag between active synovitis and the appearance of new joint erosions in their cohort. Aletaha et al recently studied a subgroup of early RA patients from the PREMIER study, who were in clinical remission (SDAI $\leq$ 3.3) at 2 years. This study showed that radiographic progression during clinical remission was actually related to level of disease activity preceding the period of radiographic assessment (269).

4. Lack of sensitivity of conventional radiography in detecting erosions

Conventional radiography is less sensitive than MRI and US in analysing radiographic progression as there may be a significant time-lag between the appearance of an erosion on MRI and the subsequent change on plain radiographs (101-104). Studies that used these advanced imaging techniques have shown that synovitis can be detected on US and MRI in apparently 'normal looking joints' (sub-clinical synovitis) or in patients who were classified in remission (270-272).

5. Scoring methodology (Scoring methods and the sequence of reading x-rays)

Although several scoring methods are available to measure structural damage, SvdH method has been shown to be better than others in relation to its sensitivity to change, smallest detectable difference and minimal clinically important difference (181;182;184). Therefore, SvdH scoring method may have a better discriminative

power in assessing longitudinal radiographic progression, particularly in patients with remission or low disease activity.

Paired reading of the x-ray films is more precise in assessing radiological progression than reading films in random order as the later method can introduce measurement error (152;157-159). However, chronological scoring of x-rays may be better than random or paired reading in assessing longitudinal radiographic progression. This is because chronological order is more sensitive in detecting radiographic progression above measurement error and in identifying clinically relevant changes, although expectation bias can occur with this method (157;160;161).

6. Treatment effects

Remission in RA can either be due to the natural course of disease ('spontaneous remission') or following therapy ('drug induced remission'). In observational studies difficulties with analysis of drug effects arise due to several factors including the large variations in drugs actually used and their timing, drug terminations due to adverse events or drug interactions, co morbidity and drug compliance. For various reasons a patient may temporarily cease important disease modifying therapy.

Some patients stop taking DMARDs once remission is achieved either on their own accord or according to their doctors' advice. This may have an influence on radiographic progression. Ten Wolde et al studied the effect of stopping DMARDs in RA patients who had stable disease and had been on treatment for at least 2 years (273). In this study, patients who fulfilled ACR remission criteria were randomised either to receive placebo or to continue with their DMARDs and were followed up for

52 weeks. Disease flares were more common in the placebo group compared to the DMARD group and the disease control was not adequate even after re-institution of DMARDs in the former group (273;274). Radiographic outcome was not analysed in this study, nonetheless, it is logical to expect relatively more radiographic progression in the placebo group who experienced increased disease flares.

Some DMARDs may be less effective and may take more time in reducing the structural damage even after a good clinical response. In the COBRA trial, Sulphasalazine as a monotherapy has been shown to be less effective in reducing radiological progression compared to aggressive combination therapy (SZP + MTX + Prednisolone). It was also demonstrated in this study that combined therapy immediately suppressed damage progression, whereas SZP did so less effectively and with a lag of 6 to 12 months (232). In the FIN-RACo study, long-term use of combination therapy (SZP + MTX + hydroxychloroquine + prednisolone) was compared with monotherapy (SZP or MTX or azathioprine ± prednisolone) in reducing joint damage in patients with early RA (252). In this study, more patients achieved remission in the combination group compared to monotherapy at 2 years but the difference was not sustained at 5 years. However, the radiographic progression (Larsen scores) was still significantly less in the combination therapy group at 5 years.

7. Progression of radiographic damage can be mediated by mechanisms other than clinical disease activity

Radiographic progression may occur independently of joint inflammation. In a study by Molenaar et al, increased urinary levels of bone turnover biomarkers such as pyridinoline, desoxypyridinoline, N-terminal telopeptide (NTX), and C-terminal

telopeptide (CTX) were found in RA patients with clinically inactive disease (258). It has also been demonstrated that urinary CTX-2 levels correlate with radiographic progression, independent of joint inflammation and disease duration, in patients in remission (275). These biomarkers of collagen breakdown and bone turnover have been shown to predict the effect of DMARDs on radiographic progression, independent of changes in clinical disease activity (276-278).

Therefore, progression of structural damage can occur despite clinical remission or disease inactivity in RA. The link between clinical disease progression and radiological damage can be variable and unpredictable, particularly in early RA and it may have an influence on outcomes.

1.7) Rationale for this thesis

This section will first report on previous similar studies to this thesis and discuss some unanswered questions and unresolved issues and in the following section the main aims & objectives of this thesis will be discussed.

A detailed list of critical appraisal of the relevant studies is included in the appendices section.

Table 1.2 shows a brief summary of the main early RA studies reporting on frequency of clinical remission using validated criteria.

RA studies that used biological agents to achieve remission are not summarised here as the study cohort investigated in this thesis is from the pre-biologic era.

Table 1.2 Previous early RA studies on remission

Study & Year	Type of study	Disease duration at study entry	No of patients	Follow-up	Remission criteria used	Frequency of remission	Predictive factors for remission
Prevoo et al, 1996 (279)	Observational	< 1 year	162	2 years	Modified ARA criteria (4 out of 5)	20%	SJC
Mottonen et al, 1996 (238)	Longitudinal	< 2 years	142	6 years	ACR criteria	32%	N/A
Eberhardt et al, 1998 (118)	Observational	< 2 years	183	5 years	1. Modified ARA criteria (4 out of 5) 2. clinical (no arthritis)	1. 20% 2. 36%	Negative RF, absence of shared epitope
Sokka et al, 1999 (280)	Two case cohorts (observational and case-control) subsequently entered into a prospective study	N/A	135	15 years	ARA criteria	24%	N/A
Mottonen et al, 1999 (239)	Multicenter, randomised controlled trial	< 2 years	Total = 195 (97 pts received combination therapy and 98 received monotherapy)	2 years	Modified ACR criteria (5 out of 5 excluding fatigue)	37% in the combination therapy & 18% in the monotherapy group	N/A
Young et al, 2000 (12)	Multicenter, observational	< 2 years	732	5 years	ARA criteria	13%	Male sex, baseline HAQ < 1.0
Harrison et al, 2000 (281)	Primary care-based inception cohort	< 1 year	231	3 years	ARA criteria (4 out of 6 excluding ESR and fatigue)	18%	Male sex, younger age (16-25 yrs) at disease onset
Svensson et al, 2000 (80)	Open, controlled study within the observational study	< 1 year	90	2 years	DAS < 1.6	36%	Male sex, low DAS and HAQ at baseline
Visser et al, 2002 (282)	Observational	< 2 years	156	2 years	Natural remission (no arthritis and no DMARDS or steroids in the last 3 months)	10%	N/A
Lindqvist et al, 2002 (11)	Observational	< 2 years	183	10 years	Modified ARA criteria	18%	No predictive factors
Gossec et al, 2004 (223)	Observational	< 1 years	191	5 years	DAS < 1.6	25% (3 yrs) 20% (5 yrs) 16% (both 3 & 5 yrs)	Baseline DAS, RAI, HAQ, CRP, Sharp score and negative RF

Study & Year	Type of study	Disease duration at study entry	No of patients	Follow-up	Remission criteria used	Frequency of remission	Predictive factors for remission
Tengstrand et al, 2004 (283)	Multicenter, observational	< 1 year	844	2 years	DAS 28 < 2.6	33%	N/A
Korpela et al, 2004 (252)	Multicenter, randomized	< 2 years	82 in the monotherapy & 78 in the combination therapy group	5 years	No swollen or tender joints and low ESR / CRP	22% in the monotherapy & 28% in the combination therapy group	N/A
Verstappen et al, 2005 (284)	Randomized clinical trial	< 1 year	562	5 years	EMS ≤ 15 mins, VAS pain ≤ 10, Thompson joint score ≤ 10 and ESR ≤ 30 for at least 6 months	36%	Baseline low pain score, negative RF, lower joint score and good response to treatment
Makinen et al, 2005 (119)	Inception cohort	Median of 5 months	127	5 years	1. ACR criteria (5 out of 5 excluding fatigue) 2. clinical remission (no tender and no swollen joints and normal ESR) 3. radiographic remission (no worsening of erosions and/or no new erosions from baseline to 5 years)	1. 17% 2. 37% 3. 55%	N/A
Svensson et al, 2005 (240)	Multicenter, open randomized trial	< 1 year	Group 1. Pred + DMARD = 119 pts Group 2. DMARD alone = 131 pts	2 years	DAS 28 < 2.6	Group 1 = 55% Group 2 = 33%	N/A
Forslind et al, 2007 (285)	Multicenter, observational	< 1 year	698	5 years	DAS 28 < 2.6	38% (2 yrs) 38% (5 yrs) 26% (both 2 and 5 yrs)	Male sex, short disease duration, low baseline DAS 28, low baseline HAQ and negative RF

Study & Year	Type of study	Disease duration at study entry	No of patients	Follow-up	Remission criteria used	Frequency of remission	Predictive factors for remission
Makinen et al, 2007 (286)	Multicenter, randomised controlled trial	< 2 years	Total = 195 (97 pts received combination therapy and 98 received monotherapy)	2 years	1. Modified ACR criteria (5 out of 5 excluding fatigue) 2. DAS 28 < 2.6	1. Sustained ACR remission at 6, 12 & 24 months = 14% (combi); 3% (mono) 2. Sustained DAS 28 remission at 6, 12 & 24 months = 51% (combi); 16% (mono)	N/A
Vazquez et al, 2007 (287)	Open-label study using step-up treatment strategy	< 2 years	115	2 years	DAS 28 < 2.6	32%	Male sex, high Hb levels, low baseline DAS, ACR 50 response and good EULAR response

As shown in table 1.2, several RA studies have already reported on frequency and prognostic factors for remission. However, there is still lack of information on long-term radiological and functional outcome in early RA patients in sustained clinical remission (period remission) rather than remission at one time point (point remission).

Moreover, the inter-relationship between clinical, radiological and functional disease progression in early RA patients in sustained remission, treated with conventional DMARDs, has not been studied in long-term observational studies.

Previous studies that have reported on radiological progression despite clinical improvement or inactivity are summarised below in table 1.3.

Table 1.3 Studies on radiological deterioration despite clinical improvement or remission in RA

Study & Year	Type of study	No of patients	Duration of study	Treatment	Clinical assessment/ remission	Criteria used for radiological progression	Number of readers & scoring sequence	Results	Prognostic factors
Scott et al, 1984 (257)	I. Short term study: Prospective study of active RA (mean duration = 6 years)	64	1 year	Penicillamine, IM Gold, auranofin, clobuzarit	Grip strength, RAI, pain, ESR, CRP, Hb, RF titre	Change in mean Larsen score	2 readers. Paired films (hands and wrists only)	Worsening of Larsen scores though ESR improved	N/A
	II. long term study: Consecutive patients with active RA (mean duration = 5.2 years)	112	10 years	Gold, penicillamine, chloroquine, azathioprine, chlorambucil, cyclo, and steroids	ESR, RF titre, Steinbrocker functional capacity	Modified Steinbrocker grading	2 readers. Scoring order not clear (hands and wrists only)	More x-ray damage though ESR, RF titre and functional capacity improved	N/A
Sany et al. 1990 (256)	Prospective, controlled study of patients with established RA (mean duration =12.9 years)	41	Mean follow-up = 31.2 months	IM MTX	Ritchie's index, Lee's index, SJC, ESR. Preliminary ARA remission criteria	Increase in the Larsen score of > 5 between two time points	2 readers. Random order (hands & feet)	84% showed x-ray progression despite clinical improvement	None
Mulherin et al, 1996 (254)	Prospective study of patients with active RA (mean duration = 2.4 years)	40	Mean follow-up = 6.1 years	DMARDs, steroids	Pain, EMS, grip strength, RAI, FBC, ESR	Actual change in Larsen score and standardized percentage change	1 reader. Scoring sequence not known (hands & feet)	Mean Larsen score worsened despite clinical improvement	N/A
Kirwan et al, 1997 (251)	Prospective, multicenter study of early RA pts (< 2 years) with active disease	93	2 years	Steroids ± DMARDS vs. placebo ± DMARDs	Thompson method (joint swelling and tenderness)	Strength of correlation between Larsen score and clinical synovitis	2 readers. Random order (hands and wrists only)	Weak correlation between synovitis and erosion score. X-ray progression in joints with no synovitis	N/A

Study & Year	Type of study	No of patients	Duration of study	Treatment	Clinical assessment/ remission	Criteria used for radiological progression	Number of readers & scoring sequence	Results	Prognostic factors
Molenaar et al, 2004 (243)	Prospective study of RA patients in remission (median disease duration = 7 years)	187	2 years	DMARDs but no steroids	Modified ACR remission criteria (4 out of 5 excluding fatigue) DAS < 1.6 Persistent remission was defined as remission at 0, 1 and 2 years	Increase in SvdH score of ≥ 5 (SDD) after 2 years (hands and feet)	2 readers. Random order	ACR remission: 7% showed x-ray progression DAS remission: 6% showed x-ray progression. 15% developed new erosions.	None
Cohen et al, 2007 (288)	Prospective study of early RA pts (< 1 year)	134	5 years	DMARDs ± steroids	DAS Persistent remission was defined as remission at 3 and 5 years	Increase in SvdH score of > 4 (SDD) between baseline and 5 years	2 readers. Chronological order	16.7% of pts in persistent remission showed significant x-ray progression and 20% developed new erosions	N/A
Brown et al, 2008 (289)	Prospective study of RA patients (median disease duration=7 yrs) in clinical remission.	102	1 year	DMARDs and steroids. 2 pts received biologics before the study.	1. Clinical remission (no joint pain, swelling and tenderness) 2. Modified ACR (5 out of 6 criteria at 0 & 2 months) 3. DAS28 < 2.6	Increase in Genant modified Sharp score of > (SDC) between baseline and 12 months. Ultrasound (US) with Power Doppler (PD) and MRI of dominant hand and wrist at baseline and 12 months.	1 reader. Paired reading.	In total, 19% showed radiographic damage > SDC at 12 months. 16% in clinical remission, 11% in ACR remission and 12% in DAS 28 remission groups showed x-ray progression above SDC	Baseline predictive factors for subsequent x-ray progression were positive PD signal (OR 12.2) and SH (OR 2.3) on US and synovitis (OR 2.9) on MRI

Table 1.3 shows that few studies have already reported radiographic progression in spite of clinical improvement or disease inactivity in RA. Nonetheless, prognostic factors for radiographic progression despite persistent clinical remission in early RA have not been reported before.

Also, long-term outcomes in a subset of early RA patients who show relentless structural damage progression irrespective of their clinical disease activity have not been studied so far.

Furthermore, influence of scoring methodology in measuring longitudinal radiographic progression in early RA patients, treated with traditional DMARDs, has not been analysed in detail previously.

Analysis of different x-ray scoring methods and reading sequence of films in this thesis may help to determine if there is any significant difference between these methods in relation to their sensitivity to change and discriminative power in detecting clinically meaningful radiographic progression in early RA and to evaluate their role as an important outcome measure.

The Early Rheumatoid Arthritis Study (ERAS) is a multicenter, inception cohort of early RA, which has recruited more than 1400 patients since 1986 with a maximum follow-up of 20 years. Standard clinical and functional assessments were recorded at baseline and then at regular intervals and serial x-rays of hands and feet were available for a majority of patients. This cohort is ideal to study the nature of disease progression in early RA and to analyse outcomes and prognostic factors.

1.8) Aims and Objectives of this thesis

The main aim of this thesis is to examine the relationship between clinical and radiological disease activity in the ERAS cohort over 5 years from disease presentation, particularly in patients with clinically inactive disease, and to analyse their long-term outcomes with a view to answer some unresolved questions such as,

1. What proportion of early RA patients continue to develop radiological damage despite being in clinical remission and what are their long-term outcomes?

2. At what stage of the disease (early vs. late) does the coupling between clinical and radiological progression of the disease become unlinked?

3. What is the influence of scoring methodology (Larsen vs. SvdH vs. SENS and random vs. chronological order) in studying the correlation between clinical disease activity and radiological progression in early RA

4. Can RA patients, who continue to develop x-ray damage despite clinical remission, be predicted early on using baseline disease variables?

In addition, this thesis will help to compare and to determine if there is any difference in radiological progression among patients with active or inactive disease based on clinical measures. Analysing disease progression and radiological damage in this inception cohort, with relevance to various disease related variables might help to identify prognostic factors that are associated with poor outcomes.

Primary objectives:

i. To study frequency of point and sustained remission based on DAS (DAS remission), in the ERAS cohort and to analyse prognostic factors for sustained DAS remission

ii. To study longitudinal radiographic progression in early RA, particularly during clinical disease inactivity

iii. To evaluate the influence of scoring methodology in measuring radiographic progression in RA

- Larsen vs. SvdH vs. SENS
- random vs. chronological order

iv. To analyse prognostic factors for progressive structural damage on x-rays despite DAS remission

v. To study clinical, radiological and functional progression over 5 years in early RA and to assess outcomes

CHAPTER 2

PATIENTS, MATERIALS AND METHODS

2: PATIENTS, MATERIALS AND METHODS

2.1 Early Rheumatoid Arthritis Study (ERAS)

2.1.1 Background

The Early Rheumatoid Arthritis Study (ERAS) is a multicenter, inception cohort of early RA, which was formed in 1986 as collaboration between nine rheumatologists, who were working in different regions of England. The primary aim of the ERAS was to recruit and to follow-up at least 1000 early RA patients receiving conventional therapies including traditional DMARDs, in ordinary clinical settings for a minimum of 10 years. Ethical approval for the ERAS was obtained from the West Hertfordshire ethics committee.

The main purpose of this observational study was to evaluate long-term outcomes, and to develop prognostic factors for clinical, radiological and functional outcomes. This study covers quite different regions of England, including rural, urban and inner city communities, and so it has been possible to investigate differences in socioeconomic effects and resource use on the outcome of RA.

2.1.2 Patient recruitment

All consecutive patients with RA of less than 2 years duration, who were seen in the rheumatology outpatient clinics in any of those participating centres, were recruited into the ERAS between 1988 and 1998.

Inclusion criteria: Patients fulfilling the 1987 revised ARA criteria for RA with disease duration of less than 2 years and no prior DMARDs at the time of study entry were included in this study. Patients who were thought to have RA by their treating physicians but only had 2 or 3 features instead of ≥ 4 out of 7 ARA classification

criteria for RA, were also included in this study and followed up to see if they fulfil the ARA criteria subsequently.

Exclusion criteria: Patients, whose initial diagnosis was RA, but later developed connective tissue diseases such as lupus or seronegative spondyloarthropathies were excluded from the study.

Recruitment stopped at 1500 in 1999 and a large proportion of patients have completed their 5 and 10 year follow-ups.

2.1.3 Data collection and storage

Each centre has recorded clinical, laboratory and functional features of all the ERAS patients at baseline, 3, 6 and 12 months in the first year and then once yearly. X-rays of hands and feet were done at baseline and then at 1, 2, 3, 5, 7 and 10 years and were digitized onto CD-ROM. X-rays of cervical spine were also done at regular intervals. Standard forms have been used across all the ERAS centres for data collection and entry both at the first visit and at follow-up visits and they are included in the appendices.

The recorded details of all the study patients were stored in a database, which was regularly checked and managed by the ERAS co-ordinator. One of the participating centres (St Albans) has co-ordinated the study, where all the data collation, entry and preliminary analyses were performed.

a) Clinical

Trained metrologists, under the supervision of rheumatologists, have recorded the standard clinical assessments for each patient at the study entry and then at regular intervals. These assessments are in accordance with the core data set recommended by

the national and international associations for rheumatology and they included, onset and pattern of joint symptoms, body mass index (BMI), duration of morning stiffness, pain score (VAS), tender and swollen joint counts, Ritchie articular index (RAI), ARA criteria, grip strength, extra-articular manifestations and co-morbid conditions. Clinical disease activity including remission in the ERAS cohort was assessed using DAS, and is calculated as follows (141;142):

$$DAS = 0.54 \times \sqrt{(Ritchie)} + 0.065 \times SJC44 + 0.33 \times \log_{nat}(ESR) + 0.224$$

In the study population, EULAR criteria were used to categorize patients into different clinical subgroups, based on their DAS scores (81):

Table 2.1 Clinical disease activity based on EULAR criteria

Disease activity score (DAS) values	**Disease activity**
DAS < 1.60	Remission
DAS ≥1.60 and ≤ 2.40	Low or mild disease activity
DAS >2.40 and ≤ 3.70	Moderate disease activity
DAS > 3.70	High or severe disease activity

b) Laboratory

Each patient had standard blood tests done at baseline and then at regular intervals and the results were entered into the ERAS database. These tests included, FBC, ESR, IgM rheumatoid factor (RF) and anti nuclear antibody (ANA). Stored blood samples were used to extract DNA. HLA-DRβ1 type was assigned using sequence

oligonucleotide typing and number of copies of the RA related shared epitope was determined, in collaboration with the Arthritis research campaign epidemiology research unit (ARC ERU) at Manchester.

c) Radiological

i) Scoring methodology for ERAS

X-rays of hands and feet from baseline up to a maximum of 10 year follow-ups for all the ERAS patients were scored, using Larsen's method in random order, by an experienced rheumatologist, Dr Csilla Solymossy (CS), who was unaware of the patients' clinical details including treatment (68;290) . Larsen scoring method that was used in the ERAS patients has already been described in the previous chapter (172). Intra-observer variability for observer CS was checked regularly using intraclass correlation coefficient (ICC) and the values were > 0 .85 (68;290).

X-rays of cervical spine were done in flexion and extension views and the treating clinicians according to the degree of damage and deformity graded the changes seen on x-rays.

ii) Scoring methodology and training for this thesis

For the purpose of this thesis, apart from the Larsen scoring method, SvdH and SENS methods were also used to score hands and feet x-rays of certain clinical subgroups of ERAS patients and these methods have already been described in detail in chapter 1 (169;170). Observer KJ (myself), have used Larsen, SvdH and SENS methods to score hands and feet x-rays of selected groups of ERAS patients from baseline up to a maximum follow-up of 5 years in chronological order. Observer KJ was blinded to patients' clinical information including treatment details and previous x-ray scores, by

masking patients' details and by giving different ids to x-rays by the ERAS coordinator. Once the films were all scored, x-ray scores from each scoring method were entered into the ERAS database and the clinical and radiographic data were all merged together by the ERAS coordinator for further analyses. Radiographic data collection, entry and storage have all been regularly checked and validated by the ERAS coordinator and research students from the University of Hertfordshire (UH).

Observer KJ had received adequate training and supervision by experienced readers in the relevant scoring methods, before start reading the x-ray films for this project. First, observer KJ learnt the Larsen scoring method by attending hands-on training sessions with Dr CS, who scored hands and feet x-rays of all ERAS patients using the Larsen method. After this, observer KJ scored a random sample of hands and feet x-rays from the ERAS cohort twice with an interval of 4 weeks between the two reading sessions in order to check inter and intra observer variability, after being blinded to patient's clinical details and previous Larsen scores. Inter and intra observer variability was calculated using ICC and they were 0.96 and 0.95 respectively.

Observer KJ had then learnt the SvdH and SENS scoring methods by attending a training workshop at the Maastricht University hospital, Maastricht, Netherlands organized by Dr Desiree van der Heijde, who introduced the SvdH and SENS methods after some modification of Sharp's original scoring technique. Dr Annelies Boonen (AB), a very experienced reader in Dr van der Heijde's unit, has conducted this session and this provided hands-on experience for observer KJ with the trainer and with other trainees. Observer KJ's scoring technique and accuracy was supervised

by the trainer and was given some practical tips and positive feedback at the end of the session.

Few weeks after this training session, observer KJ was asked to score 20 sets of hands and feet x-rays (SvdH method) from Maastricht rheumatology unit's research database twice with an interval of 4 to 6 weeks between the two scoring sessions in order to check the inter and intra observer variability. Inter and intra observer variability for SvdH method was calculated using ICC and are as follows: erosion 0.88 (inter) 0.95 (intra); narrowing 0.88 (inter) 0.97 (intra) and total score 0.81(inter) 0.97 (intra). After these scoring sessions, observer KJ has attended a further session with the trainer, Dr AB, to go through some of the x-rays and to clarify some minor discrepancies in the SvdH scores between the two readers.

d) Functional

Functional ability of the ERAS patients was assessed at the time of study entry and then at regular intervals using Steinbrocker's FG and HAQ, as described in the previous chapter. Using Steinbrocker's FG, functional ability was graded from I to IV: Grade I = ability to perform normal activity; Grade II = moderate restriction of normal activities; Grade III = marked restriction of day to day activities; Grade IV = incapacitated, bed-ridden or confined to a wheelchair.

Modified HAQ was used in the ERAS to assess patients' functional capacity in 8 different physical domains with scores ranging between 0 and 3, as described earlier. Grip strength was assessed using standard handgrip measure with scores ranging between 20 and 300, the higher scores indicating better grips.

e) Other outcomes

Outcome measures other than clinical, radiological and functional assessments were also recorded at baseline, 3 and 5 years. This included job status, social service benefits and allowances, use of standard aids and appliances such as splints, walking aids and major adaptations (wheel chair, stair lifts, hoists). All types of orthopaedic surgeries were also recorded and for study analysis they were grouped as minor (nodule removal, arthroscopy), intermediate (synovectomy, tendon repair, excision arthroplasty, arthrodesis) and major (joint replacements, cervical spine fusion). Other details including joint range of movement, accommodation, social class, education, co-morbid conditions and in-patient episodes were also included in the ERAS outcome assessment forms.

2.1.4 Treatment profile

All centres followed the framework of the published UK guidelines for management of RA, which include the provision of therapy services, appropriate orthopaedic interventions, and sequential use of DMARDs together with symptom relieving measures, with judicious use of steroids when required. DMARD combination therapy was used in severe and non-responsive RA and biological agents were not used. The DMARDs used were chosen according to the physician's preference, although dosage schedules employing graduated regimens were previously agreed according to standard practice for each drug.

Reasons for discontinuation of DMARDs were based on clinical judgements and coded according to loss or lack of effect, to adverse events, both reasons, remission, or miscellaneous (e.g. pregnancy).

2.1.5 Statistics

Statistical Package for Social Sciences (SPSS) was used to analyse the ERAS database. A number of collaborations including the Clinical Operational Research Unit (CORU) at University College London, ERU at the School of Hygiene, London, Health Research Development and Support Unit (HRDSU) at the University of Hertfordshire (UH), ScHARR, Sheffield, and Department of Mathematics, Keele University, Keele, Staffordshire have provided statistical support for the ERAS projects.

For this thesis, statistical support was mainly provided by the HRDSU, UH and Keele University, Keele. Dr Annelies Boonen (AB) from the University Hospital, Maastricht, Netherlands has kindly provided the necessary advice and appropriate guidance on specific statistical tools to be used for the radiological data analyses and reporting for this project.

Summary statistics have been used to analyse the study data and to report results. Continuous variables were expressed as mean with standard deviation (SD) or median with interquartile ranges (IQR) and categorical variables were shown as counts with percentages.

Chi square (χ^2) for categorical variables and Mann Whitney U (MWU) or Kruskal-Wallis H (KWH) for non-parametric and ANOVA for parametric data were used to compare the study groups. Wilcoxon signed rank test or paired samples t-test were used to assess the significance of difference in outcomes between different time points within the individual study groups. Pearson or Spearman correlation tests have been

used to assess the strength of association between clinical or laboratory measures and x-ray scores in the study groups.

Radiographic progression at group level was analysed using summary statistics and absolute scores, whereas at individual level smallest detectable difference (SDD) was used to detect significant x-ray progression i.e. progression above measurement error (185).

Reliability analysis for inter and intra observer agreement for different x-ray scoring methods was performed using intraclass correlation coefficients (ICC) and Bland and Altman scatter plot graphs. Intraclass correlations, termed intra-cluster correlations for readings and inter-cluster correlations for readers, were estimated using one-way random effects ANOVA.

Univariate analysis using odds ratios (OR) with 95% confidence interval (CI) and multiple logistic regression, using stepwise procedure were used to examine prognostic factors for radiological progression. Variables used for the multivariate model were chosen from the univariate analysis and a p-value of ≤ 0.05 (two sided) was considered statistically significant.

CHAPTER 3

REMISSION IN EARLY RHEUMATOID ARTHRITIS

3. REMISSION IN EARLY RHEUMATOID ARTHRITIS

3.1 Background

Patients with active rheumatoid arthritis (RA) usually progress to develop more radiological damage and poor outcomes compared to inactive disease or remission (7;8;106). Therefore, the ultimate goal of treatment in RA is to achieve remission as early as possible (291). Maintaining disease inactivity after remission induction is also important to have a favourable influence on subsequent disease progression and long-term outcomes.

Remission either occurs spontaneously or can be achieved by using specific anti-rheumatic drugs such as disease modifying anti rheumatic drugs (DMARD), steroids and/or biological agents. Some RA patients can maintain remission even after stopping the treatment and remission can be described as spontaneous, drug induced or DMARD/biologics-free, based on current or previous treatment (233).

In RA studies, ARA and EULAR criteria have been widely used to assess clinical disease activity including remission (79;118). The EULAR criteria is based on DAS or DAS28, which is calculated using swollen joint count (SJC), tender joint count (TJC) or Ritchie articular index (RAI), erythrocyte sedimentation rate (ESR) and patients global health (GH) (79;84;142). Previous RA studies have reported frequency of remission varying between 7 and 65 % depending upon the patient demographics, study design and type of remission criteria used (292). Studies that have examined duration of remission and prognostic factors have also shown inconsistent results

[270,273,274,276] and there is only limited information on the effect of sustained clinical remission on long-term outcomes in early RA.

3.2 Objectives

1. To study frequency of point and sustained remission based on DAS (DAS remission), at years 3, 4 and 5 from disease presentation in the ERAS cohort
2. To study prognostic factors for:
    i. Sustained DAS remission
    ii. Sustained DMARD-free remission
3. To assess outcomes in patients in sustained DAS remission

3.3 Patients and Methods

Patients

For the purpose of this analysis, a total of 704 patients from the ERAS who had completed at least 5yr follow-up and had DAS recorded at the 3rd, 4th and 5th year follow-up visits were selected. Patients who did not complete 5 year follow-up were excluded from the analysis (n=304, reasons as follows: attends other hospital (n=7, 2 %); moved (n=25, 8 %); unable to attend (n=3, 1 %); declined (n=18, 6 %); patient reported remission (n=9, 3 %); deceased (n=195, 64 %); discharged (n=1); not known (n=20, 7 %); not traced (n=26, 9 %). A separate analysis of these patients with less than 5 yr follow-ups has shown similar disease characteristics except that mean age of disease onset (60 vs. 54, $p < 0.001$) and baseline disease activity was slightly higher (DAS 4.5 vs. 4.2, $p < 0.01$) in this group.

Study assessments

Patients were assessed at 0, 3 and 6 months in the first year and then annually. Standard clinical measurements were recorded at baseline and then annually as described in the previous chapter. X-rays of hands and feet were performed at 0, 1, 2, 3 and 5 years and the films were scored using Larsen's method in random order by an independent observer (CS), unaware of the clinical details. Disease outcomes were recorded at 3 and 5 years using standard forms.

Definition of DAS remission

DAS remission was defined as DAS < 1.6, either at one time point (point remission) or at consecutive time points (sustained remission). For this study, sustained DAS remission was defined as DAS < 1.6 at years 3, 4 and 5 from disease presentation.

Definition of sustained DMARD-free remission

1) No current use of DMARD or steroids 2) No swollen joints and 3) Confirmation of DMARD-free remission by the patient's rheumatologist. Patients had to fulfil all three criteria and absence of swollen joints had to have been observed by a rheumatologist for at least one year after discontinuation of DMARD-therapy to ensure sustained remission.

Predictive factors for DAS remission

Predictive factors for DAS remission at year 3 (point remission) and at years 3, 4 and 5 (sustained remission) were analysed in patients who have had DAS recorded at all the above study points (n=704).

Predictive factors for sustained DMARD-free remission were also analysed in the ERAS patients who had at least two consecutive annual clinical assessments at some point during their follow up (n=895). This particular analysis was done as part of a collaboration with another similar cohort, which used this definition of remission as the optimal target in the management of RA. The ERAS cohort was used to validate the findings in the Early Arthritis Cohort (EAC) from Leiden, The Netherlands. DMARD free remission rates and strength of prognostic markers for this were compared.

Treatment

Study cohort was treated with standard DMARDs as described earlier, either as sequential monotherapy or combination therapy and/or steroids. None of the patients received biological agents as the study period was in the pre-biologic era.

Statistical analysis

Summary statistics have been used to demonstrate the differences in clinical and laboratory features with disease outcomes. Continuous variables were expressed as either mean ± standard deviation (SD) or median with interquartile ranges (IQR) and categorical variables were shown as counts with percentages. Chi square (χ^2) for categorical variables and Mann Whitney U (MWU) for continuous data were used to compare the study groups. Wilcoxon signed rank test was used to test the difference in outcomes between 3 and 5 years within the remission and non-remission groups.

Univariate analysis using odds ratios (OR) with 95 % confidence intervals (CI) was used to assess predictive value of baseline variables for DAS clinical remission and

multivariate analysis was performed using the stepwise procedure. For continuous variables, median values were used as cut off points to dichotomise them into categorical variables except Larsen scores, where 75^{th} percentile was used because of a large number of patients with non-erosive disease at baseline. Baseline variables with significant ORs in the univariate analysis were entered in the multivariate model and a p-value of ≤ 0.05 (two sided) was considered statistically significant.

Predictive factors for sustained DMARD-free remission were analysed in conjunction with the Departments of Rheumatology and Medical Statistics, Leiden University Medical Centre, Leiden, The Netherlands. To take into account the difference in follow-up times among patients, analyses were performed by Cox regression analysis, after verification that the proportional hazards assumption was satisfied. In the Cox regression model the dependent variable is the "time-to-event", which consisted of the time to remission for the remission patients, and the time to last follow-up (with a maximum of 10 years) for the non-remission patients.

In order to investigate the predictive ability of baseline characteristics in univariate analysis, each variable was included as a covariate in a separate non-conditional analysis. The results of the univariate analyses were subjected to correction for multiple testing by the Holm method. Subsequently, multivariate Cox regression analysis was performed to identify significant independent predictors for achieving remission. As possible explanatory variables, all baseline variables with a p-value below 0.10 in univariate analysis were included in the model. A two-step modelling approach was performed, which in the first step identified independent predictive variables by a backward step selection procedure that removed variables with a

p-value greater than 0.10. To verify that the identified predictive variables were indeed independent predictors for the entire cohort, they were then entered as covariates into a second multivariate Cox regression analysis (enter model).

3.4 Results

Baseline demographics of the study cohort (n=704) are shown in table 3.1, which is very much representative of early RA.

Table 3.1 Baseline disease characteristics

Baseline variable	**Whole study cohort (n=704)**	**Remission [#] (n=78)**	**Non-remission (n=626)**	**p-value**
Women∗	66% (462)	45% (35)	68% (427)	< **0.001**
Age of disease onset (years)	54 (± 13.7)	53 (±14.7)	54 (±13.6)	0.77
Duration of symptoms (months)	8.5 (± 6.3)	7 (±5.8)	8.7 (±6.4)	0.16
RF positive∗	66 % (461)	59% (46)	66% (415)	0.20
Shared epitope∗	57% (402)	54% (42)	57% (360)	0.63
Erosions∗	26% (182)	23% (18)	27% (164)	0.58
RAI	13.1 (± 11)	7.5 (±6.7)	13.8 (±11.2)	0.98
SJC	16.9 (± 13.3)	12 (±11.1)	17.5 (±13.5)	< **0.001**
ESR	42.5 (± 28.5)	37.5 (±24.9)	43.2 (±29)	0.25
DAS	4.2 (± 1.6)	3.4 (±1.3)	4.3 (±1.6)	0.31
HAQ	1.0 (± 0.717)	0.8 (±0.7)	1.1 (±0.7)	< **0.001**
Larsen [Median (IQR)]	0 (0-4)	0 (0-3)	0 (0-4)	-
DMARD use at 1yr ∗	76% (537)	65% (51)	78% (486)	**0.005**

Values are expressed as mean (± SD) unless otherwise indicated

∗ % (count)

[#] Persistent remission (DAS < 1.6) at 3, 4 and 5 yr follow-ups

RF = Rheumatoid factor

RAI = Ritchie articular index, SJC = Swollen joint count

ESR = Erythrocyte sedimentation rate, DAS = Disease activity score

HAQ = Health assessment questionnaire

DMARD = Disease modifying anti-rheumatic drug

DMARDs either as mono or combination therapy were used in 76% of patients at year 1 (mono=60%, combi=16%) and the respective figures at 3 and 5 years were 83 % (mono=51%, combi=32%) and 85% (mono=46%, combi=39%). Mean DMARD use at 1 year 0.96 (range 0-5), at 3 years 1.25 (range 0-6) and at 5 years 1.52 (range 0-6). Median time to the start of first DMARD after study entry was 2 months (1-5.5). Sulphasalazine (SSZ) was the most commonly used first line DMARD (80%) followed by intramuscular (i.m) gold injection (7%) and D-penicillamine (6%). Methotrexate (MTX) was the most commonly used second line DMARD (51%) followed by gold injection (18%). Oral steroids were used in 15% of patients by 5 years and most of them (81%) have had ≤ 7.5 mg/day of prednisolone.

DAS remission

179 patients (25%) achieved DAS remission at 3 years and the corresponding figures at 4 and 5 years were 183 (26%) and 158 (22%) respectively. Amongst patients in remission at year3, disease inactivity persisted for 12 months in 63% and for 24 months in 44%. Frequency of sustained DAS remission was 11% (n=78) at all three study points (year3, 4 and 5) and 13% (n=95) at time points 3 and 5 years only (17 pts had a disease flare at year4 but were in remission at yr3 and 5). DMARDs were used in 70% of patients who were in sustained DAS remission at year5 (mono=60%; combi=10%).

The study cohort (n=704) was divided into two subgroups, to analyse outcomes and prognostic factors in relation to clinical disease activity. Patients with a DAS of < 1.6 at all three study points (yr 3, 4 and 5) were grouped as remission (n=78) and the rest as non-remission (n=626).

Use of DMARDs in the remission group was 65% (mono=63%, combi=2%) at yr1 and 70% (mono=60%, combi=10%) at both 3 and 5 year visits. DMARDs either as mono or combination therapy were used more frequently in the non-remission group compared to remission group at all time points (yr1 = 78% vs 65%, p=.006; yr3 = 85% vs 70%, p=.002; yr5 = 87% vs 70%, p=.000). Mean DMARD use in remission group was 0.83 (range 0-3) at the end of 3 and 5 years and in the non-remission group it was 1.3 (range 0-6) at yr3 and 1.6 (range 0-6) at yr5.

In both groups, sulphasalazine (SSZ) was the most common first line DMARD followed by i.m gold and D-penicillamine. SSZ+MTX were the most frequently used combination therapy in the non-remission group and no combination therapy was used in the persistent remission group. Median time to the start of first DMARD from disease onset was 3 months (1-7) in the remission group and 2 months (1-5) in the non-remission group. Although more patients were treated with oral steroids in the non-remission group (16% vs. 9%, p=0.5), the difference was not statistically significant.

Predictive factors for DAS remission

Predictive value of baseline variables for point remission (year3) and sustained remission (year3, 4 and 5) are shown in tables 3.2 & 3.3.

Table 3.2 Predictive factors for DAS remission on univariate analysis

Baseline variable	**Remission at year 3** OR (95% CI)	**Sustained remission at year 3, 4 and 5** OR (95% CI)
Men	2.0 (1.4-2.8)	2.6 (1.6-4.2)
Duration of symptoms < 6 months at study entry	1.6 (1.1-2.2)	1.6 (1.0-2.7)
Social class I, II	2.2 (1.5-3.4)	2.4 (1.4-4.1)
Rheumatoid factor (RF) negative	1.0 (0.7-1.5)	1.4 (0.9-2.2)
Shared epitope (SE) negative	1.1 (0.7-1.7)	1.2 (0.7-2.1)
American College of Rheumatology (ACR) diagnostic criteria < 4	1.6 (1.1-2.3)	1.8 (1.1-2.9)
No erosions	1.1 (0.7-1.6)	1.2 (0.7-2.1)
Pain score < 45 (Visual analogue scale)	1.4 (1.0-1.9)	2.1 (1.3-3.6)
Early morning stiffness (EMS) < 1 hour	1.7 (1.2-2.4)	1.6 (1.0-2.6)
Grip strength >140 (range 0-300)	1.8 (1.3-2.6)	1.6 (1.0-2.7)
Ritchie articular index (RAI) < 10	2.1 (1.5-3.0)	3.0 (1.7-5.0)
Swollen joint count (SJC) < 13	1.6 (1.1-2.3)	1.9 (1.1-3.0)
Erythrocyte sedimentation rate (ESR) < 37	1.0 (0.7-1.4)	1.1 (0.7-1.8)
Disease activity score (DAS) < 4.1	2.2 (1.5-3.1)	2.7 (1.6-4.6)
Health assessment questionnaire (HAQ <1.0)	1.7 (1.2-2.5)	2.1 (1.3-3.6)
Larsen score < 4	1.2 (0.8-1.9)	1.6 (0.8-3.0)

Table 3.3 Predictive factors for sustained DAS remission on multivariate analysis

Baseline variable	**OR**	**95% CI**	**p-value**
Men	2.6	1.5 – 4.5	< 0.001
Symptom duration < 6 months	3.2	1.0 – 9.8	0.046
Ritchie articular index (RAI) < 5	3.7	1.3 – 10.9	0.016

OR = Odds ratio, CI = confidence interval

On univariate analysis, male sex, higher social class (I&II), RAI <10, DAS < 4.1 and HAQ < 1.0 at baseline have shown better predictive value for remission, whereas, ESR, RF, shared epitope, and Larsen score did not show any prognostic value in this study cohort. Although there was a significant difference in DMARD use between remission and non-remission groups, early use of DMARDs i.e. within 1 year of disease presentation did not show any predictive value for remission in this study.

Using multiple logistic regression, male sex, shorter duration of symptoms and lower RAI at baseline showed significant independent predictive value for sustained DAS remission.

Predictive factors for sustained DMARD-free remission

Predictive abilities of baseline disease variables for sustained DMARD-free remission (n=84, 9.4%) are shown in tables 3.4 and 3.5.

Table 3.4 Predictive factors for sustained DMARD-free remission on univariate analysis (Cox regression method)

Baseline variable	***Hazard Ratio #***	***95% CI***	***p-value***
Age of onset	1.00	0.98-1.01	0.58
Gender	0.78	0.50-1.22	0.28
Duration of symptoms at presentation	0.96	0.92-1.00	**0.038**
Smoking, n (%)	0.54	0.29-1.02	0.059
Family history of RA	0.87	0.53-1.44	0.59
Body mass index (BMI) mean (SD)	0.98	0.93-1.04	0.54
Acute onset of symptoms	1.71	1.10-2.67	**0.017**
Symmetrical onset	1.18	0.67-2.07	0.56
Rheumatoid factor (RF)	0.31	0.20-0.50	**<0.001**
Shared epitope	0.47	0.28-0.78	**0.003**
Ritchie articualr index (RAI)	0.91	0.88-0.95	**<0.001**
Swollen joint count (SJC)	0.97	0.95-0.99	**0.005**
Erythrocyte sedimentation rate (ESR)	0.99	0.99-1.0	0.21
Disease activity score (DAS)	0.65	0.55-0.76	**<0.001**
Health assessment questionnaire (HAQ)	0.51	0.36-0.71	**<0.001**
Larsen score	0.94	0.88-1.00	**0.050**

Hazard ratio is the effect measure generated by Cox regression analysis and it can be interpreted similar to an odds ratio i.e. higher hazard ratio signifies a higher chance of remission.

Table 3.5 Predictive factors for sustained DMARD-free remission on multivariate analysis (Cox regression)

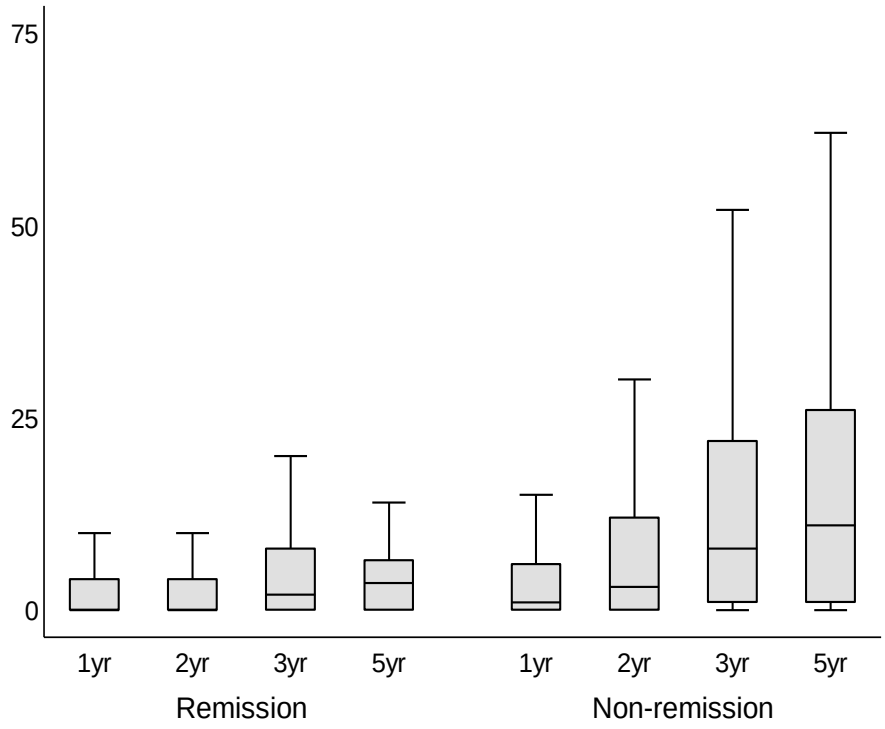
Baseline variable	*Hazard Ratio*	*95% CI*	*p-value*
Duration of symptoms at presentation	0.94	0.89-0.99	0.029
Acute onset of symptoms	2.03	1.15-3.59	0.015
Rheumatoid factor (RF)	0.28	0.16-0.49	<0.001
Shared epitope	0.44	0.26-0.73	0.002
Ritchie articular index (RAI)	0.92	0.88-0.97	0.001
Health assessment questionnaire (HAQ)	0.66	0.44-0.99	0.044

As shown in the above tables, baseline variables such as nature of disease onset, duration of symptoms, RF, shared epitope, clinical disease activity, HAQ and x-ray scores (Larsen) showed prognostic value for sustained DMARD-free remission.

Disease progression and outcomes at 5 yrs

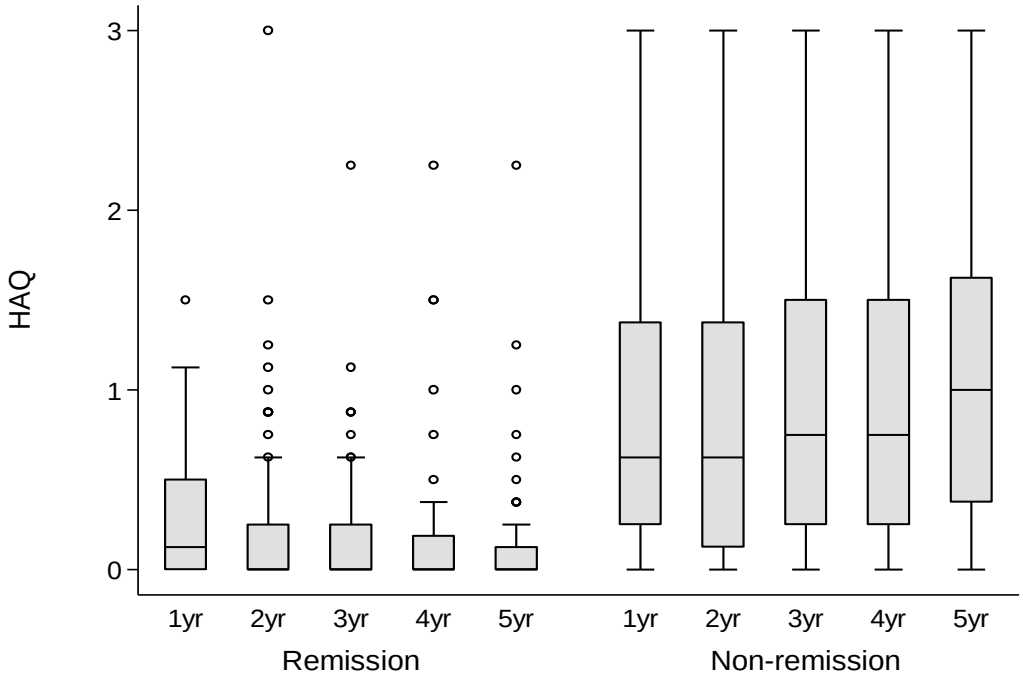
Radiological and functional disease progression during the study period and outcomes at 3 and 5 years were analysed in the DAS remission and non-remission groups and this is shown in figures 3.1 & 3.2 and table 3.6

Figure 3.1 Radiological (Larsen) progression between 1 and 5 years



In Fig 3.1, Larsen scores are shown as median values (horizontal line) within quartile ranges (boxes) for remission and non-remission groups between 1 and 5 years (yr). Whiskers (vertical lines) extend to values within 1.5 box lengths

Figure 3.2 Functional (HAQ) progression between 1 and 5 years



In fig 3.2, Health assessment questionnaire (HAQ) scores are shown as median values (horizontal line) within quartile ranges (boxes) for remission and non-remission groups between 1 and 5 years.

Whiskers (vertical lines) extend to values within 1.5 box lengths

Outliers are shown as circles and clinical details of these patients were identified from the database. Three of the outliers had relevant co-morbidities that may explain HAQ scores higher than expected for inactive RA: Patient1 with a HAQ of 3 at yr2 and 2.25 at yr3, 4 and 5 had myelopathy secondary to degenerative cervical spine disease, Patient2 with a HAQ of 0.88, 1.50 and 0.63 at yr3, 4 and 5 had polymyalgia rheumatica, and Patient3 with a HAQ of 1.13, 1.50 and 1.25 at yr3, 4 and 5 had osteoarthritis of knees.

Table 3.6 Outcomes at 3 and 5 years in the DAS remission and non-remission groups at same time points

Variables	At 3 years			At 5 years		
	Remission (n=78)	**Non-remission (n=626)**	**p-value**	**Remission (n=78)**	**Non-remission (n=626)**	**p-value**
Erosions	36 (46%)	434 (69%)	**0.000**	42 (54%)	486 (78%)	**0.000**
Extra-articular disease	16 (20%)	164 (26%)	0.33	16 (20%)	222 (35%)	0.06
Functional Grade III & IV	1 (1%)	56 (9%)	**0.000**	1 (1%)	95 (15%)	**0.000**
Job status						
Continue to work	42 (54%)	238 (39%)	**0.01**	36 (48%)	198 (33%)	**0.02**
Stopped working	3 (4%)	62 (10%)	**0.01**	8 (11%)	101 (17%)	**0.02**
Due to RA	1 (33%)	49 (79%)	0.07	1 (13%)	74 (73%)	**0.001**
Unrelated to RA	2 (67%)	8 (13%)	0.07	6 (75%)	19 (19%)	**0.001**
Not known	-	5 (8%)	-	1 (12%)	8 (8%)	**0.001**
Disability allowance	3 (4%)	78 (14%)	0.07	6 (7%)	121 (22%)	**0.03**
Appliances						
Minor	37 (47%)	469 (77%)	**0.000**	42 (54%)	456 (78%)	**0.000**
Major	1 (1%)	31 (5%)	**0.000**	1 (1%)	63 (11%)	**0.000**
Orthopaedic surgery						
Minor & Intermediate	3 (4%)	29 (5%)	**0.007**	4 (5%)	46 (8%)	**0.002**
Major	0	25 (4%)	**0.007**	0	48 (8%)	**0.002**

Total number of patients with erosive disease increased between 3 and 5 years in both groups. However, radiographic progression at group level was worse in the non-remission group ($p<0.001$), and only mild & not statistically significant in the remission group ($p=0.08$).

Mean HAQ score in the remission group decreased from 0.17 to 0.13 (-0.04, $p<0.001$), whereas in the non-remission group, it increased from 0.92 to 1.1 (+0.18, $p<0.001$) during the study period. More patients in the non-remission group had advanced from Steinbrocker's FG I & II (favourable) to FG III & IV (worse) between 3 and 5 years (+6%, $p<0.001$), whereas in the remission group there was no change. The total number of patients receiving disability allowances increased significantly in the former group (+8%, $p<0.001$ vs. +3%, $p=0.10$).

Although more patients stopped working between 3 and 5 year follow-ups in both groups, RA was the most frequent cause of work disability in the non-remission group, but not in the remission group. The number of patients who required major adaptations at home such as stair lifts and hoists and the rate of major orthopaedic surgeries such as joint replacements was significantly greater between 3 and 5 years in the non-remission group (+6%; $p<0.001$ and +4%; $p<0.001$ respectively). More patients in the non-remission group died after 5 years of disease presentation compared to remission group but the difference was not statistically significant (23% vs 15%, $p=0.14$)

3.5 Discussion

Frequency of sustained DAS remission at 3, 4 and 5 years follow-up in this study was 11% and much lower than the remission rate at individual time points (year3-25%; year4-26%; year5-22%). Remission occurred slightly less frequently in 9.4% of ERAS patients using the different criteria of sustained DMARD-free remission. The baseline variables age, acute onset of symptoms, absence of RF and SE showed predictive value for DMARD-free remission but not for remission based on DAS. Male sex showed strong independent predictive value for DAS remission but not for sustained DMARD-free remission. Duration of symptoms, RAI and HAQ at disease presentation all showed prognostic value for subsequent remission irrespective of the remission criteria used.

Comparisons with other studies are complicated by the different remission criteria used (ARA, DAS, DAS 28, clinical, sustained, DMARD-free). Most other studies have also shown that sustained disease inactivity in RA is less frequent than remission at a single time point, but reports on prognostic markers and their relative predictive value vary considerably (116;118;223;238;253;279). This latter point may be due, at least partially, to the many and different definitions of clinical remission.

The modified ARA criteria were reported in a previous ERAS report in 732 patients. The remission rate at 5 year was 13%, which is less than reported in this thesis using DAS (22%), but prognostic markers were similar, male sex and baseline HAQ of < 1 were predictive of remission (12). Wolfe et al reported ARA remission rates of 18% and median remission duration of 12 months in a large prospective cohort of 458 RA patients with mean disease duration of 7.7 years. They reported male sex, disease

onset > 60 yrs and absence of erosions at baseline as predictive factors for subsequent remission (116).

In a prospective study of 142 early RA patients (< 2 yrs) with a mean follow-up of 6.2 years, Mottonen et al reported ARA remission in 20%, 27% and 32% at year 1 , 2 and last visit, but only 19% were in remission both at year2 and at the last visit (238). These higher remission rates may be partly due to the more intensive treatment strategies employed in this study. These results are consistent with the findings reported in this thesis that remission at individual time points was greater than sustained remission rates.

Eberhardt et al prospectively studied disease course for 5 years in 183 early RA patients and in this study 37 patients (20%) achieved modified ARA remission. Mean duration of remission was 20.5 (range 6-48) months and the presence of RF and SE reduced the chances of remission in their cohort (118). It is interesting that in this thesis, although RF and SE showed independent predictive value for sustained DMARD-free remission, they were not of any prognostic significance for sustained DAS remission. This again confirms previous findings that other than disease characteristics and treatment effect, remission criteria may also influence the prognostic value of standard disease variables in RA.

In a study by Molenaar et al, 187 patients with established RA who were in modified ARA remission were followed-up for 2 years. At the study start, only 59% and 81% of the patients fulfilled preliminary ARA and DAS remission criteria respectively and only 57% fulfilled both sets of criteria. At the end of 2 years, modified ARA remission persisted in 52% of patients and DAS remission persisted in 42% (243).

Two large prospective early RA studies analysed influence of sex on disease course including remission, based on DAS28, over 2 and 5 years (283;285). Similar to this thesis, those studies also showed that the frequency and duration of remission was higher in men and in the later study, male sex, short disease duration, RF negativity, low DAS28 and HAQ at baseline were predictive of remission (285)

In a French multi-centre, prospective study of early RA patients (n=191) with a mean disease duration of 3.3 months, frequency of DAS remission at year3, year5 and at both study points were 25%, 20% and 16% respectively. 80% of patients in remission at 3 years were also in remission at 5 years. In that study, baseline DAS, RAI and Sharp score showed independent predictive value for both point and sustained DAS remission (223), similar to this thesis findings.

Several studies have compared different remission criteria. Prevoo et al studied the relationship of ARA remission criteria with DAS in their observational study of early RA (< 1 yr) and found that 37% fulfilled modified ARA remission criteria at least once and 21% on two consecutive visits. DAS of < 1.6 correlated with ARA criteria for remission in their study and SJC was the most influential factor in deciding remission (279).

Makinen et al compared 3 sets of remission criteria in an inception cohort of early RA over 5 years. Frequency of clinical remission was 39%, 37% and 21% at 2 years, 5 years and at both 2 and 5 years respectively. Among patients in clinical remission at 2 years, remission persisted in less than 50% of patients at 5 years. 17% had modified ACR remission and 55% had radiographic remission (no new erosions or worsening

of erosions) at 5 years (119). These findings confirm that frequency of remission may vary depending upon the type of remission criteria.

A comparative analysis of DMARD-free remission in ERAS patients with a similar inception cohort (EAC) in the Netherlands showed different remission rates but similar, but not identical predictive markers. In the EAC (study patients=454), frequency of DMARD-free remission was 15% compared to 9.4% in the ERAS (study patients=895), partially explained by the study design of EAC, which was likely to recruit milder RA. Baseline variables such as symptom duration, RF, shared epitope (SE) and radiographic damage showed predictive value for subsequent remission in both cohorts. Other features such as onset of symptoms, RAI and HAQ in the ERAS, but not in the EAC showed independent predictive value for DMARD-free remission. CRP and anti-CCP antibodies showed prognostic value for remission in the EAC, but these variables were not collected in the ERAS patients (293). Few studies have validated a set of prognostic markers generated in one cohort in a similar but independent cohort in this way. For uncommon outcomes and therefore small numbers like remission, this is a powerful tool, and sound evidence for reliability.

A French cohort reported radiographic and functional progression during the period of sustained DAS remission (288). Although 5 out of 30 patients (16.7%) showed clinically meaningful x-ray progression, no significant radiographic damage progression was noted at group level during sustained DAS remission, consistent with findings from this thesis. There was a significant functional progression (HAQ) between the remission and non-remission groups at 3 and 5 years but no difference between 3 and 5 years in the French study.

However in this thesis, there was a significant difference between the study points within the DAS remission and non-remission groups in relation to radiological and functional progression, with the former group showing significantly less progression. Moreover, patients in sustained DAS remission had fewer requirements for supportive aids & major appliances and orthopaedic surgeries compared to non-remission group. Although, there were fewer deaths in patients in sustained DAS remission (15% vs 23%), the difference was not statistically significant.

The strengths of this study are large numbers of early RA patients with a long duration of follow-up. Details of work disability, orthopaedic surgery and mortality in relation to sustained remission in early RA, treated with traditional DMARDs, have not been reported in any of the previous observational studies. It is encouraging to see in this study of pre-biologic era that patients in sustained DAS remission maintained or improved their functional ability with fewer requirements for orthopaedic surgeries.

Limitations of this study include possible patient selection effects. Observational studies involving only patients attending secondary care may not include patients who go into remission early and do not attend hospital (left censoring). In contrast, patients who died or became too unwell to continue to attend could not be included in analysis (right censoring). Secondly, DAS was recorded only annually and there is a possibility of disease exacerbations in between. However, patients were assessed clinically every 3 to 6 months as part of normal practice and no change in therapy was noted to suggest any flare-ups.

In conclusion, frequency of sustained remission can be much lower than point remission. Frequency of remission and prognostic value of baseline disease variables may vary depending upon the remission criteria used. In this early RA cohort, male sex, short duration of symptoms and low RAI at baseline showed significant predictive value for sustained DAS remission. Persistent clinical disease inactivity in the study cohort has had a positive impact on radiographic, functional and surgical outcomes. Therefore, remission induction and maintenance should both be considered as equally important and as ideal therapeutic targets to achieve better long-term outcomes.

CHAPTER 4

RADIOGRAPHIC DISEASE PROGRESSION IN EARLY RHEUMATOID ARTHRITIS

4. RADIOGRAPHIC DISEASE PROGRESSION IN EARLY RHEUMATOID ARTHRITIS

4.1 Background

Disease progression in RA is usually assessed by standard clinical, laboratory and radiological measures. X-rays of hands and feet at regular intervals help to assess radiographic disease progression in RA. A number of scoring methods have been developed to quantify radiographic damage and the most commonly used methods are Larsen's and Sharp's and their modifications (150).

The advantage of radiographic assessment using validated scoring systems is that the structural damage seen on x-rays is largely irreversible and it represents the cumulative measure of disease activity and disability (161). Also, quantification of x-ray damage is an important outcome measure in RA, as it strongly correlates with key outcomes such as, function, work disability, surgery and use of health resources (7;231).

Structural damage in RA is progressive and some prospective studies have shown that by 3 years from disease onset, 60-80% of patients developed joint erosions (68;88;92). The relationship of x-ray damage with time is uncertain and different models of x-ray progression including flat, linear, square-root, first-order kinetics and sigmoid types, have been proposed, as described in chapter1 (90;100).

The relationship between clinical disease activity and radiographic damage can be inconsistent and unpredictable, particularly in early stages. It has been shown that the link between structural damage and disability is weak early in the disease course (< 5 years duration), but is stronger late in the disease (107). This is because that in patients with early RA, persisting joint inflammation rather than structural damage accounts for functional disability or high HAQ scores (55;107).

Nonetheless, there is only limited information from early RA observational studies on longitudinal radiographic progression and its relationship to clinical and functional measures in patients treated with traditional disease modifying anti-rheumatic drugs (DMARDs). Therefore, this study aimed to analyse the above in the ERAS cohort.

4.2 Objectives

1. To study the nature of radiological progression over 5 years in the ERAS cohort
2. To analyse the correlation between radiographic progression and other standard measures of disease activity in early RA

4.3 Patients and Methods

Patients

Only those ERAS patients who completed at least 5year follow-up and had serial x-rays of hands and feet were included for this analysis (n=712). 172 (14%) patients did not complete 5yr follow-up for the following reasons: deceased (60, 35%), moved

(16, 9%), declined follow-up mainly for social and work related reasons (19, 11%), patient reported remission (6, 4%) and lost to follow-up (71, 41%). A separate analysis of these excluded patients showed that baseline disease characteristics were similar to the study cohort except that mean age of disease onset and baseline disease activity were slightly higher in this group, as described in the previous reports (12).

Study assessments

Details on standard clinical, laboratory and functional assessments in the ERAS cohort have already been described in detail in the previous chapters.

Radiographs of the hands and feet were performed at baseline, 1, 2, 3, and 5yrs and were digitized onto CD-ROM. The films were scored randomly using Larsen's method by a trained independent observer who was unaware of the clinical details including treatment. Intra-observer reliability was checked using ICC as described before (68;290).

Treatment

The study cohort was treated with standard DMARD therapy, either as sequential monotherapy or as combination therapy, as described in the earlier chapters and steroids were used in a small proportion of patients.

Statistics

Statistical help for this research project was obtained from the Department of Mathematics, Keele University, Keele. Results are presented as summary statistics, which include median and inter quartile ranges, means with standard error & deviations, & 95% confidence intervals, where appropriate. The rates over all one

year periods were compared using the paired sample t-tests, with Bonferroni correction for multiple testing. Pearson correlation was used to study the relationship of continuous variables. Independent groups were compared using independent samples t-test and ANOVA.

4.4 Results

Table 4.1 Baseline disease characteristics of the study cohort

Baseline variable	**Study cohort (n=712)**
Women*	65% (462)
Age of disease onset in years	53 (± 13.4)
Duration of symptoms in months [Median (IQR)]	6 (4-11)
Rheumatoid factor (RF) positive*	62 % (442)
Shared epitope (SE)*	66% (405)
Erosions*	23% (163)
Ritchie articular index (RAI)	12.4 (± 10.7)
Swollen joint count (SJC)	17.2 (± 13.2)
Erythrocyte sedimentation rate (ESR)	40.6 (± 28.6)
Disease activity score (DAS)	4.1 (± 1.6)
Health assessment questionnaire (HAQ)	1.0 (± 0.75)
Larsen score Mean (± SD) Median (IQR)	3 (± 7.6) 0 (0-3)
Disease modifying anti-rheumatic drug (DMARD) use at 1yr *	72% (514)

Values are expressed as mean (± SD) unless otherwise indicated

* % (count)

Baseline demographics of this subgroup are similar to rest of the ERAS cohort and are typical of early RA patients. DMARDs were used in 72% (n=514, monotherapy 58%; combination therapy 14%) of patients at year1 and the respective figures at year3 and year5 follow-up were 81% (mono 51%; combi 30%) and 83% (mono 43%; combi 40%). Median (IQR) time to start of first DMARD was 2 (0-4) months and

sulphasalazine (SSZ) was the most frequently used first line DMARD followed by methotrexate (MTX). Steroids were used in 15% percentage of patients both at year3 and 5 and majority of patients were treated with a prednisolone dose of ≤ 7.5 mg/day.

Radiographic progression

At baseline, 248 (35%) had radiological evidence of joint damage, and by 5yrs this had risen to 519 (73%). Radiographic progression over 5 years is reported as mean or median change in Larsen score over time and is as follows:

Table 4.2 Larsen score progression from year 1 to 5

Larsen score	**Baseline**	**Yr1**	**Yr2**	**Yr3**	**Yr5**
Mean (SD)	3.0 (7.6)	5.2 (10.1)	7.5 (12.1)	12.2 (16.2)	15 (19.7)
Median (IQR)	0 (0-3)	1 (0-6)	2 (0-9.75)	6 (1-18)	7 (1-21)

Figure 4.1 Larsen score progression from 1 to 5 years

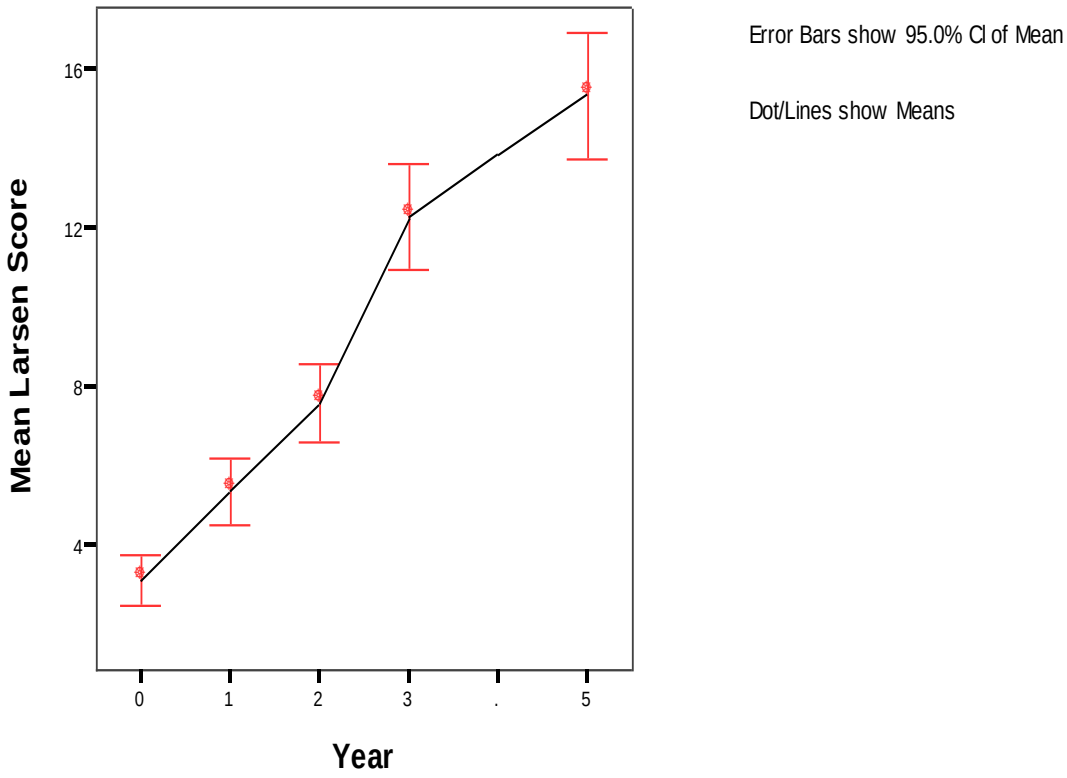


Figure 4.1 shows that the rate of change in mean Larsen scores over the first 5yr of RA was approximately constant except for an accelerated phase between years 2 and 3. Further analysis showed that the steeper (accelerated) curve seen in Larsen scores between years 2 and 3 was significantly different from years 0&1, 1&2, and 3&5 (interpolation over 2yrs since x-rays were not performed at 4yrs).

To assess whether the increased rate of change in the mean Larsen scores between year 2 and 3 apparent from the graph was significant, the change in Larsen score was calculated for each period (taking the mean yearly increase between the study points). The slope between years two and three was then tested against the other three slopes to see if it was significantly steeper.

Table 4.3 Radiographic progression between year 2 and 3 in comparison to other study points (paired samples t-test)

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	*slp23 - slp01	2.49017	9.43226	.35349	1.79616	3.18418	7.045	711	.000
Pair 2	**slp23 - slp12	2.46067	9.27232	.34749	1.77844	3.14291	7.081	711	.000
Pair 3	***slp23 - slp35	3.27317	9.43719	.35367	2.57880	3.96754	9.255	711	.000

*slp23 – slp01 = difference in x-ray (Larsen score) progression between year2 to year3 and baseline to year1

**slp23 – slp12 = difference in x-ray (Larsen score) progression between year2 to year3 and year1 to year2

***slp23 – slp35 = difference in x-ray (Larsen score) progression between year2 to year3 and year3 to year5

After multiplying each p-value by 3 (Bonferroni correction for multiple testing), it is obvious that the increase in Larsen score between year 2 and 3 is significantly greater that that between the other time points ($P < 0.01$).

Possible explanations for the accelerated x-ray progression between year 2 and 3

1. Worsening disease activity at this time or possibly earlier (i.e. 1-2yrs from baseline) to allow for any effect of inflammatory activity to be reflected on x-ray progression

2. DMARD effects. Loss of or resistance to DMARD therapy, or temporary cessation due to drug toxicities, or inadequate dosage

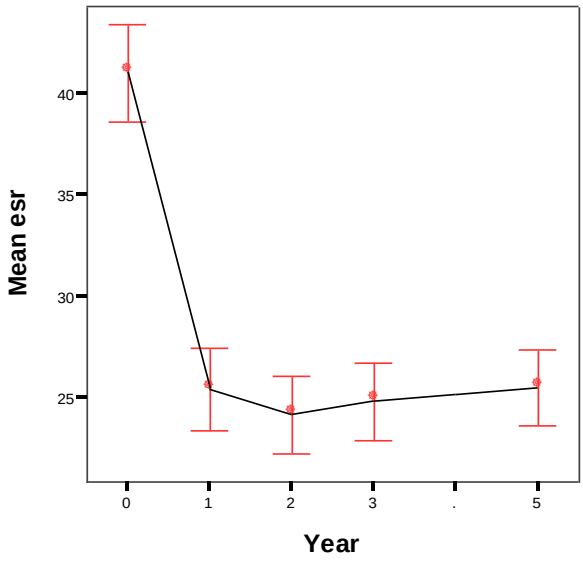
3. Disease heterogeneity: a radiological subtype of RA with a rapid progressive phase early in RA, not related to clinical disease or treatment

4. X-ray scoring methodology – Random scoring of x-ray films, using Larsen method, could have contributed to the variation in x-ray progression.

1. Is accelerated radiographic damage related to preceding disease activity?

In contrast to x-ray progression, clinical and laboratory measures such as ESR, DAS & HAQ improved from baseline, stabilised, and then gradually deteriorated around 4-5yrs as shown below.

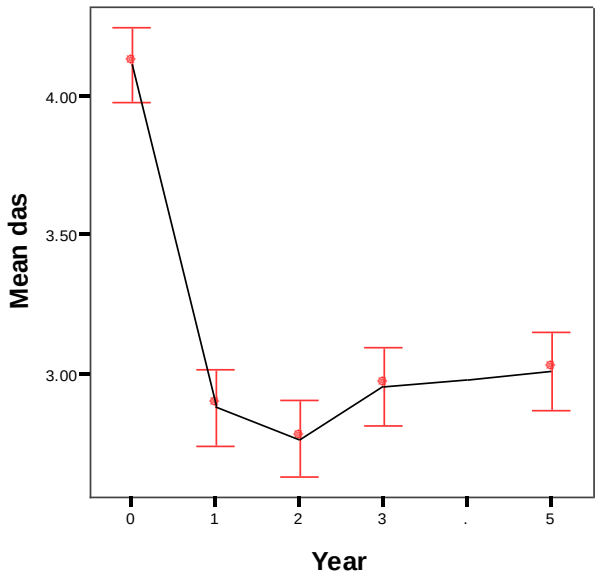
Figure 4.2 Progression of erythrocyte sedimentation rate (ESR) over 5 years



Error Bars show 95.0% CI of Mean

Dot/Lines show Means

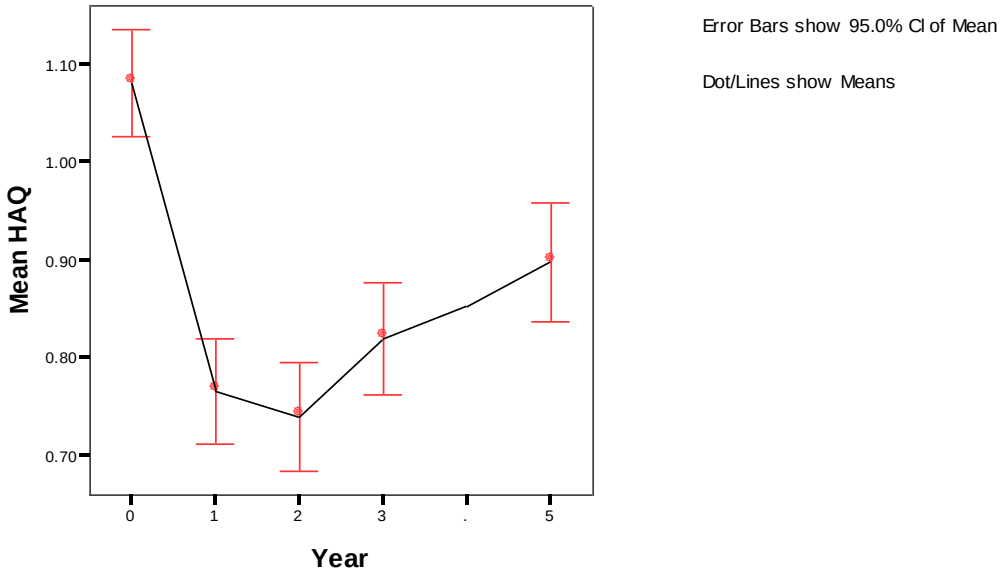
Figure 4.3 Progression of disease activity score (DAS) over 5 years



Error Bars show 95.0% CI of Mean

Dot/Lines show Means

Figure 4.4 Progression of health assessment questionnaire (HAQ) over 5 years



The above figures do not support an immediate time related effect of disease activity measures on the accelerated phase of radiological progression.

In addition, associations between Larsen scores and HAQ, joint score, ESR, DAS at the same time points (0 to 5yrs) were very modest. Correlation between Larsen scores and other disease measures at individual time points are shown in the table below.

Table 4.4 Correlation between Larsen score and other disease measures at baseline, year1, 2, 3 and 5

		Other disease measures at baseline			
		HAQ	**ESR**	**Swollen joint count (SJC)**	**DAS**
Larsen score at baseline	Pearson Correlation	.070	.119	.044	.083
	p-value	.06	.001	.24	.02

		Other disease measures at Year 1			
		HAQ	**ESR**	**Swollen joint count (SJC)**	**DAS**
Larsen score at Year 1	Pearson Correlation	.177	.179	.023	.078
	p-value	.000	.000	.55	.04

		Other disease measures at Year 2			
		HAQ	**ESR**	**Swollen joint count (SJC)**	**DAS**
Larsen score at Year 2	Pearson Correlation	.198	.209	.156	.180
	p-value	.000	.000	.000	.000

		Other disease measures at Year 3			
		HAQ	**ESR**	**Swollen joint count (SJC)**	**DAS**
Larsen score at Year 3	Pearson Correlation	.195	.192	.105	.125
	p-value	.000	.000	.006	.001

		Other disease measures at Year 5			
		HAQ	**ESR**	**Swollen joint count (SJC)**	**DAS**
Larsen score at Year 5	Pearson Correlation	.200	.179	.121	.158
	p-value	.000	.000	.002	.000

HAQ = Health assessment questionnaire

ESR = Erythrocyte sedimentation rate

DAS = Disease activity score

Pearson correlation coefficients never reached 0.3 (range 0.02 to 0.21). Changes in standard clinical measures do not appear to explain the accelerated phase in x-ray progression shown in Fig 4.1

Having examined the association between Larsen score & disease activity measures at individual time points & found none, the possibility that the steeper Larsen scores between years 2 and 3 could be related to cumulative disease activity measures was then explored.

Area under the curve (AUC) was calculated for DAS, HAQ, ESR & joint score between years 0-2. The correlations between these summary measures and the slope of the 2-3 year Larsen score were calculated, with only those of HAQ and ESR being statistically significant with coefficients of 0.13 and 0.16 respectively. These appear to be too small to be clinically relevant and achieve statistical significance due to the large sample size.

To investigate the possibility that the increased slope could be due to a delayed effect, mean DAS in years 0-1 and years 1-2 were calculated and correlated with the 2-3 year slope for Larsen score. This was only statistically significant for the 1-2 year correlation, but at 0.11 was not large enough to be of interest. This analysis supports the conclusion drawn from the above graphs that the accelerated radiological progression at 2-3yrs is only weakly related to disease activity measured at yearly intervals.

2. Could the accelerated x-ray progression be due to treatment effect?

Another possible explanation for the accelerated phase between 2 and 3 year could be suboptimal DMARD therapy leading to inadequate disease control. The time from onset of symptoms to presentation and from presentation to the initiation of the first DMARD were only weakly correlated with Larsen scores (0.12 & 0.10 respectively).

Figure 4.5 Larsen score (mean) progression in 4 different treatment groups

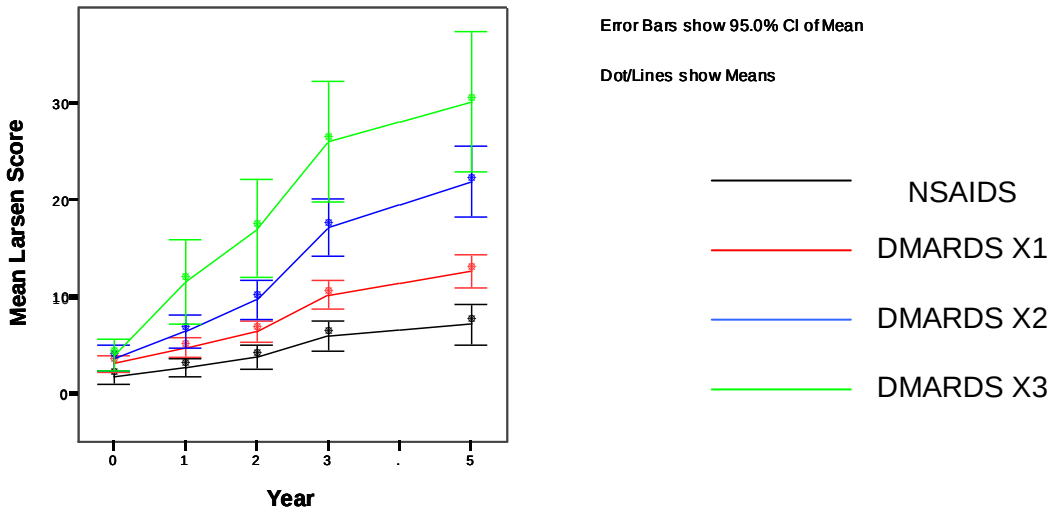


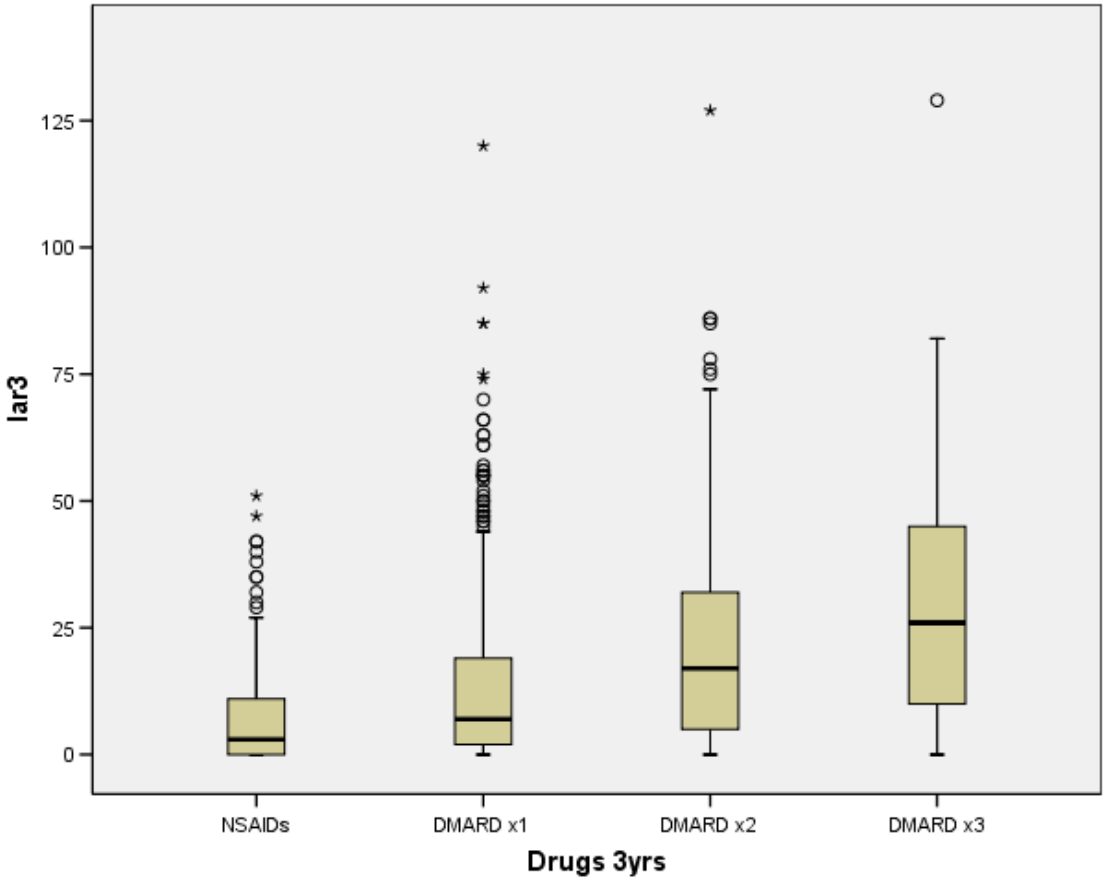
Figure 4.5 shows mean and 95% CI for Larsen scores over 5yrs in the 4 different drug groups

Legend for Figure 4.5

NSAIDS = patients treated with NSAIDs alone
DMARDS ×1 = patients treated with one DMARD only
DMARDS × 2 = patients who have had 2 DMARDs
DMARDS × 3 = patients who have had 3 DMARDs

The rate and magnitude of x-ray progression was greater the more DMARDs were used, including the accelerated phase**.** The difference in the five-year Larsen scores when analysed between the drug groups was significant (ANOVA $F=31.25$ $p<0.001$). Similarly, the rate of x-ray progression as measured by calculating the slope of the regression line through the 0-5 year x-ray scores was also significantly different between the drug groups (ANOVA $F=30.23$, $p<0.001$).

Figure 4.6 Larsen score at year 3 (lar3) in 4 different treatment groups at 3 year follow-up (Drugs 3yrs)



Legend for Figure 4.6

NSAIDs = Patients treated with NSAIDs alone

DMARD x 1 = Patients treated with one DMARD only

DMARD x 2 = Patients who have had 2 DMARDS

DMARD x 3 = Patients who have had 3 DMARDS

Larsen scores are shown as median values (thick horizontal line) within quartile ranges (boxes) for each of 4 treatment groups by 3yrs. Whiskers (vertical lines) extend to values within 1.5 box lengths

O indicates outliers (between 1.5 and 3 IQRs from top of box)

* indicates extreme values (more than 3 IQRs from top of box)

Since clinicians base their decisions on the use of, and changes in, drug therapies mainly on disease activity measures, these were also compared to DMARD use. Similar to x-ray scores & drug therapy shown in above Figures 4.5 & 4.6, disease activity scores were worse the greater the number of DMARDs used. There was a significant difference in mean DAS over years 0-3 across the drug groups ($F=3.82$; $p<0.05$). Similar significant differences across the drug groups were seen for HAQ, ESR and joint scores.

These findings imply that drug therapies were escalated in line with the severity of disease and were also related to radiological progression. The main exception to this was those patients who had marked x-ray changes by 3years, shown as Larsen scores greater than 75^{th} percentiles in Figure 4.6, but who had been treated with either none (n=25) or only one DMARD (n=86). This raises the question whether these patients were being under treated, and whether delayed therapy was responsible for the accelerated radiological progression.

As previously shown in Fig 4.1 to 4.4, correlations between disease activity over 3yr and Larsen scores were low and this was consistent within each of the four drug therapy groups. Of the 25 patients with high Larsen scores not on DMARDs, 19 had low disease activity. 6 had DAS scores in the higher ranges (mean >3.0), and did not receive DMARDs because of either co morbidity (n=4), preference for steroid use (1) or patient choice (1). Of the 86 patients with marked x-ray progression treated with 1 DMARD only over 3yrs (6 also on steroids), 40 had low DAS. The remaining 46 had DAS in higher ranges and 20 reported major problems with DMARD therapy: 6 had marked adverse events and 14 had problems with co morbidity.

These findings suggest that in terms of x-ray damage these patients were not treated optimally, but probably were treated appropriately based on clinical measures, individual patient responses and treatment practices of the 1980/90s era. The important finding was the small subgroup of 59 patients (19+40) in whom the marked x-ray progression was out of proportion to low disease activity. The details of the other patients who received more than 1 DMARD were reviewed for interrupted drug therapies and whether drug toxicity, poor compliance or co-morbidity were major factors. This was not the case as most drug terminations were due to lack or loss of effect.

3. Disease heterogeneity as a possible reason for accelerated x-ray damage

Rates of x-ray progression were compared to baseline features, including age of onset, gender, RF, socio-economic status, type of employment, genetics, and Larsen score.

Table 4.5 Baseline features compared to Larsen scores at baseline and 5yrs

			Larsen scores			
			Baseline		5yrs	
			Mean	SD	Mean	SD
Total	712	100%	3.0	7.60	15.0	19.66
Gender						
Men	250	35%	3.0	6.16	14.1	17.78
Women	462	65%	3.1	8.29	15.5	20.61
Age onset						
<45	184	26%	1.9	4.93	15.7	8.05
45-60	295	41%	2.8	8.95	14.7	19.04
>60	233	33%	4.2	8.57	14.8	18.55
*RA symptoms						
0-3	162	23%	2.3	4.13	13.5	17.13
4-6	197	28%	2.3	4.93	14.5	19.05
7-12	227	32%	2.7	6.26	14.2	19.01
13-24	126	18%	5.6	13.77	19.2	23.86
#Rheumatoid Factor						
Neg	187	26%	2.0	4.01	9.3	14.01
-/+	82	12%	2.9	5.97	11.5	16.22
+	184	26%	2.9	5.64	17.6	21.14
++	258	36%	3.9	10.61	18.4	21.91

* Rheumatoid arthritis (RA) symptom duration in months at the time of study entry

Rheumatoid factor test results at baseline

Neg = negative

-/+ = borderline positive

+ = positive

++ = strongly positive

There was no significant difference in the mean 2-3 years slope between males and females (independent samples t-test) and no significant correlation of the mean 2-3 year slope with age of onset or duration of RA symptoms to study entry. There were significant differences (ANOVA $F=3.18$; $p<0.05$) in the means of the 2-3 year slope in none, one or two copies of the DRB1 HLA shared epitope, although the difference in the means was fairly small at 3.41 (SD 7.1), 5.04 (8.1) and 5.51 (9.1) respectively. The higher the RF titre, the greater the rate of progression between 2 and 3year (ANOVA $F=4.9$; $p<0.05$).

4. Could the difference in x-ray progression be due to the scoring methodology?

In order to determine whether Larsen's scoring method itself favoured different rates of progression according to site, rates of progression within each of the different domains of the Larsen score were analysed. Separate scores for metatarsal, metacarpal and proximal inter phalangeal and wrist joints all exhibited similar accelerated phases between 2-3yrs, most noticeable in the wrist.

Possible influence of scoring methodology i.e. x-rays scoring method and scoring sequence of films, on longitudinal radiographic progression is discussed in detail in the next chapter.

4.5 Discussion

In this inception cohort of early RA, 248 patients (35%) already had radiological evidence of joint damage at baseline and this was 519 (73%) by 5 years. The increase in radiographic damage, as measured by Larsen scores over the first 5yrs of disease, was constant except between years 2 and 3 without any clear explanation for this

accelerated phase. Correlations between radiographic damage and measures of disease activity and function at the same time points were weak. An important finding was a small subgroup of patients with marked x-ray progression, which was out of proportion to disease activity.

The progression of joint damage with time in this cohort compares broadly with other published reports (7;69;88;90;92). Some of these studies have shown that radiographic damage is most rapid within the first 2yrs of disease (88;90;92). Could the accelerated phase of radiological progression in the ERAS cohort represent the slow/fast pattern as described previously? (90;100).

The accelerated phase could reflect a delay between inflammatory activity early on before x-ray changes become apparent by years 2-3. A time lag between high disease activity and structural damage has been reported (268), but does not explain fully the accelerated phase at 2-3yrs. Certainly, when compared to MRI and ultrasound, analysis of radiographs is relatively insensitive as there is a significant time-lag between the appearance of an erosion on MRI to subsequent change on plain film (101;102). There are few studies of repeated MR scans in early RA, but one report on wrist changes showed that only one in four MRI erosions progressed to x-ray erosions over one year, possibly owing to healing, observer error or technical limitations of radiography at the wrist (103).

Could this phenomenon therefore be a methodological problem where Larsen scoring of radiographs does not adequately demonstrate structural joint damage in years 1 &

2? Larsen's method was used to score x-rays in the ERAS patients from the start of the study in 1988. However, since then SvdH method has been shown to be better than Larsen's in relation to its sensitivity to change and in detecting minimal clinically important difference (181;182). For greater objectivity, radiographic scoring of films was performed randomly in the ERAS. However, chronological scoring seems to be better than random reading in detecting radiological progression above measurement error (157). This is going to be discussed in detail in the next chapter.

Variation in disease activity has been reported to affect radiological outcomes (245). This study results show that measures of disease activity and function (HAQ), and structural joint damage, as measured by Larsen, correlate weakly in early RA at the same time points. The main reasons for this are firstly, local swelling and inflammation of joints rather than deformity are the main causes of disability in early disease and often in the presence of normal x-rays (55).

Secondly, in contrast to x-ray scores, clinical scores were reversible and varied considerably with time in individuals particularly in early disease. Most clinical measures including HAQ characteristically improved from disease-onset, stabilised before a gradual deterioration with time, in contrast to radiographic scores, which increased progressively from onset. This finding is entirely consistent with previous reports (7;12). Later in disease, the correlation between structural damage and disability becomes stronger as joint deformity becomes more prominent and other factors such as reduced range of movement of small & large joints also contribute to overall disability (12;172;231).

Furthermore, HAQ at disease-onset is a poor predictor of radiographic outcome in the medium term (3 & 5 years) (55;68) but correlation is strengthened if HAQ at 1 year from onset is adopted as a predictor (68). Structural damage in early RA may be a surrogate marker for disability later in disease.

An important finding was that marked radiological deterioration was out of proportion to disease activity in a small but important group of patients. Many of these patients' disease activity measures were low with appropriate treatment, yet x-ray progression was marked. One explanation is possible difference in the pathogenesis between synovitis and erosions (254). Another could be the delay in detecting erosions with conventional radiography compared to US and MRI (102), especially early in RA when disease activity may be high.

Might this accelerated phase be related in some way to drug therapy? This thesis has investigated the relationship between disease activity, DMARD therapy and radiographic change, and the possible effects of delay to or under use of DMARDs and time lost from drug withdrawal due to toxicity or co morbidity. The majority (80%) of ERAS patients were prescribed sulphasalazine (SSZ) as their first DMARD, with methotrexate (MTX) the most frequently used second drug (38%). This was common practice in the UK in the 1980/90s (12). Lack of efficacy was the commonest reason for discontinuation and only 10% due to toxicity.

As with other DMARDs, the benefit of SSZ often wears off after an initial favourable response, a pharmacological characteristic termed 'drug resistance'. It is possible

therefore, that accelerated joint damage in years 2-3 is a consequence of the resistance to SSZ developing in year 2 or before. This concept is potentially important as it would indicate that timing of any change in drug therapy for RA may be critical in preventing subsequent joint damage. There were not enough patients in this study whose first drug was MTX to compare with SSZ.

The strength of this study lies in the large number of patients studied and low drop out rates. A weakness, typical of longitudinal studies, is that measurements of clinical activity and x-rays are only performed yearly and do not coincide with initiation or changes in therapy. Possible sources of bias in this study are left or right censoring as described in the previous chapter and treatment effects.

In summary, this study of early RA patients showed that radiographic progression was accelerated between year 2 and 3 and correlations with clinical, functional and laboratory measures at the same time points were only modest. A small, but significant proportion of patients developed marked x-ray damage in spite of low clinical disease activity. Although ultra sound & MRI are more sensitive to change, they are still not widely available in standard clinical settings. Only by performing yearly x-rays in early RA can clinicians identify the small subgroup of patients with radiographic progression despite low-grade clinical disease.

CHAPTER 5

INFLUENCE OF SCORING METHODOLOGY ON RADIOGRAPHIC PROGRESSION IN RHEUMATOID ARTHRITIS

5. INFLUENCE OF SCORING METHODOLOGY ON RADIOGRAPHIC PROGRESSION IN RHEUMATOID ARTHRITIS

5.1 Background

Quantification of radiographic damage in rheumatoid arthritis (RA) is important to determine disease progression, treatment response and outcomes. Although several scoring methods are available, Larsen, Sharp and their modifications e.g. SvdH and SENS have been widely used for this purpose (150).

The ability of a scoring method to detect a real change in radiographic progression over time is called sensitivity to change. In assessing longitudinal radiographic progression in RA, it is important to use a scoring method with high sensitivity to change and so better discriminative power. Methods such as smallest detectable difference (SDD) or change (SDC) have been used to assess the sensitivity to change of a particular scoring method (185;192).

However, each of these methods has a different score range and so it would be difficult to directly compare the results in RA studies using absolute numbers and mean or median values alone. SDD and its relation to minimal clinically important difference (MCID) have been used to compare different scoring methods (181). The lower the SDD value the higher the sensitivity of a scoring method in detecting radiographic progression that are considered clinically important.

SvdH method has shown to be superior to others in relation to its sensitivity to change and discriminative power in detecting MCID (182). Other methods such as linear transformation of scores from their original scale to a scale of 0 to 100 and percentage or mean percentage of the maximum possible score have also been suggested to make direct comparisons between scoring methods (185;189).

Serial x-rays of hands and feet can be read in random (single film at a time), paired (films read without known sequence) and chronological order (serial films read with known sequence) (160). Although each of this scoring sequence has its own advantages and disadvantages, chronological reading of x-ray films has shown to have increased sensitivity to change in detecting radiographic progression over time (157).

As described in the previous chapter, radiographic progression in the ERAS cohort was accelerated between 2 and 3 years from disease presentation without any correlation to other disease specific measures. Therefore, this thesis wanted to explore whether the scoring methodology i.e. scoring method and reading order of the films, has had any influence on the nature of radiographic progression in the ERAS cohort.

This study also wanted to compare Larsen, SvdH and SENS methods in a subgroup of the ERAS patients to see if there was any significant difference between them in assessing longitudinal radiographic progression, as there is only limited information on this.

5.2 Objectives

1. To compare random and chronological scoring of x-rays using Larsen method in a subset of early RA patients from the ERAS cohort.
2. To analyse radiographic progression using Larsen, SvdH and SENS scoring methods in a subgroup of the ERAS patients

5.3 Patients and Methods

The analysis was carried out in three steps in three different subgroups of the ERAS patients as follows: 1. Random versus Chronological order of x-ray scoring using Larsen method (n=62); 2. Larsen versus SvdH (n=38); and 3. Larsen versus SvdH versus SENS methods (n=278)

Patients

The study sample for each of these analyses was randomly selected from the ERAS cohort, as long as patients had completed 5 year follow-up and had serial x-rays of hands and feet available from baseline up to 5 years.

Radiographic assessment

X-rays of hands and feet of the study population were done at baseline, 1, 2, 3 and 5 years as described in the previous chapters. All serial x-rays of the ERAS patients were digitized onto CD-ROM and scored by an independent observer (CS), using Larsen method in random order.

For this study, observer KJ has scored serial x-rays of a selected group of patients using Larsen method in chronological order. Observer KJ has also used SVDH and SENS methods to analyse radiographic progression in a subgroup of patients and compared it with Larsen scores from the ERAS database. As described earlier, observer KJ had received adequate hands-on training and supervision from experienced readers in all three scoring methods before scoring the x-rays for the study patients and was unaware of the clinical details including treatment and previous Larsen scores from observer CS, whilst reading x-rays.

After scoring all the study films using different methods or reading order, the x-ray scores were then entered on to the ERAS database by the ERAS coordinator. The x-ray data were then merged together with other clinical details for further analysis.

Comparison of scoring methods

Direct comparisons between the scoring methods were made using summary statistics. Other methods such as SDD and mean percentage of maximum possible score (mean % MPS) have also been used to analyse and report radiographic data, based on different scoring methods.

Statistical analysis

Statistical help for this project was obtained from Maastricht University Hospital, Maastricht, Netherlands. Summary statistics using mean (SD) and median (IQR) values were used to compare the x-ray data at group level, whereas SDD was used to compare radiographic data at individual level in the study population and was calculated as follows:

$SDD = \pm 1.96 \times SD_{difference} / \sqrt{k}$

$SD_{difference}$ is the standard deviation of difference between two readings and k represents the number of readings or observers used for the actual analyses of a trial.

For this study, SDD for Larsen and SvdH methods were 4 and 5 respectively.

Reliability of scoring techniques was tested by inter and intra observer variability using intraclass correlation coefficients (ICC) and Bland Altman scatter plot graphs.

5.4 Results

Reliability test results

Intraclass correlation coefficient (ICC) values*

Larsen method (Global score)

Inter observer reliability = 0.96

Intra observer reliability = 0.95

SvdH method: Erosion score

Inter observer reliability = 0.88

Intra observer reliability = 0.95

SvdH method: Narrowing score

Inter observer reliability = 0.88

Intra observer reliability = 0.97

SvdH method: Total score

Inter observer reliability = 0.81

Intra observer reliability = 0.97

* Maximum score for ICC is 1, indicating perfect reliability and higher the ICC values better the reliability of the observer.

Bland and Altman graphs

Figure 5.1 Larsen score – Inter observer reliability

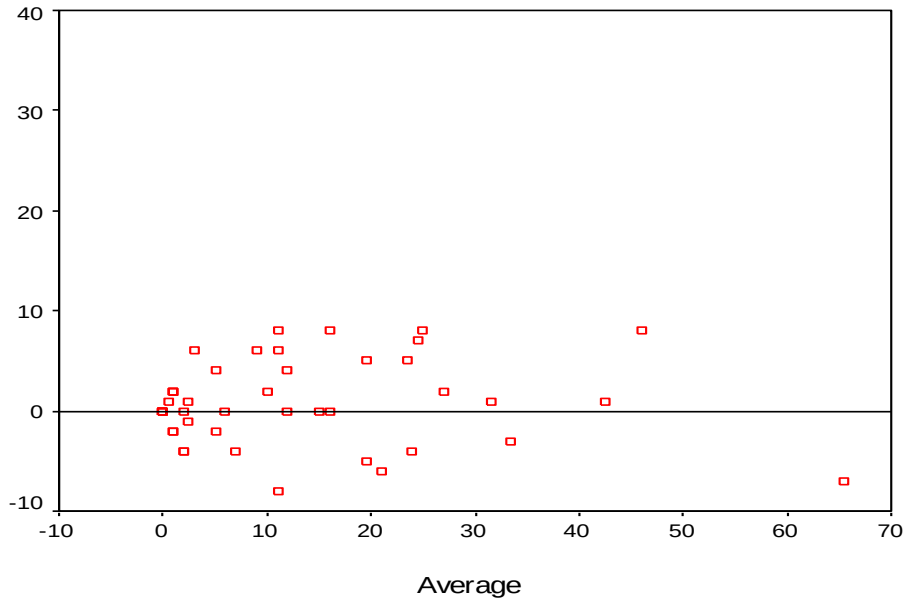
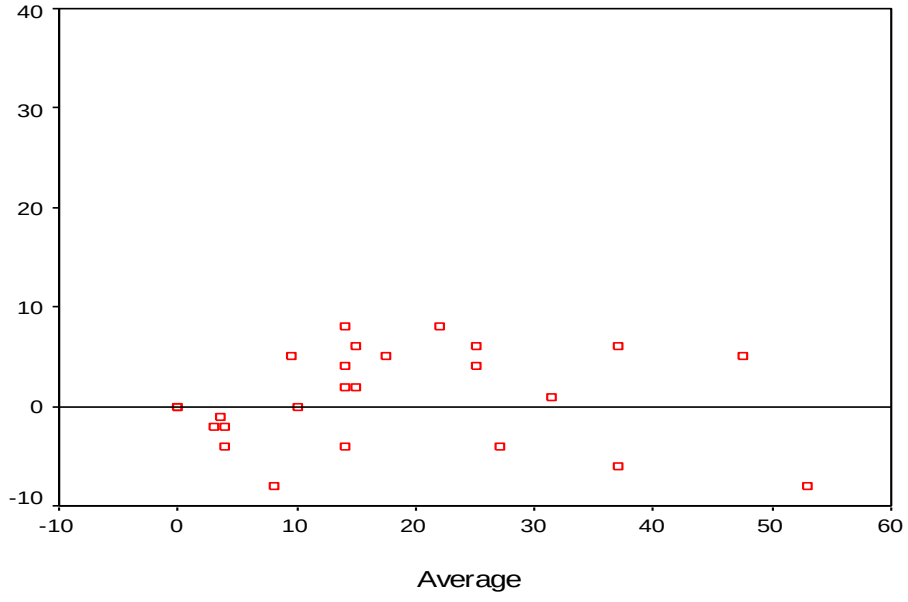


Figure 5.2 Larsen score – Intra observer reliability



SvdH score – Intra observer reliability

Figure 5.3 Erosion score

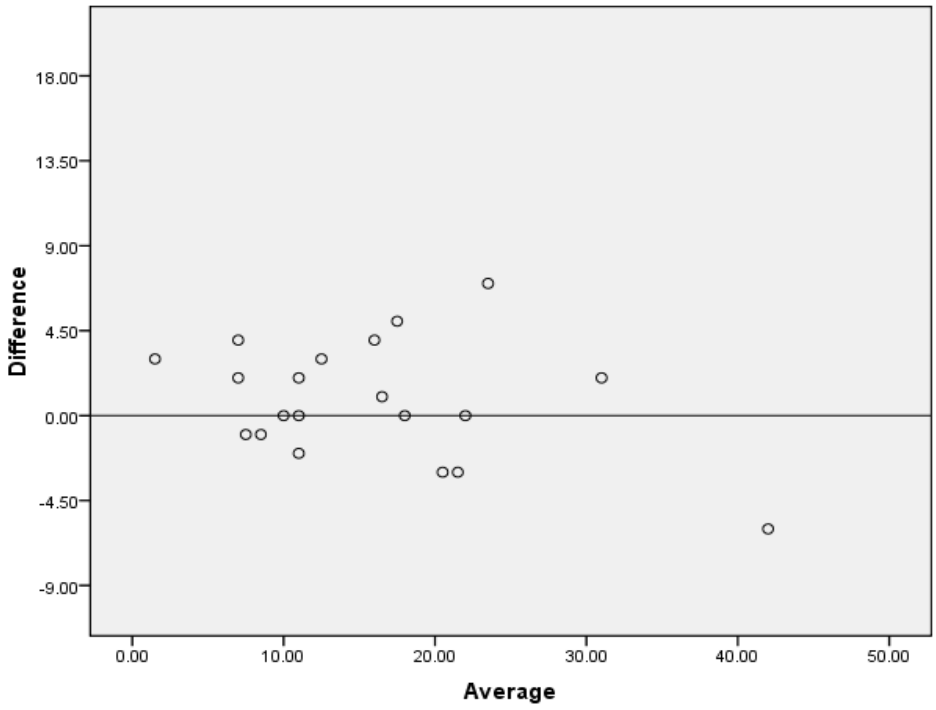


Figure 5.4 Narrowing score

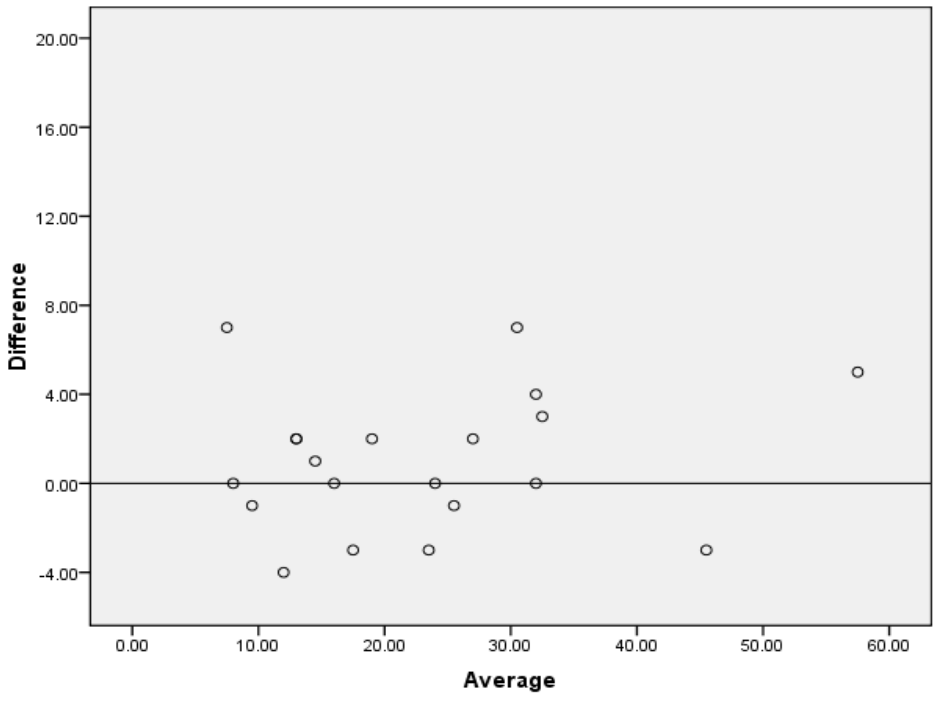
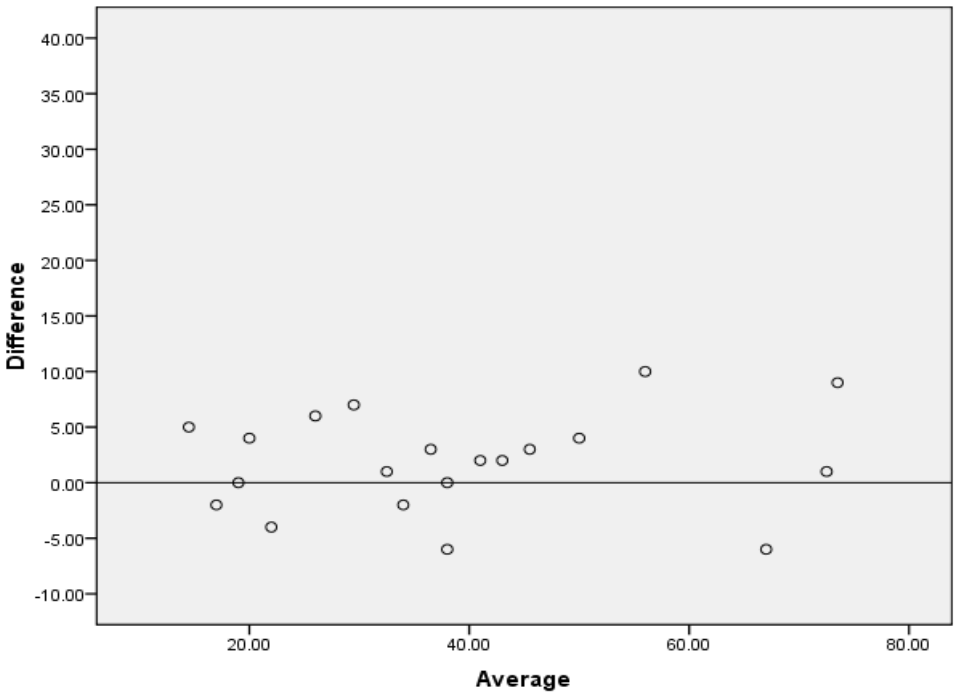


Figure 5.5 Total score



In figures 5.1 to 5.5, difference of the observers' scores (y axis) is plotted against the mean of the observers' scores (x axis). This is to reveal whether there is a systematic difference between either two observers (inter) or two readings from the same observer (intra). The ideal situation would be for all points to be situated on or close to y = 0. These figures show that the scatter plots are close to reference line y = 0, suggesting good inter and intra observer reliability for this study.

Analysis 1: Random versus chronological scoring of x-rays using Larsen method

Baseline disease characteristics of the study group are shown in the table below, which are similar to the rest of the ERAS cohort.

Table 5.1 Baseline disease characteristics (n=62)

Women*	43 (69%)
Age of disease onset (years)	52.7 (13)
Duration of symptoms (months)	8.7 (6)
Rheumatoid factor (RF) positive*	45 (73%)
Erosions*	25 (40%)
Erythrocyte sedimentation rate (ESR)	46.7 (32.8)
Disease activity score (DAS)	3.8 1.5)
Health assessment questionnaire (HAQ)	1.0 (0.7)
Disease modifying anti-rheumatic drugs (DMARDs) at year 1	47 (76%)

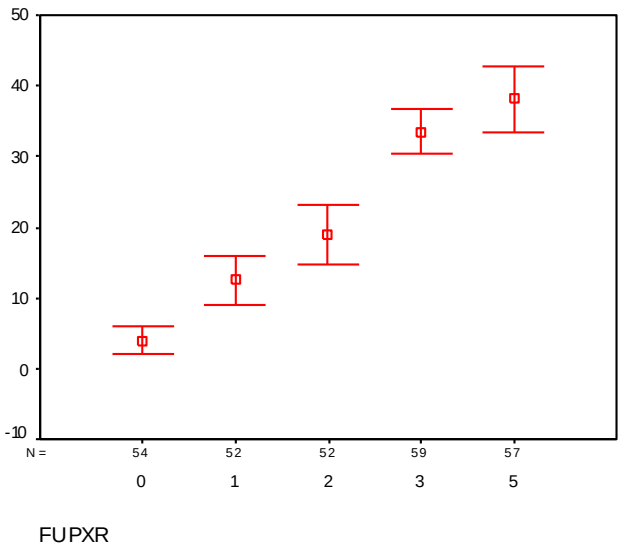
Values are expressed as mean (SD) unless otherwise indicated

*Count (%)

Table 5.2 Radiographic progression using Larsen score: random vs chronological

Scoring methodology (Larsen)		Baseline	Year 1	Year 2	Year 3	Year 5
Random	Mean (SD)	4.0 (7.6)	12.5 (12.1)	18.9 (15.5)	33.5 (12.0)	38.1(17.6)
	Median (IQR)	0.5 (0-4)	10 (2-17)	18 (5-30)	31 (23-40)	38 (28-48)
Chronological	Mean (SD)	3.7 (6.0)	8.8 (8.8)	13.4 (12.4)	18.8 (14.1)	27.8 (17.3)
	Median (IQR)	0 (0-5)	6 (0-15)	10 (4-21)	15 (9-26)	24 (15-37)

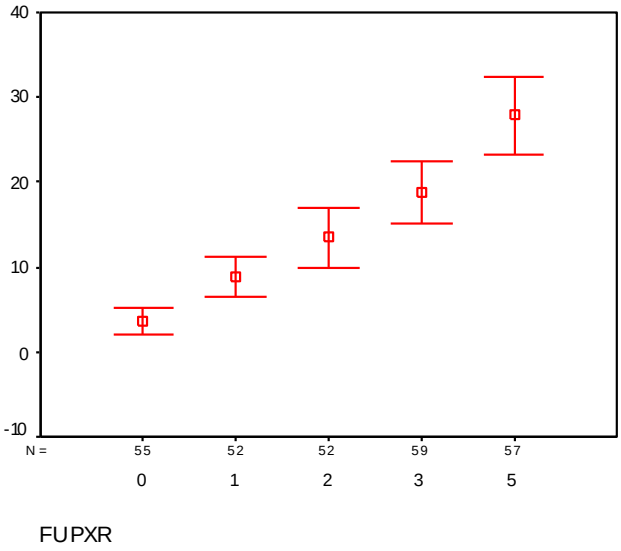
Figure 5.6 Larsen score progression based on random reading (Observer CS)



SE = Standard error, TSX = Larsen score

FUPXR = Follow-up years

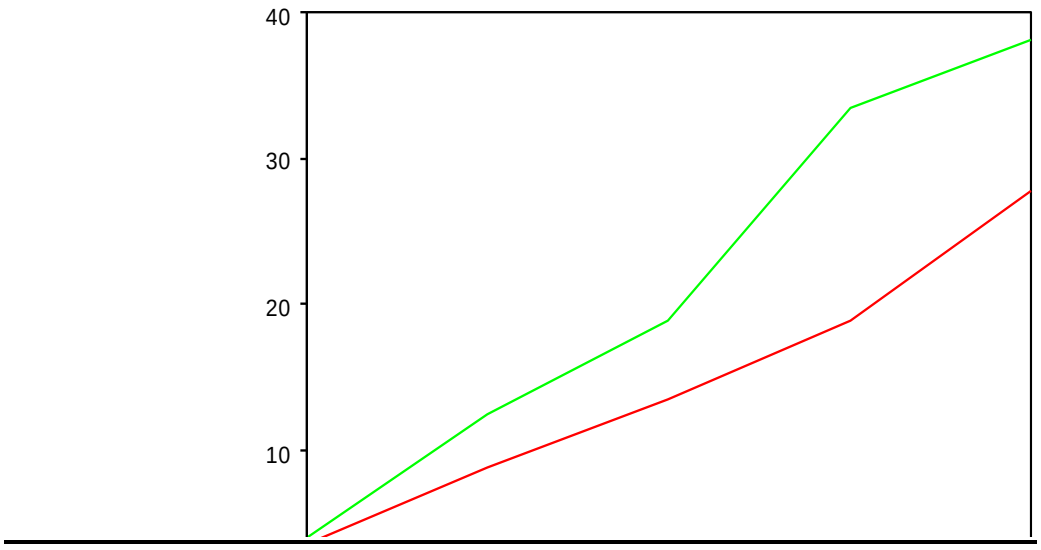
Figure 5.7 Larsen score progression based on chronological (Observer KJ)



SE = Standard error, TS = Larsen score

FUPXR = Follow-up years

Figure 5.8 Radiographic progression from 1 to 5 years (Larsen): random (ran) vs chronological (chrono)



Radiographic progression using Larsen score in random order by observer CS and in chronological order by observer KJ are shown in table 5.2 and figures 5.6, 5.7 and 5.8. As shown in the above figures, chronological reading of x-rays did not show accelerated change of mean Larsen score between year 2 and 3 as seen on random reading.

Analysis 2: Radiographic progression using Larsen and Sharp-van der Heijde (SvdH) methods

Baseline demographics of this subgroup was also similar to the rest of the ERAS cohort and is shown in the table below

Table 5.3 Baseline disease characteristics (n=38)

Women*	26 (68%)
Age of disease onset (years)	54.2 (12.8)
Duration of symptoms (months)	9.1 (6.3)
Rheumatoid factor (RF) positive*	27 (71%)
Erythrocyte sedimentation rate (ESR)	45.8 (35.2)
Disease activity score (DAS)	3.6 (1.4)
Health assessment questionnaire (HAQ)	1.0 (0.7)
Disease modifying anti-rheumatic drugs (DMARDs) at year 1*	26 (68%)

Values are expressed as mean (SD) unless otherwise indicated

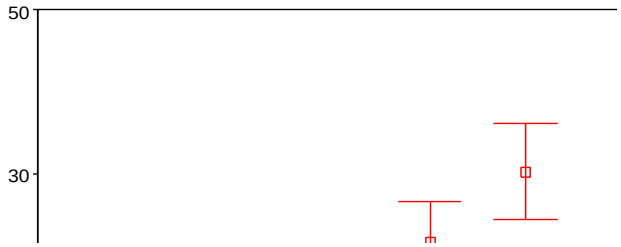
*Count (%)

Table 5.4 X-ray progression based on Larsen and SvdH methods

Study points	Larsen		SvdH Erosion		SvdH Narrowing		SvdH Total score	
	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
Baseline	3.8 (6.0)	2 (0-4)	2.7 (2.6)	3 (0-4)	8.7 (10.6)	4 (2-10)	11.4 (12.5)	8 (4-14)
Year 1	8.9 (8.8)	6 (2-15)	7.0 (6.0)	6 (3-10)	17.2 (11.1)	16 (8-22)	24.2 (15.1)	20 (13-32)
Year 2	14.6 (13.7)	10 (4-23)	14.0 (10)	12 (7-19)	24.9 (13)	22 (14-34)	38.9 (19.4)	33 (21-50)
Year 3	21.6 (5.4)	17.5 (10-32)	21.1 (13.2)	19.5 (12-28)	31.2 (13.4)	30.5 (21-39)	52.4 (22.3)	46.5 (36-66)
Year 5	30.2 (18)	26.5 (15-42)	27.7 (14.4)	27.5 (17-37)	41.3 (14.3)	39 (34-47)	68.8 (25.2)	63 (54-87)

<u>Radiographic progression, based on Larsen method (chronological reading)</u>

Figure 5.9 Total Larsen score



Radiographic progression based on SvdH method (chronological reading) at 0, 1, 2, 3 and 5 year follow-ups (FUP)

Figure 5.10 Erosion score

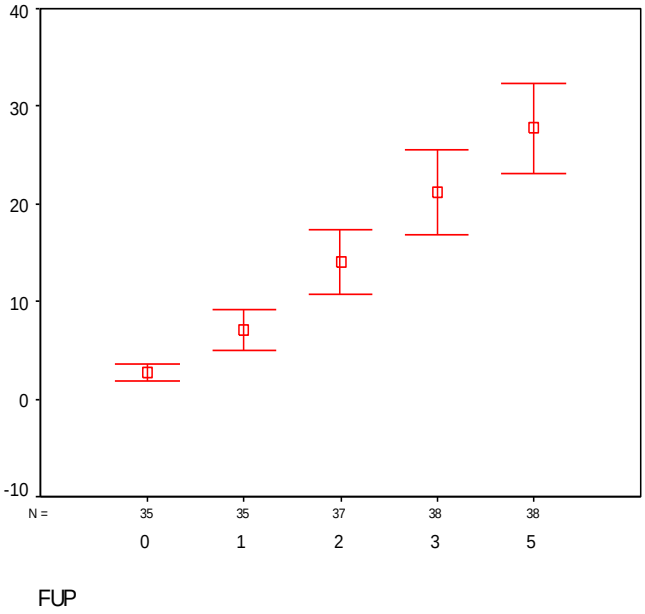


Figure 5.11 Narrowing score

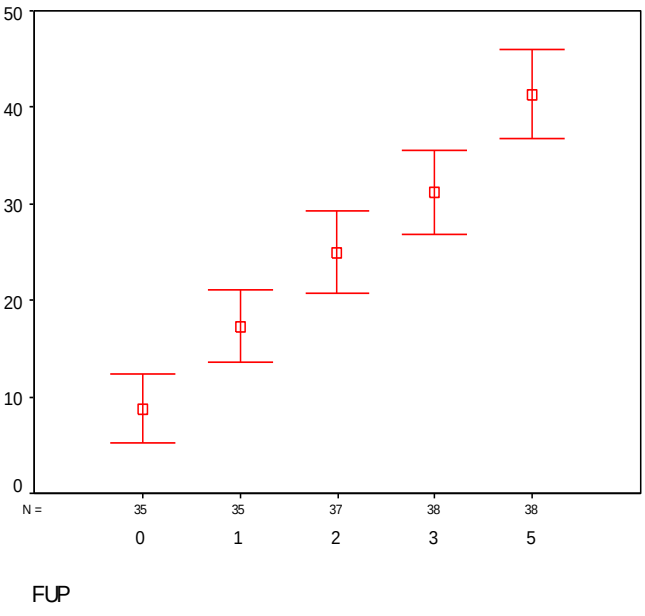
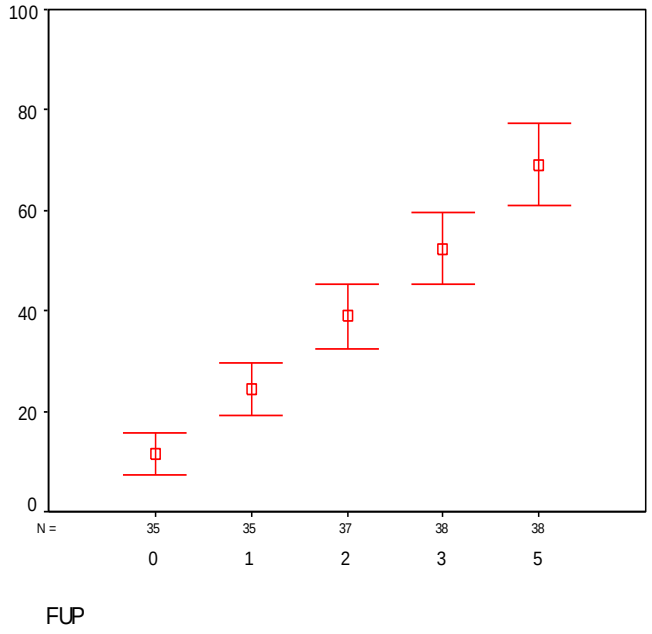


Figure 5.12 Total SvdH score



Radiographic progression between 1 and 5 years from disease presentation is shown in table 5.4 as well as in figures 5.9 to 5.12. Both Larsen and SvdH scoring methods showed fairly constant yearly rate of radiographic progression, based on chronological reading, over 5 years in this cohort.

Radiographic progression, based on Larsen and SvdH methods was analysed at individual level using SDD, which was 4 for Larsen and 5 for SvdH in this study. This means that patients with a change in Larsen score of > 4 between baseline and year5 were described as having significant x-ray progression i.e. progression above measurement error, whereas in the SvdH method, significant x-ray progression was defined as an increase in total score of > 5 between the study points.

According to Larsen method, 35 out of 38 patients (92%) showed significant x-ray progression and the corresponding figure for SvdH was 37 (97%). 3 out of 37 patients (8%), who showed clinically relevant radiological progression on SvdH method failed to do so on Larsen scoring (based on SDD).

Analysis 3: Radiographic progression using Larsen, Sharp-van der Heijde (SvdH) and Simplified Erosion Narrowing Score (SENS) methods

Table 5.5 Baseline disease characteristics (n=278)

Women*	178 (64%)
Age of disease onset (years)	52.7 (13.9)
Duration of symptoms (months)	8.0 (5.9)
Rheumatoid factor (RF) positive*	164 (59%)
Erythrocyte sedimentation rate (ESR)	37.9 (26.5)
Disease activity score (DAS)	3.9 (1.5)
Health assessment questionnaire (HAQ)	1.0 (0.7)
Disease modifying anti-rheumatic drugs (DMARDs) at year1*	191 (69%)

Values are expressed as mean (SD) unless otherwise indicated

*Count (%)

Table 5.6 Radiographic progression based on 3 different scoring methods

Scoring method	**Baseline** Mean (SD) Median (IQR) % of MPS	**Year1** Mean (SD) Median (IQR) % of MPS	**Year2** Mean (SD) Median (IQR) % of MPS	**Year3** Mean (SD) Median (IQR) % of MPS	**Year5** Mean (2 SD) Median (IQR) % of MPS
Larsen (range 0-200)	3.1 (9.7) 0 (0-2) 1.6 %	3.7 (9.8) 0 (0-4) 1.9 %	6.4 (12.9) 0 (0-7) 3.2 %	10.5 (16.2) 4 (0-14) 5.3 %	12.7 (18.1) 5 (0-20) 6.4 %
SvdH (range 0-448)	7.3 (18.5) 3 (0-9) 1.6 %	13.2 (22.7) 9 (2-17) 2.9 %	17.8 (25.3) 12 (3-25) 4 %	22.7 (29.2) 15 (5-31) 5.1 %	29.6 (34.2) 19 (8-42) 6.6 %
SENS (range 0-86)	3.5 (5.8) 2 (0-5) 4.1 %	6.6 (7.9) 5 (1-9) 7.7 %	8.7 (9.2) 7 (2-13) 10.1 %	10.8 (10.4) 8 (3-16) 12.6 %	13.4 (11.8) 10 (5-19) 15.6 %

Figure 5.13 Progression of SvdH erosion score

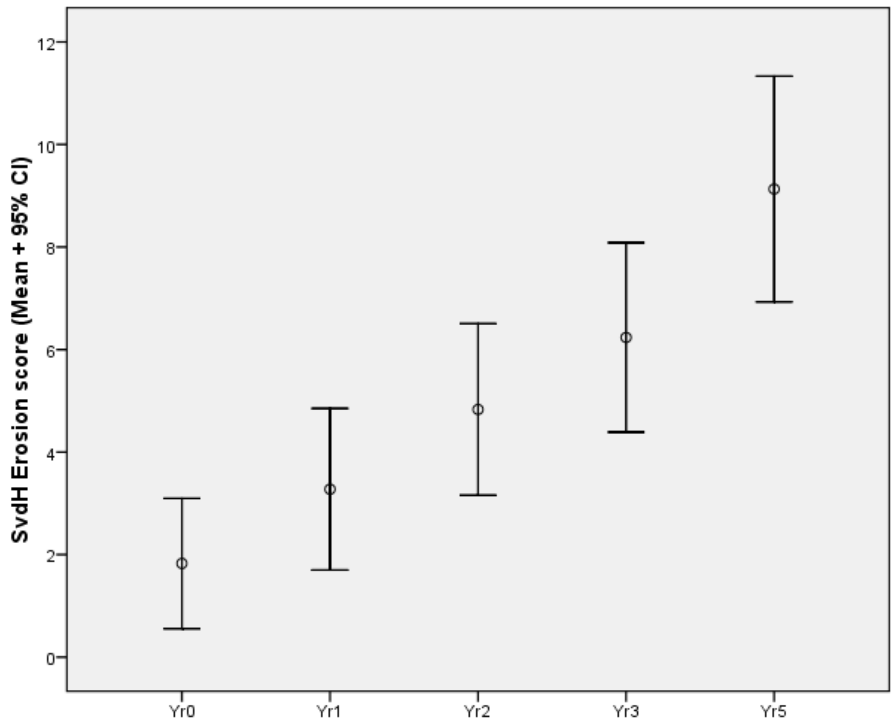


Figure 5.14 Progression of SvdH narrowing score

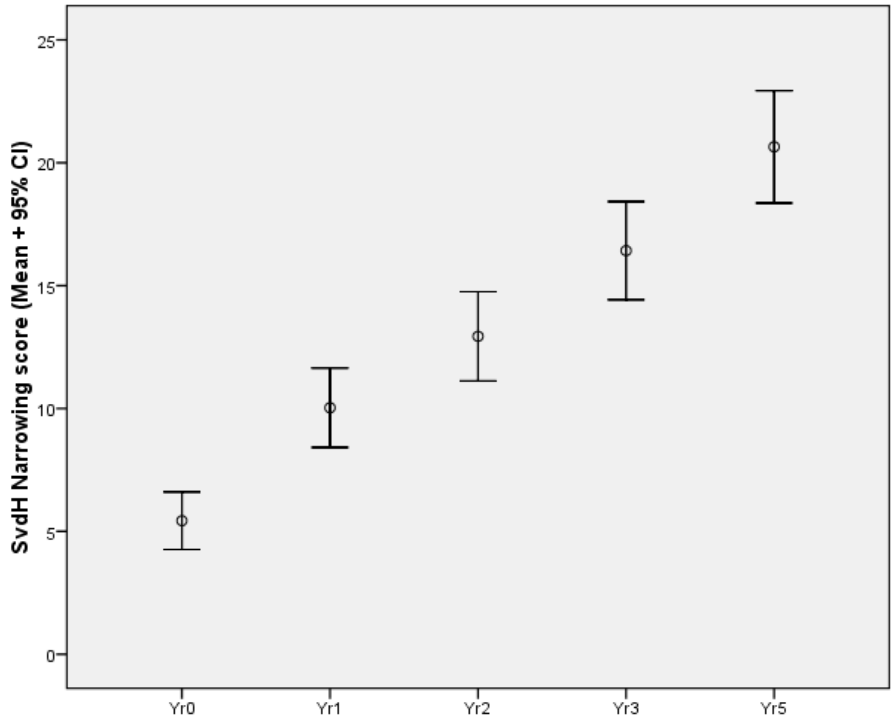


Figure 5.15 Progression of SvdH total score (Mean)

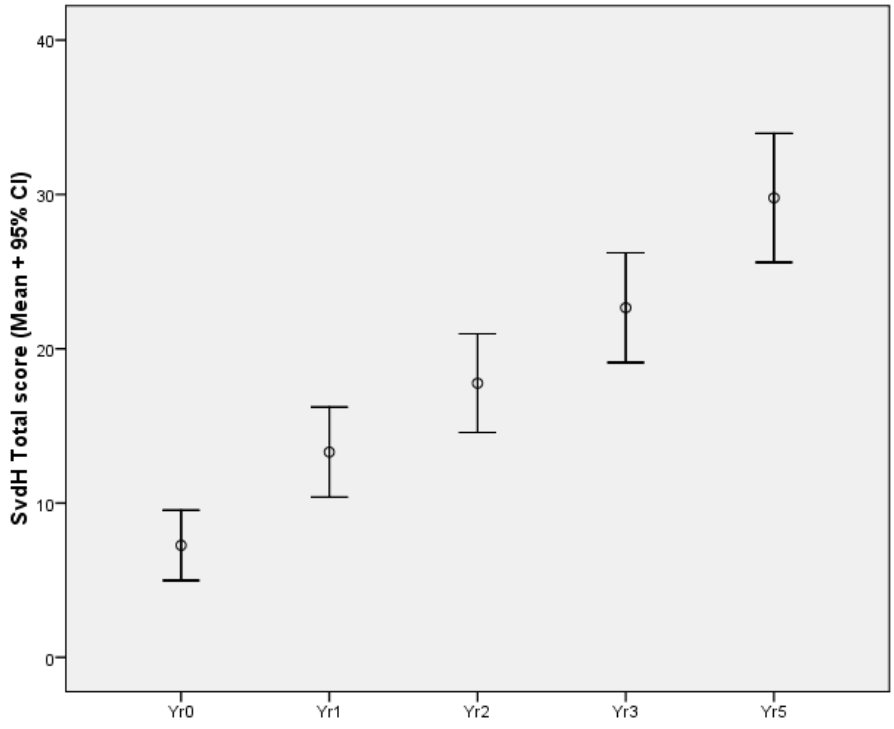


Figure 5.16 Progression of SvdH total score (Median)

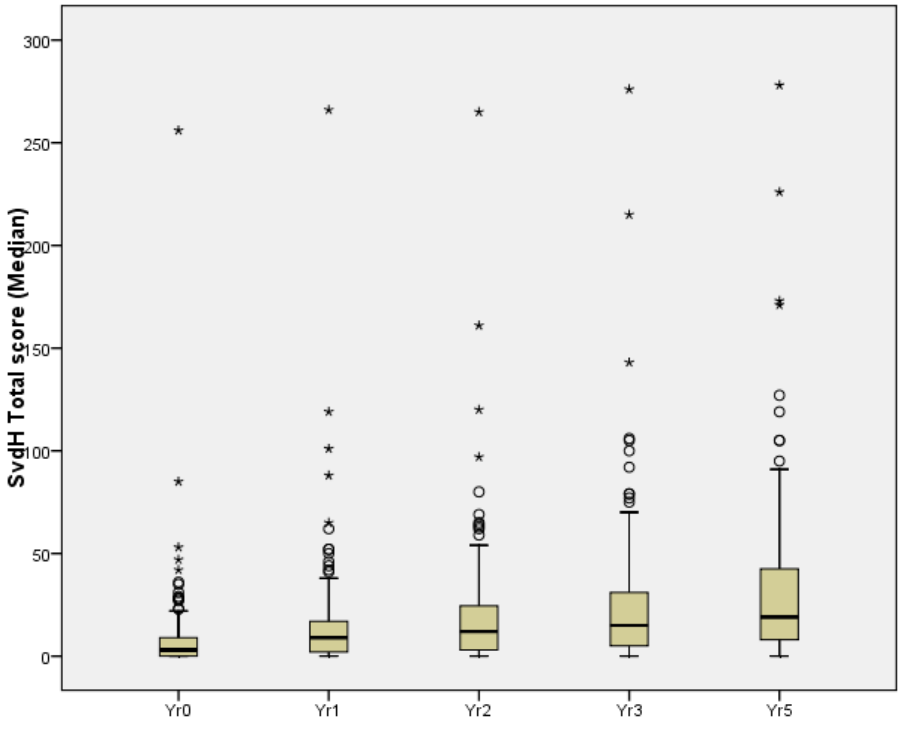


Figure 5.17 Progression of SENS erosion score

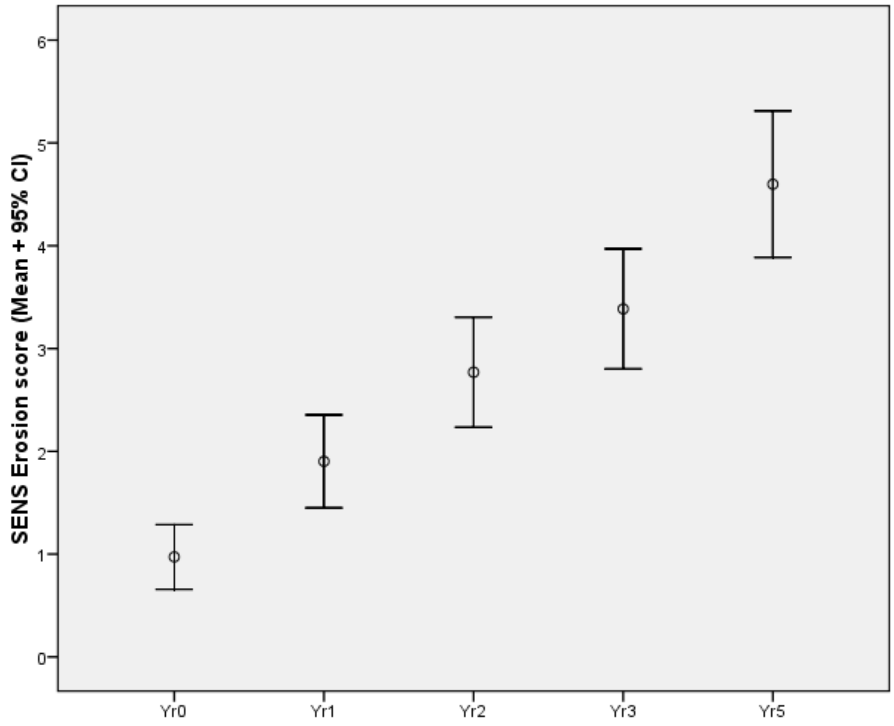


Figure 5.18 Progression of SENS narrowing score

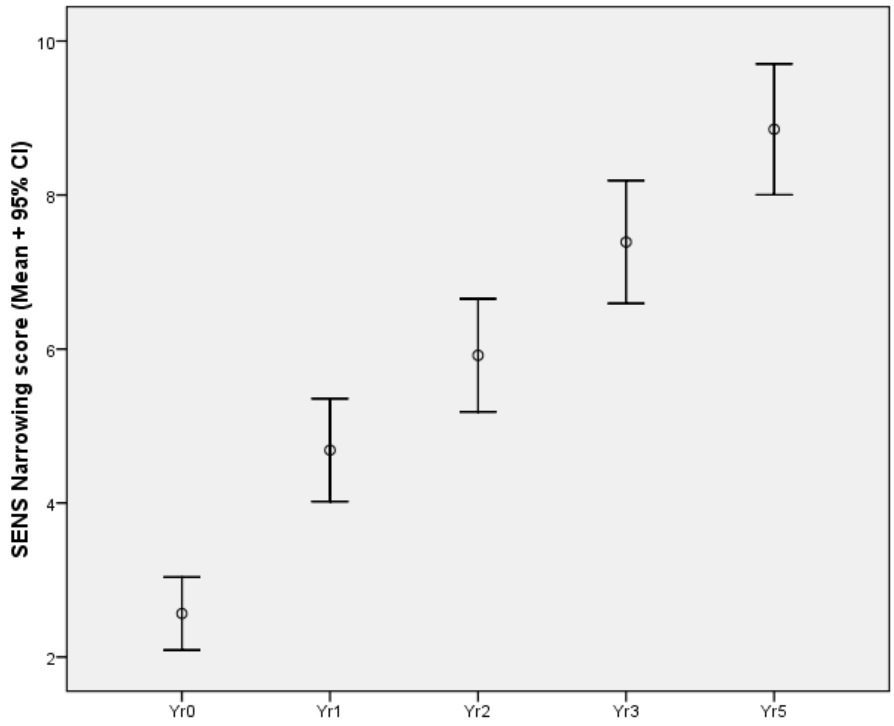


Fig 5.19 Progression of SENS total score (Mean)

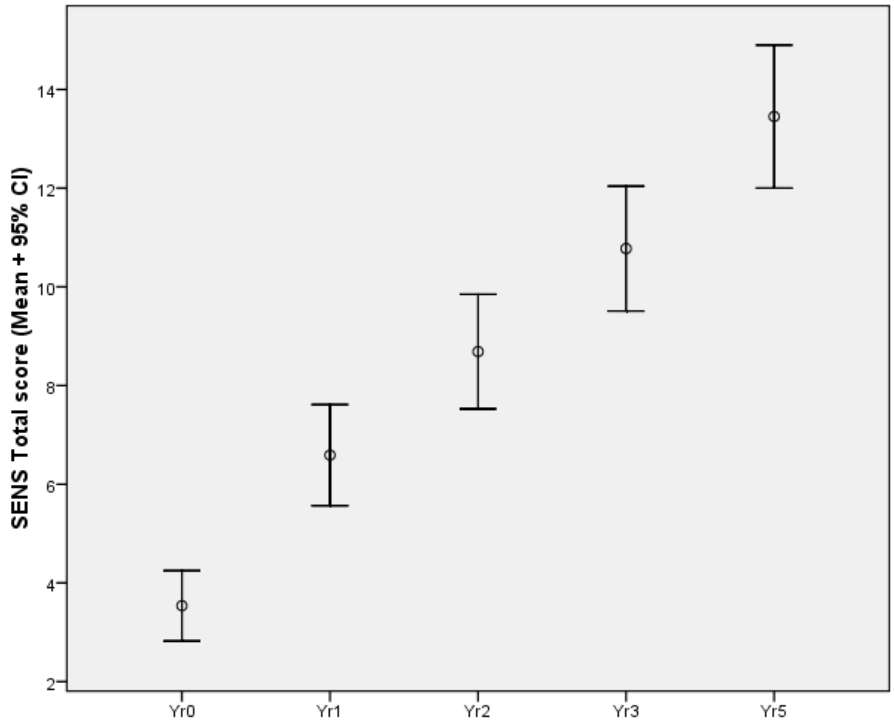


Figure 5.20 Progression of SENS total score (Median)

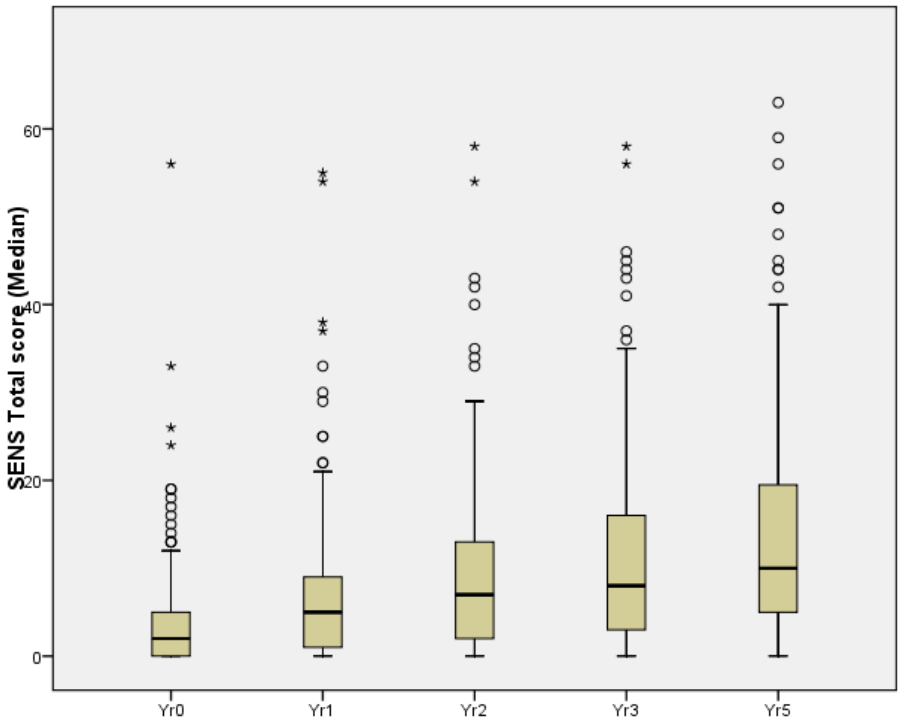


Figure 5.21 Progression of Larsen score (Mean)

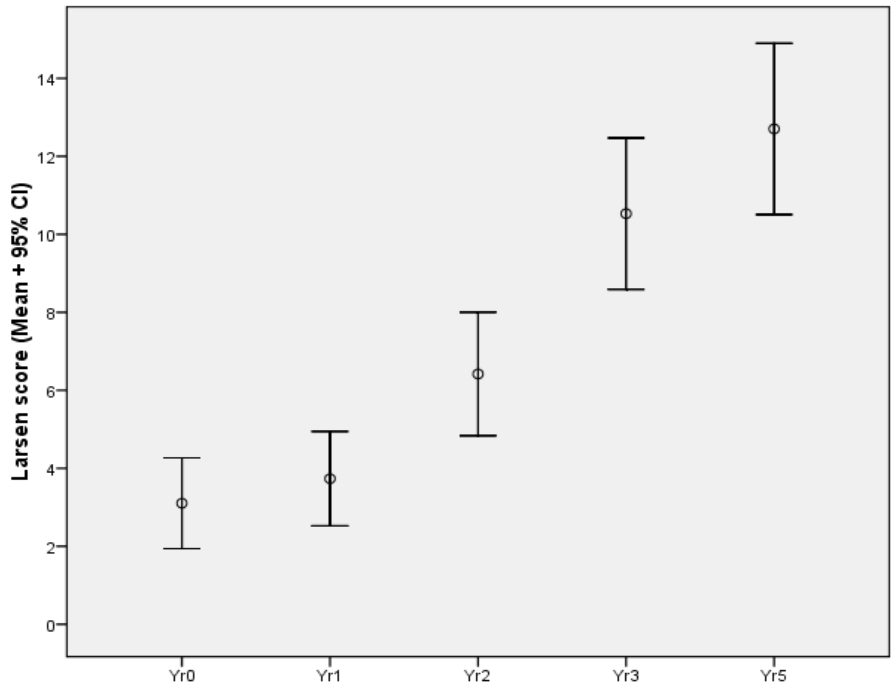
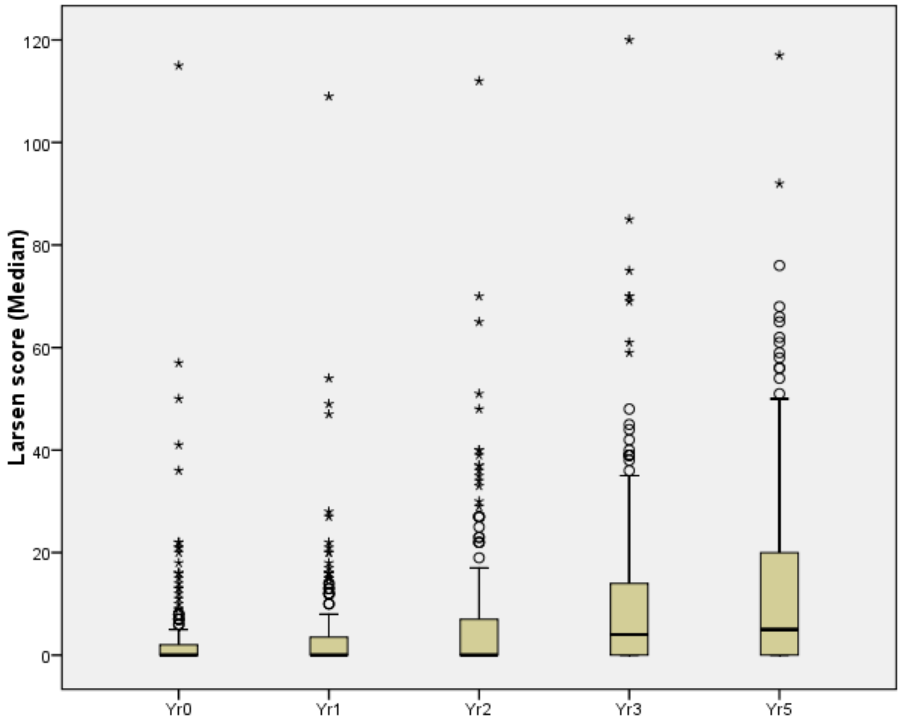


Figure 5.22 Progression of Larsen score (Median)



The above tables and figures show that radiographic progression at group level was essentially linear between baseline and 5 years using SvdH and SENS (chronological scoring) methods. However, using Larsen's method and random scoring, x-ray progression was not uniformly linear but exhibited an accelerated phase between year2 and year3. This latter finding was expected and described in the previous chapter, but in a larger number of patients in the ERAS cohort. This could be related to the scoring methodology, as this phase of accelerated progression between year 2 and 3 was not seen with SvdH method nor with chronological reading of x-rays in a subgroup of patients using the same Larsen method.

According to Larsen method, 21% of patients (n=59) had erosions at baseline, which progressed to 65% (n=182) at the end of 5 years. However, using SvdH and SENS methods, the frequency of erosive disease was slightly higher both at baseline (32%; n=85 out of 263) and at 5 years (71%; n=191 out of 270).

5.5 Discussion

This study has shown that radiological progression at group level was constant and linear from baseline up to 5 years, despite using three different scoring methods, as long as the x-ray films were read in chronological order. Nonetheless, a subgroup analysis showed that x-ray progression between year 2 and 3, based on random and chronological reading was different even though the same Larsen scoring method was used. This could either be due to difference in scoring order of the films or due to variability in scoring techniques by observers CS and KJ.

It has been suggested that reading films randomly can introduce measurement error, as the reader will not be able to correct for variation in positioning of hands and films or for the quality of the films (160). Also, with the random reading, there is a possibility of introducing measurement error by limiting the information to the reader, that the signal is lost in the noise (signal-to-noise ratio). On the other hand, chronological reading has increased sensitivity and more discriminative power in detecting x-ray progression that is clinically meaningful, although an overestimated progression of joint damage by the readers (expectation bias) can't be ruled out (157).

Observer KJ was trained in the Larsen method by observer CS and inter observer reliability between CS and KJ using ICC was very close to 1 (0.96), indicating good reliability between the readers. However, it has been shown that in patients with high disease activity and/or with higher radiographic damage, inter observer agreement can be unreliable (149). Therefore, it is difficult to say that the difference in x-ray progression between random and chronological reading in this study is entirely due to scoring order of the films.

Larsen, SvdH and SENS are the most commonly used scoring methods and they all have their own strengths and limitations. The advantage of Larsen score is that an experienced reader can perform it quickly, whereas SvdH method is more time consuming (180). However, inclusion of soft tissue swelling in the Larsen's score may lead to a relatively high score at baseline, decreasing with response to treatment. This may reduce the total possible increased score due to progressive damage, contributing to low sensitivity to change (149).

On the other hand, SENS method, a simplified version of SvdH, is a quick and reliable technique, which can be practised in the day-to-day clinical setting as well. Previous studies have compared Larsen, SvdH and SENS scoring methods in RA patients with conflicting results. In general, SvdH method seems to be superior to others in relation to its sensitivity to change and discriminative power in detecting x-ray progression that is considered clinically meaningful by clinicians (181;182).

In this study, x-ray progression at group level was essentially linear during the study period using three different scoring methods, but there were differences with Larsen between year2 and 3. Furthermore, at individual level, SvdH and SENS methods showed that more patients had erosive disease at baseline (32% vs 21%) and at 5 years (71% vs 65%) compared to Larsen method. This may be due to the difference between individual scoring methods or due to measurement error between the readers. Usually inconsistency between readers and scoring methods is greater in late disease than early RA, because of the difficulty in scoring advanced changes (149). Adequate training in a particular scoring method is very important for the readers as the quality and consistency of the observers are considered to be more important than the actual method used on analysing radiographic progression (149).

Also, the validation of a scoring method relies on the reproducibility in terms of inter and intra observer reliability, which was very good in this study with ICC values closer to 1. However, wide range of x-ray scores can influence the ICC results with extreme values having the greatest effect. In contrast, Bland and Altman's scatter plot graph is not affected by values at extreme range and in this study it showed good inter and intra observer reliability. Therefore, difference in scoring methodology rather than

measurement error is the more likely explanation for the observed variation in x-ray progression in this study cohort.

As far as is known, these three scoring methods have not been analysed together in relation to their sensitivity to detect significant x-ray progression over 5 years in early RA patients, treated in routine outpatient clinics. Also, the influence of scoring order of the films on measuring structural damage progression in early RA has not been reported before.

This study, however, has some limitations. One of them is that different subgroup analyses were performed with relatively less number of patients and so the results may lack statistical power. Also, direct comparisons between different scoring order of the films or various scoring methods can be complex and difficult, particularly if different observers were involved.

In conclusion, progression of structural damage on x-rays appeared to be similar in this study cohort, although different scoring methods were used. However, the type of radiographic progression based on random and chronological reading of x-rays was different, despite using the same scoring method. SvdH and SENS methods revealed higher frequency of erosive disease compared to Larsen method. SvdH method in chronological order showed better discriminative power in detecting significant x-ray progression in this study. Therefore, apart from disease characteristics and treatment effect, scoring methodology may also have an influence on radiographic progression in RA.

CHAPTER 6

PROGRESSION OF X-RAY DAMAGE DESPITE REMISSION IN EARLY RHEUMATOID ARTHRITIS

6. PROGRESSION OF X-RAY DAMAGE DESPITE REMISSION IN EARLY RHEUMATOID ARTHRITIS

6.1 Background

The ultimate goal of treatment in rheumatoid arthritis (RA) is remission as early as possible to avoid structural damage and to improve outcomes (74). Several studies have shown that structural damage on x-rays does not progress significantly in patients with clinically inactive disease compared to active disease (7;80;239). However, it has also been demonstrated that radiographic damage in RA can progress despite clinical remission and various reasons have been suggested to explain this dissociation, including difference in pathogenesis between joint inflammation and destruction (243;254;288).

There is only limited information from previous early RA studies on longitudinal x-ray progression during persistent clinical remission. A majority of the clinical studies or drug intervention trials usually report x-ray progression using mean or median radiographic scores from validated scoring systems. However, this type of traditional analysis would not reveal the true nature of structural damage progression on x-rays at individual level, particularly in patients with low or inactive disease.

Methods such as smallest detectable difference (SDD) or change (SDC) have been suggested as reliable measures in clinical trials, to detect clinically meaningful radiographic progression at individual level, i.e. progression above measurement error (185;192). However, only very few prospective studies have analysed x-ray progression in RA using SDD or SDC during clinical remission and these studies

have shown that significant radiographic progression including new erosions could occur despite clinically inactive disease (243;288). Also, as described in chapter 4, previous analysis of x-ray progression in the ERAS cohort showed that a small proportion of patients had significant structural damage progression in spite of low clinical disease activity.

This study therefore aimed to analyse radiographic progression in detail in early RA patients, who were in sustained remission based on DAS (sustained DAS remission). Prognostic factors for radiological progression despite sustained DAS remission and outcomes in relation to clinical and radiological disease progression were also analysed.

6.2 Objectives

1. To study radiological disease progression over 3 years, at group as well as at individual level, in early RA patients during sustained DAS remission
2. To analyse baseline predictive factors for radiographic progression despite sustained DAS remission in early RA
3. To assess if there is any difference in outcomes between patients in DAS remission with x-ray progression and those in DAS remission without x-ray progression

6.3 Patients and Methods

Patients

For the purpose of this study, only those ERAS patients who have had their DAS recorded at 1, 2 and 3 year follow-ups were included (n=1003). A separate analysis of patients who could not complete at least 3 year follow-ups due to various reasons (moved (n=11, 8 %); unable to attend (n=2, 1 %); declined (n=3, 2 %); patient reported remission (n=3, 2 %); deceased (n=116, 79 %); discharged (n=1); not known (n=4, 3 %); not traced (n=6, 4 %) were excluded from this study. A separate analysis of these patients (n=146) showed that mean age of disease onset (62 vs. 54, $p<0.001$) and disease activity score (DAS) were slightly higher (4.5 vs. 4.2, $p <0.05$) in this group at baseline.

Study assessments

Patients were assessed at 0, 3, 6 and 12 months and then annually. Standard clinical assessments including blood tests were recorded at each study visit as described earlier. X-rays of hands and feet were performed at baseline and then yearly during the study period. The films were scored using Larsen method (total score 0 – 200) in random order by an independent observer and the intra-observer variability was checked using intraclass correlation coefficient (> 0.85) as described in the previous chapters.

Outcome measures including HAQ, Steinbrocker's functional grade (FG I-IV), work disability and surgery were recorded at the 3rd year follow-up.

DAS remission

Remission in the study cohort was assessed using the original 3-variable DAS, based on EULAR criteria, as described in chapter 3. Sustained DAS remission in this study was defined as DAS < 1.6 at 1st, 2nd and 3rd year follow-ups.

Radiographic progression

Progression of structural damage on hands and feet x-rays of the study cohort was assessed in detail, both at group and at individual level. Radiographic progression at group level was assessed and reported using mean and median Larsen scores, whereas at individual level, clinically meaningful x-ray progression or progression above measurement error was calculated using SDD, as described in the earlier chapters.

SDD for this study was calculated by scoring twice a random sample of 20 pairs of hands and feet radiographs, representative of the study population and it was ≥ 4.

Also, frequency of erosive disease or new erosions in patients in sustained clinical remission was analysed.

Prognostic factors and outcomes

Prognostic value of baseline variables to predict progressive x-ray damage in patients in persistent DAS remission was studied. Various outcomes at 3 years were analysed in patients in sustained DAS remission to see if there was any difference in outcomes in relation to x-ray progression.

Treatment

The study cohort was treated with standard DMARDS as described previously using sequential monotherapy or combination therapy and/or steroids. None of the patients received biological agents as the study was in the pre-biologic era.

Statistical analysis

Summary statistics have been used to characterise the data. Continuous variables were expressed as either mean ± standard deviation (SD) or median with interquartile ranges (IQR) and categorical variables were shown as counts with percentages. Chi square (χ^2) for categorical and Mann Whitney U for continuous variables were used to compare the study groups. Wilcoxon signed rank test was used to test the difference in disease outcome between the study points within individual groups. Spearman's correlation coefficient was used to assess the strength of association between various clinical indices and x-ray scores at different study points.

Univariate analysis using odds ratios (OR) and multiple logistic regression, using the stepwise procedure were performed to study predictive factors for radiological progression. Variables used for the multivariate model were chosen from the univariate analysis and a p-value of ≤ 0.05 (two sided) was considered statistically significant.

6.4 Results

Table 6.1 Baseline demographics of the study cohort

Baseline variable	Whole study cohort (n=1003)	Persistent remission at yr 1, 2 & 3 (n=90)	Non-remission (n=913)	p-value
Women*	65% (655)	53% (48)	67% (607)	< **0.01**
Age of disease onset (years)	54 (± 14.2)	53 (± 15.3)	54 (± 14.1)	0.36
Duration of symptoms (months)	8.2 (± 6)	7.2 (± 5.7)	8.3 (± 6)	< **0.05**
RF positive*	63 % (633)	62% (56)	64% (577)	0.81
Shared epitope*	55% (550)	48% (43)	55% (507)	0.69
Erosions* (Larsen score ≥ 2)	26% (259)	24% (22)	26% (237)	0.80
RAI	13.2 (± 11.2)	7.2 (± 7.2)	13.8 (± 11.4)	< **0.01**
SJC	17.1 (± 13.1)	12.7 (± 11.5)	17.6 (± 13.2)	< **0.01**
ESR	42.2 (± 28.9)	39.5 (± 28.1)	42.5 (± 29)	0.34
DAS	4.2 (± 1.6)	3.4 (± 1.4)	4.3 (± 1.6)	< **0.01**
HAQ	1.1 (± 0.7)	0.8 (± 0.7)	1.1 (± 0.7)	< **0.01**
Larsen Mean (± SD) Median (IQR)	 4.3 (± 10) 0 (0-4)	 2.8 (± 6.7) 0 (0-2.5)	 4.5 (± 10.2) 0 (0-4)	 0.07
DMARD use at 1year	76% (760)	70% (63)	76% (697)	< **0.05**

Values are expressed as mean (± SD) unless otherwise indicated

* % (count)

RF = Rheumatoid factor, RAI = Ritchie articular index

SJC = Swollen joint count, ESR = Erythrocyte sedimentation rate

DAS = Disease activity score, HAQ = Health assessment questionnaire

DMARD = Disease modifying anti-rheumatic drug

Baseline disease characteristics of whole of the study population as well as the individual study groups are shown in table 6.1

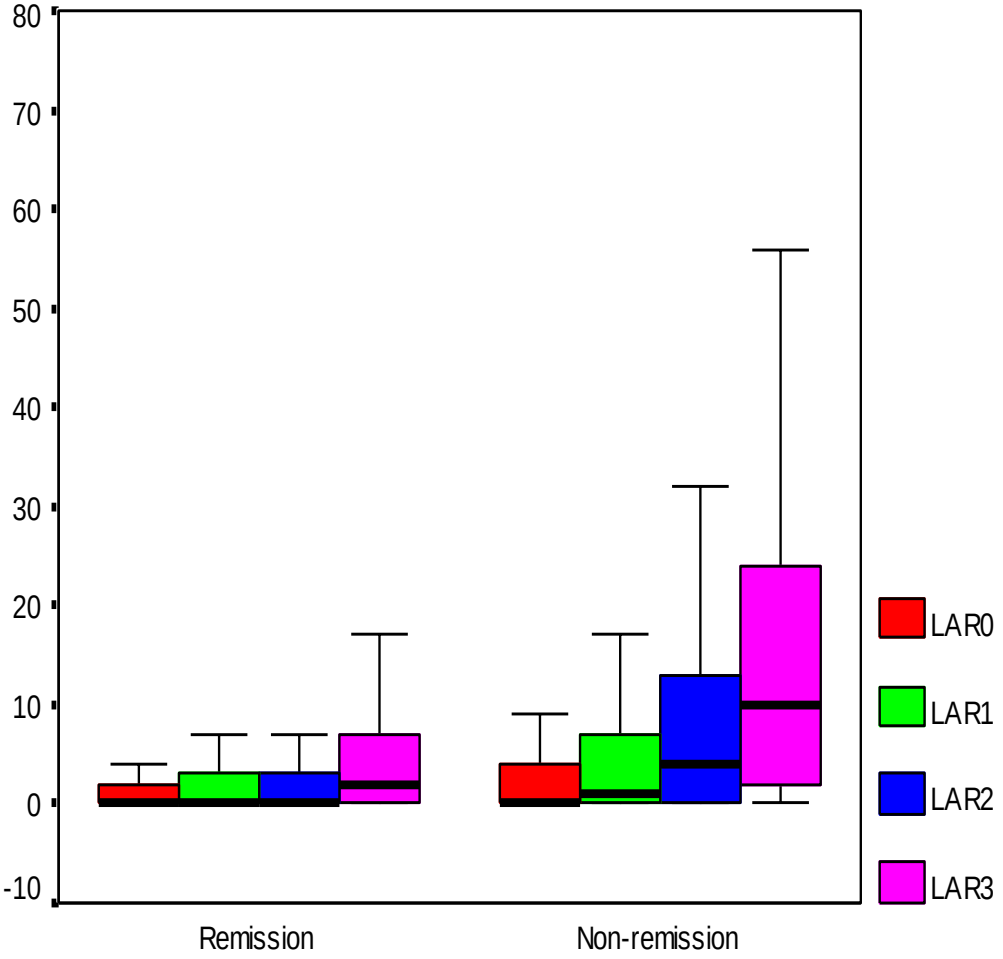
DAS remission

90 out of 1003 patients (9%) were found to be in sustained DAS remission at 1, 2 and 3 years although more patients achieved remission at individual time points (yr 1 = 21%; yr 2 = 25%; yr 3 = 23%). Out of 209 patients who were in remission at yr 1, 63% (n=132) remained in remission at year 2 and 43% (n=90) remained in remission at both yr 2 and 3.

DMARD use in the remission group was 70% (mono=66%, combi=4%) at yr1 and 72% (mono=68%, combi=4%) at year 3. DMARDs, either as mono or combination therapy were used more frequently in the non-remission group and the difference was significant at year 3 (83% vs 72%; $p < 0.001$). In both groups, median time to the start of first DMARD was 2 months and SSZ was the most commonly used DMARD followed by MTX. Mean DMARD use in remission group was 0.77 (range 0-2) at the end of 3 years and in the non-remission group it was 1.3 (range 0-6). Although more patients received oral steroids in the non-remission group (16% vs. 9%), the difference was not statistically significant (p=0.4)

Radiological progression

Figure 6.1 Radiological progression (Larsen) in relation to cumulative clinical disease activity



Legend for figure 6.1

LAR0 = Larsen score at baseline

LAR1 = Larsen score at year 1

LAR2 = Larsen score at year 2

LAR3 = Larsen score at year 3

Figure 6.1 shows that structural damage on hands and feet x-rays has progressed in both groups during the study period but it was relatively less in patients with persistent DAS remission. In the remission group, median Larsen score progressed from 0 to 2 (mean 2.8 → 6.6; p <0.001) between baseline and yr 3, whereas in the non-remission group, it increased from 0 to 10 (mean 4.5 →16.5; p <0.001).

Radiographic progression was also analysed at individual level in patients who had serial x-rays throughout the study period [remission = 78 (87%); non- remission= 719 (79%)]. 17 out of 78 patients (22%) in the remission group showed radiographic progression above SDD (≥ 4) i.e. an increase in Larsen score of ≥ 4 during the study period, and the corresponding figure in the non-remission group was 363 (50%).
Amongst patients showing significant x-ray progression, a majority of them did so between yr 2 and 3 (82% and 64% in the remission and non-remission groups respectively). Although only 17 out of 78 patients (22%) showed Larsen score progression of ≥ 4 (above SDD) during the study period, 19 patients (24%) actually developed new erosions during this time, (2 pts at yr 2, 16 pts at yr 3 and one patient at both time points) and 5 (26%) of them were DMARD naïve.

Radiographic progression despite DAS remission

Patients in DAS remission who had serial x-rays (n=78) throughout the study period were divided into two subgroups, based on SDD, for further analysis:

Group1 = DAS remission without significant x-ray progression (n=61)

Group2 = DAS remission with significant x-ray progression (n=17)

Table 6.2 Baseline disease characteristics in Group1 (DAS remission without significant x-ray progression and Group2 (DAS remission with significant x-ray progression)

Baseline variable	**Group1** (n=61)	**Group2** (n=17)	**p-value**
Women∗	64% (39)	24% (4)	< **0.01**
Age of disease onset (years)	52.4 (± 15.3)	51.9 (± 14.1)	0.87
Duration of symptoms (months)	6.6 (± 5.1)	8.1 (± 6.2)	0.43
RF positive∗	61% (37)	59% (10)	0.89
Erosions∗	18% (11)	47% (8)	< **0.05**
ESR	37.3 (± 23.9)	46.8 (± 36)	0.53
DAS	3.4 (± 1.5)	3.4 (± 1.2)	0.78
HAQ	0.90 (± 0.75)	0.88 (± 0.78)	0.97
Larsen [Median (IQR)]	0 (0-1.75)	3 (0-15)	-

Values are expressed as mean (± SD) unless otherwise indicated

∗ % (count)

RF = Rheumatoid factor

ESR = Erythrocyte sedimentation rate

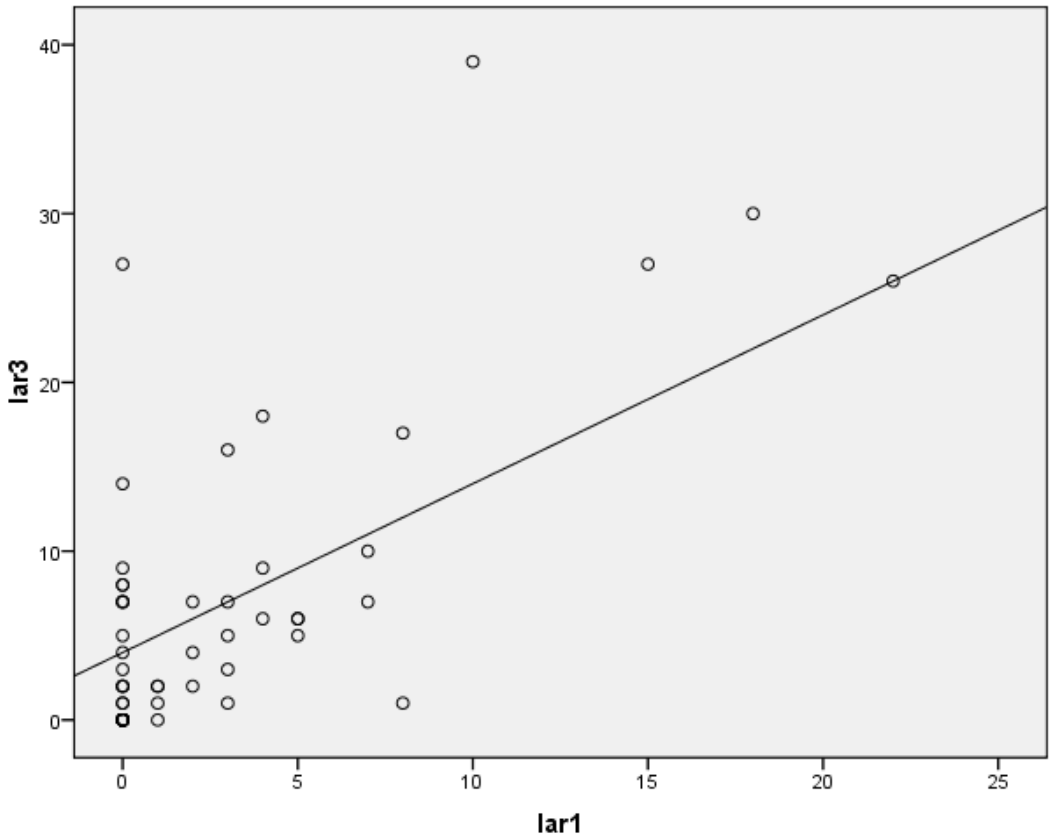
DAS = Disease activity score

HAQ = Health assessment questionnaire

Baseline disease characteristics of patients in persistent remission with or without x-ray progression are shown in the above table. There were fewer women and more patients with erosive disease at baseline in Group2 who went onto have x-ray progression despite clinical remission.

There was no significant difference in the DMARD use between Groups 1 and 2 at yr1 (67% vs 71%; p=0.95), and by 3 years 71% of patients were on DMARDs in both groups. SSZ was the most frequently used first line DMARD in both groups and there was no significant difference in the time to initiate first DMARD between the two groups. Steroid use by 3 years was 8% and 12% in Groups 1 and 2 respectively (p=0.78).

Fig 6.2 Scatter plots showing change in Larsen scores from yr1 (lar1) to yr3 (lar3) in patients in persistent DAS remission (n=78)



X-axis = Larsen score at year 1

Y-axis = Larsen score at year 3

Reference line indicates smallest detectable difference (SDD) for this study

Circles on or above the reference line are patients who had increase in their Larsen score of ≥ 4 (significant x-ray progression) between year 1 and 3 (n=17), whereas circles below the reference line indicate patients with a change in Larsen score of < 4 (non- significant x-ray progression) during the study period (n=61).

Predictive factors for x-ray progression despite DAS remission

Table 6.3 Baseline predictive factors using univariate and multivariate analyses

Baseline variable	Univariate		Multivariate		
	OR	**95% CI**	**OR**	**95% CI**	**p-value**
Men	5.7	1.6 – 19.8	5.3	1.4 - 20	< **0.05**
Erosive disease	4.0	1.2 – 12.8	1.5	0.3 – 9.1	0.67
Larsen score	5.0	1.5 – 15.9	3.3	0.6 - 20	0.18
Age of onset	0.7	0.2 – 2.3			
Duration of symptoms	1.3	0.4 – 4.0			
RF	0.9	0.3 – 2.7			
Shared epitope	0.7	0.1 – 2.5			
ESR	1.0	0.3 – 2.9			
DAS	1.9	0.2 – 17.0			
HAQ	1.1	0.3 – 3.5			
DMARD by 1 year	1.0	0.3 – 3.5			

OR = Odds ratio, CI = Confidence interval

RF = Rheumatoid factor

ESR = Erythrocyte sedimentation rate

DAS = Disease activity score

HAQ = Health assessment questionnaire

DMARD = Disease modifying anti-rheumatic drug

Men, erosive disease and Larsen score at baseline showed prognostic value for subsequent x-ray progression in this study. However, only male sex showed independent predictive value for radiographic progression despite sustained DAS remission and other variables including age of onset, duration of symptoms, RF and DMARDS at 1 year did not show any prognostic value.

Outcomes

Table 6.4 Outcomes at 3 years in Groups 1 & 2 in relation to x-ray progression

Disease groups	**Erosions**	**Larsen score** Median (IQR)	**HAQ** Mean (SD)	**FG I & II**	**Stopped working**	**Surgery**
DAS remission without significant x-ray progression (n=61)	25 (41%)	1 (0-4.5)	0.16 (0.32)	61 (100%)	2 (3%)	3 (5%)
DAS remission with significant x-ray progression (n=17)	13 (76%)	16.5 (8-29)	0.04 (0.07)	17 (100%)	1 (6%)	1 (6%)
p-value*	**<0.05**	**<0.001**	0.31	-	0.86	0.85

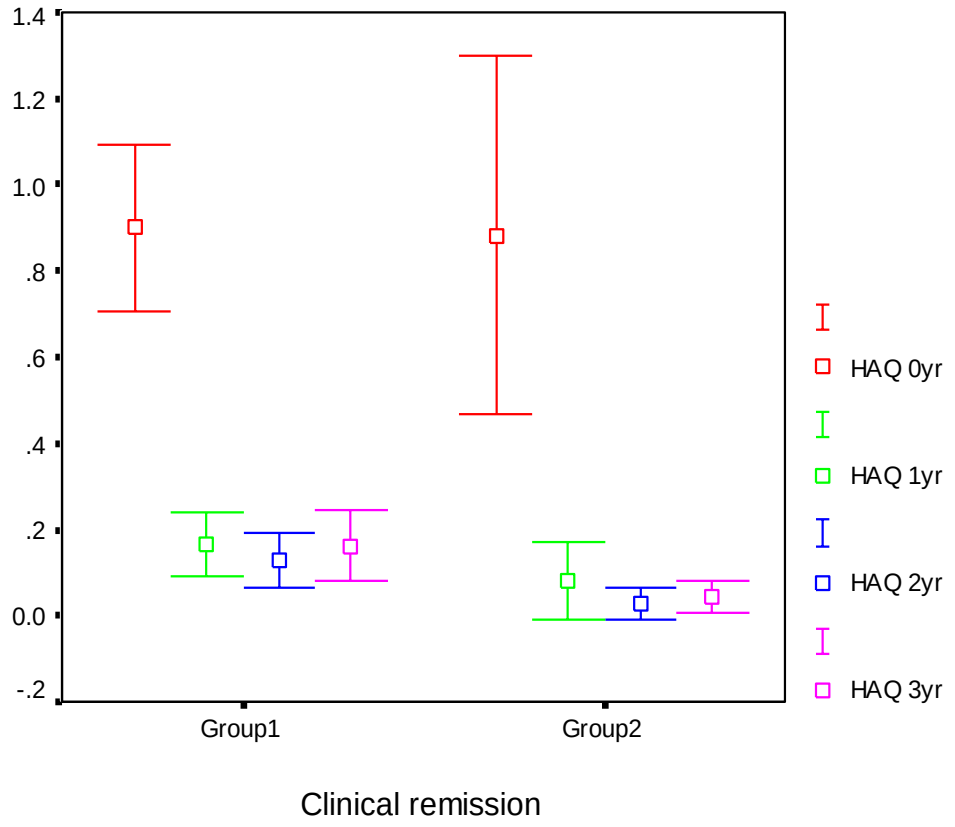
* p-value based on chi-square (categorical variables) and Mann Whitney tests (HAQ)

DAS = Disease activity score

HAQ = Health assessment questionnaire

FG = Functional grade

Figure 6.3 Functional (Health assessment questionnaire/HAQ) progression in Groups 1 & 2



Legend for figure 6.3

HAQ 0yr = HAQ score at baseline

HAQ 1yr = HAQ score at year 1

HAQ 2yr = HAQ score at year 2

HAQ 3yr = HAQ score at year 3

In Group1 (DAS remission without significant x-ray progression), 41% had erosive disease at 3 years and median Larsen score increased from 0 to 1 (mean 1.2 → 2.6; $p<0.005$) during the study period. However, in Group2 (DAS remission with significant x-ray progression), 76% had erosive disease at 3 years and median Larsen score progressed from 4 to 16.5 (mean: 5.9 → 21.5; $p<0.005$) between the study points.

Further attempts to explore the correlation between Larsen scores and various clinical and laboratory disease indices in Group 2 did not explain the dissociation between clinical and x-ray progression in this group.

HAQ score was not significantly different between Groups 1 and 2 at yr-3 (0.16 vs 0.04; $p=0.44$) and both groups were very similar in their functional ability. Also, there was no significant difference in other outcomes such as extra-articular disease, work disability and orthopaedic surgery between the two sub-groups, although there was a marked difference in radiographic progression.

6.5 Discussion

The results of this study are consistent with previous reports that sustained remission is less frequent than remission at individual study points and structural damage can progress despite clinically inactive disease (243;254). Although several studies have looked at the frequency of remission in early RA, there is only limited information from prospective studies about longitudinal radiographic progression during sustained remission. The results so far have been conflicting, as some studies have shown reduced radiographic progression in patients with clinically inactive disease (80;239),

whereas in other studies significant x-ray damage progression was noted despite remission (243;288).

In a study by Molenaar et al, 187 RA patients (median disease duration 7 years) who were in modified ARA remission for at least 6 months were followed-up for 2 years (243). Remission persisted in 52% of patients at 2 years and clinically relevant radiographic progression despite remission (above SDD) was noted in 7%. DAS area under the curve (AUC) was a stronger predictor of radiographic progression than was the absence of persistent remission and 15% of patients developed new erosions despite disease inactivity.

In a French, multi-centre, prospective study of early RA patients (n=191), frequency of DAS remission at year3, year5 and at both study points were 25%, 20% and 16% respectively (223;288). Radiological damage progression at group level was not significant during sustained remission. However at individual level, 5 out of 30 patients (16.7%) showed x-ray progression above SDD and 20% developed new erosions.

In the ERAS cohort, 22% showed significant x-ray progression despite DAS remission (above SDD) and 24% developed new erosions. Male sex and baseline x-ray damage showed predictive value for subsequent radiographic progression despite DAS remission. In this cohort, Larsen method was used to assess x-ray progression as opposed to above two studies, which used SvdH method. Furthermore, x-rays were scored in random order in the ERAS cohort, as was in the study by Molenaar et al, whereas in the French study the films were scored in chronological order. As described in the previous chapter, apart from disease characteristics, scoring

methodology in these studies could have influenced the different results observed in these cohorts. Nonetheless, all these studies including the ERAS have shown that the total number of patients who had developed new erosions during the study was actually higher than those reported to show significant radiographic progression (above SDD). Therefore, although SDD can be used to show x-ray progression above measurement error, there is a chance that patients below the SDD cutoff may still have clinically significant progressive disease.

There may be other explanations for progressive x-ray damage despite remission, and these include: 1) residual tender or swollen joint counts despite fulfilling DAS or DAS 28 remission criteria because of the weighting in the formulas (264-266); 2) lag time between clinical disease activity and the appearance of erosions on x-rays (268;269); 3) presence of sub-clinical synovitis in apparently normal looking joints, shown up only on US or MRI (270).

Brown et al studied radiological progression in RA patients in clinical remission using x-rays, US and MRI. At 12 months, a majority of patients in clinical remission showed evidence of inflammation on US and MRI (289). Radiographic progression in this cohort was analysed using SDC and 16% of patients with asymptomatic joints (no pain, swelling or tenderness) showed significant x-ray progression and the respective figures in the ACR and DAS 28 remission groups were 11% and 12%. Baseline predictors for subsequent x-ray progression in this study were positive power Doppler (PD) signal (OR 12.2) and synovial hypertrophy (OR 2.3) on US and presence of synovitis (OR 2.9) on MRI.

Other possible reason for radiographic progression despite inactive disease could be treatment effect, as discussed in chapter 4. Only 72% of the study patients in clinical remission were on DMARDs by 3 years and out of them 4% received combination therapy. Also, SSZ was the most common DMARD in this study and it has been shown that SSZ as monotherapy may be less effective in reducing joint damage (232). None of the study patients received biological agents and it has been shown that these novel agents could reduce radiographic progression independent of clinical improvement (247). It may be due to the inhibitory effect of anti-TNF on osteoclast induced bone resorption, independent of clinical disease activity, mediated via specific molecules such as receptor activator of nuclear factor kappa β ligand (RANKL) and osteoprotegerin (248).

The advantage of this study is that it was observational and patients were managed in a 'real life setting' with traditional DMARDs. Also, it is the first to report on baseline disease variables, particularly male sex, as predictors of progressive structural damage despite DAS remission in early RA.

One of the study limitations, as described earlier, is that the assessments were made annually and so possibility of disease exacerbations in between the study assessments. Nonetheless, patients were reviewed in the clinic every 3 to 6 months and there was no evidence of disease flares that required treatment change.

In conclusion, this study showed that significant x-ray damage could still occur during sustained DAS remission. Gender and radiographic status of the disease at baseline may have a prognostic value in determining subsequent radiographic progression in

patients in sustained DAS remission. Patients in persistent DAS remission had better outcomes despite differences in radiographic progression.

X-rays of hands and feet at regular intervals in early RA may prove to be crucial in monitoring disease progression, even in patients with clinically inactive disease. This in turn might influence the treatment decisions and may have an impact on long-term outcomes. Further long-term randomised studies may be of more prognostic value in studying radiographic progression in clinically inactive or low-grade RA.

CHAPTER 7

DISEASE PROGRESSION AND OUTCOMES IN EARLY RHEUMATOID ARTHRITIS

7. DISEASE PROGRESSION AND OUTCOMES IN EARLY RHEUMATOID ARTHRITIS

7.1 Background

The natural course of rheumatoid arthritis (RA) can be variable and unpredictable in many patients. Although the most common disease course is chronic and progressive, it can vary or fluctuate depending upon the patients' or disease characteristics and treatment effect (5;6). The level of clinical disease activity at a given time point or over a period of time can be graded as remission, low, moderate and high using the disease activity scores (DAS & DAS28), based on EULAR criteria (79;84)

Active RA is usually associated with progressive x-ray damage, which is monitored by x-rays of hands and feet at regular intervals. Structural damage seen on x-rays is quantified by various scoring methods and they are considered as vital outcome measures in most of the RA clinical trials (87;149;222). Although several scoring methods have been developed over the years, Larsen, Sharp and their modifications e.g. Sharp-van der Heijde method (SvdH) are the most commonly used (181-184;186-188).

Patients with active disease often develop progressive decline in their functional ability and this is usually assessed by patient self-reported health assessment questionnaires (HAQ) (124). Other measures that have been used to assess functional disability include Steinbrocker's functional grade (FG I-IV) and grip strength (12;124).

Outcomes in RA can either be due to the disease itself (disease specific) or due to the consequence of the disease (non-disease specific). Remission, radiographic damage, functional disability and orthopaedic surgeries are examples for disease specific outcomes, whereas work disability, costs and mortality reflect non-disease specific outcomes. There is an overwhelming evidence to suggest that high disease activity and radiological damage is associated with poor outcomes including deformity, disability, high socioeconomic and other health care costs (12;114;115).

Several studies have already reported on disease progression and outcomes in RA. However, there is only limited information on the inter-relationship between clinical, functional and radiological disease progression over the first 5 years in early RA patients, treated with traditional disease modifying anti rheumatic drugs (DMARDs). Also, as far as is known, long-term outcomes in early RA patients who have persistent low disease or remission for as long as 5 years in the pre-biologic era has not been reported before.

Therefore, this study aimed to analyse the clinical and radiological disease progression (Larsen score) over 5 years in this early RA cohort and to examine the link between disease activity and radiological damage. This study also aimed to analyse long-term outcomes, both disease and non-disease specific, in the ERAS cohort in relation to cumulative clinical disease activity.

Furthermore, as part of this study, a subgroup analysis of radiological progression in patients in sustained DAS remission from year1 to year5, using SvdH method in chronological order, was also carried out. This is because of the earlier findings

described in chapter 6. It showed that around one fifth of ERAS patients in sustained DAS remission from year1 to year3 developed significant x-ray progression, using Larsen method in random order, with no worsening of 3-year functional outcomes. However, previous studies have shown that both Larsen method and random reading of x-rays may not be as sensitive as SvdH and chronological scoring, to detect clinically meaningful radiographic progression i.e. progression above measurement error (157;160;161;181-184;186-188). Therefore, it was the intention of this thesis to analyse longitudinal x-ray progression, using SvdH method in chronological order, in a subgroup of ERAS patients who were in sustained DAS remission for as long as 5 years. 5-year outcomes in relation to x-ray progression were also analysed.

7.2 Objectives

1. To study clinical, functional and radiological disease progression over 5 years in the ERAS cohort
2. To evaluate long-term outcomes in relation to cumulative disease activity
3. To analyse radiographic progression, using SvdH method in chronological order, in a subgroup of patients who were in persistent DAS remission from year1 to year5

7.3 Patients and Methods

Patients

For the purpose of this study, only those ERAS patients who have completed at least 5 year follow-up and have had their annual DAS recorded between baseline and year5 were selected (n=653). A total of 304 patients failed to complete 5 year follow- up due to various reasons as follows: attends another hospital (n=7; 2%), moved (n=25; 8%), unable to attend (n=3; 1%), declined (n=18; 6%), patient reported remission (n=9; 3%), deceased (n=195; 64%), discharged (n=1), not known (n=20; 7%) and not traced (n=26%; 9%).

A separate analysis of this patients who were excluded from the study showed that baseline disease characteristics were similar to the study cohort except that mean age of disease onset (60 vs 54; $p < 0.001$) and clinical disease activity (DAS 4.5 vs 4.2; $p < 0.05$) were slightly higher at study entry in this group.

Clinical assessment

Details of patient recruitment and study assessments for the ERAS have already been described in detail in the previous chapters. Standard assessments including age of onset, disease duration, ACR diagnostic criteria, swollen joint count (SJC), Ritchie articular index (RAI), erythrocyte sedimentation rate (ESR), IgM RF, HLA-DRß shared epitope (SE) status and extra-articular disease were recorded at baseline and then at regular intervals.

Clinical disease activity in the study cohort was assessed using the original 3-variable as described earlier (141) and disease activity was graded as remission, low, moderate or high, based on DAS, using the EULAR response criteria (79)

.	DAS < 1.60	-	remission
	DAS ≥1.60 and ≤ 2.40	-	low disease activity
	DAS >2.40 and ≤ 3.70	-	moderate disease activity
	DAS> 3.70	-	high disease activity

For the purpose of this analysis, study patients were grouped as persistent low disease, persistent moderate or high disease and fluctuating disease, based on their cumulative DAS at 1st, 2nd, 3rd, 4th and 5th year follow-ups. Patients who had DAS ≤ 2.40 at all the study points were classified as persistent low disease and patients with DAS of > 2.40 through out the study period were grouped as persistent moderate or high disease and the remaining patients with variable DAS were named as fluctuating disease group.

A further subgroup analysis of patients in the persistent low disease group, who had DAS < 1.6 at all the study points (persistent DAS remission), was also carried out to explore radiographic progression using SvdH method and prognostic factors.

Radiographic assessment

X-rays of hands and feet were done at baseline and then at 1, 2, 3 and 5 years. Details of storage of films on CD-ROM and scoring of x-rays using Larsen method (total score 0 – 200) in random order by an independent observer (CS) have already been described.

X-ray scoring methodology for the subgroup analysis

As a subgroup analysis, observer KJ has scored radiographic progression in patients in persistent DAS remission, using Sharp van der Heijde (SvdH) method in chronological order. This is because previous analyses in this thesis showed that

SvdH method in chronological order is more sensitivity in detecting radiographic progression at individual level. The films were retrieved by the ERAS coordinator from the original database and observer KJ was unaware of the clinical details including treatment and Larsen scores by observer CS, whilst reading the x-rays. Serial x-rays of ERAS patients with different levels of disease activity were also randomly selected and mixed together with x-rays of persistent remission subgroup to avoid expectation bias for the reader and to make the analysis valid.

Functional assessment

Functional ability of the ERAS patients was assessed at the time of study entry and then at regular intervals using Steinbrocker's functional grade and HAQ as described in the earlier chapters.

Other outcome assessments

Outcome measures other than clinical, radiological and functional assessments were also recorded at baseline, 3 and 5 years. This included job status, allowances, use of standard aids and appliances such as splints, walking aids and major adaptations (wheel chair, stair lifts, hoists). All types of orthopaedic surgeries were also recorded and other details including co-morbidities and mortality were also recorded.

Treatment

The study cohort's treatment profile was similar to the rest of the ERAS cohort. Patients were treated with standard DMARD therapy either as sequential monotherpy or as step-up combination therapy depending upon the disease severity and physician's choice. Steroids were used in a small proportion of patients.

Statistical analysis

Summary statistics have been used to demonstrate the differences in clinical and laboratory features with disease outcomes. Continuous variables were expressed as either mean with standard deviation (SD) or median with interquartile ranges (IQR) and categorical variables were shown as counts with percentages. Chi square (χ^2) for categorical variables and Mann Whitney U (MWU) or Kruskal-Wallis H (KWH) for non-parametric and ANOVA for parametric data were used to compare the study groups.

Radiographic progression at group level was analysed using summary statistics and absolute scores, whereas at individual level smallest detectable difference (SDD) was used to detect significant x-ray progression i.e. progression above measurement error (185). SDD for SvdH method in this study was calculated as described in the previous chapters and the values are as follows: SDD for erosion = 3; narrowing = 4; and total score = 5.

Univariate analysis using odds ratios (OR) and multiple logistic regression, using stepwise procedure were performed to study prognostic factors for radiological progression. Variables used for the multivariate model were chosen from the univariate analysis and a p-value of ≤ 0.05 (two sided) was considered statistically significant.

7.4 Results

Baseline disease characteristics of the whole study cohort as well as the individual study groups are shown below.

Table 7.1 Baseline demographics

Disease variables	Whole cohort (n = 653)	Low disease (n = 101)	Mod/High disease (n = 222)	Fluctuating disease (n = 330)
Women *	428 (65%)	52 (52%)	170 (77%)	206 (62%)
Age of onset (years)	54 (13.7)	54 (14.2)	57 (13.2)	52 (13.6)
Disease duration (months) #	7 (4-12)	5 (3-8)	7 (4-12)	7 (4-12)
RF positive *	425 (65%)	61 (61%)	138 (62%)	226 (69%)
SE positive*	372 (71%)	51 (67%)	137 (72%)	184 (71%)
Erosions *	173 (27%)	25 (25%)	66 (30%)	82 (25%)
DAS	4.2 (1.6)	3.4 (1.4)	4.9 (1.6)	3.9 (1.4)
HAQ	1.0 (0.7)	0.8 (0.7)	1.3 (0.7)	0.9 (0.7)
Larsen #	0 (0-4)	0 (0-2)	0.5 (0-5)	0 (0-4)
DMARDs by 1 year *	492 (75%)	69 (68%)	181 (82%)	242 (73%)
Extra-articular disease*	116 (18%)	17 (17%)	46 (21%)	53 (16%)

Values are expressed as mean (± SD) unless otherwise indicated

*Count (%), # Median (IQR)

RF = Rheumatoid factor, SE = Shared epitope,

DAS = Disease activity score, HAQ = Health assessment questionnaire

DMARDs = Disease modifying anti-rheumatic drugs

Table 7.1 shows that patients who went on to have persistently low disease had less disease activity (DAS) and low disability score (HAQ) at baseline with better prognostic features (men, short disease duration, and negative RF) compared to other two groups.

Treatment

DMARDs were used less frequently in patients low disease (Group1) compared to patients with moderate/high disease (Group2) or fluctuating disease (Group3) at all time points. DMARD use at year 3 was: Group1 = 71% (monotherapy 60%; combination therapy 11%), Group2 = 92% (mono 42%; combi 50%), Group3 = 82% (56%; combi 26%); p <0.001 and at year 5: Group1 = 72% (mono 58%; combi 14%), Group2 = 93% (mono 28%; combi 65%), Group3 = 85% (mono 45%; combi 40%); p <0.001. Steroids were used in 11%, 19% and 14% of patients in Groups1, 2 and 3 respectively at 5 years (p =0.10).

Sulphasalazine (SSZ) was the most frequently used first line DMARD in all three groups (Gr1 = 82%, Gr2 = 80%, Gr3 = 80%; p =0.90) and methotrexate (MTX) was the most common second line DMARD (Gr1 = 59%, Gr2 = 52%, Gr3 = 50%; p <0.005). Median time to start of first DMARD was 2 months in all three groups.

Clinical disease progression

Cumulative clinical disease activity during the study period is shown below.

Table 7.2 Clinical disease progression based on DAS

Disease activity	Disease activity score (DAS)					
	Baseline	**Year1**	**Year2**	**Year3**	**Year4**	**Year5**
Low (Gr1) Mean (SD)	3.4 (1.4)	1.3 (0.5)	1.2 (0.4)	1.3 (0.5)	1.2 (0.4)	1.4 (0.5)
Mod/High (Gr2) Mean (SD)	4.9 (1.6)	4.4 (1.3)	4.5 (1.4)	4.7 (1.4)	4.8 (1.4)	4.6 (1.4)
Fluctuating (Gr3) Mean (SD)	3.9 (1.4)	2.6 (1.3)	2.4 (1.2)	2.6 (1.3)	2.6 (1.3)	2.8 (1.3)

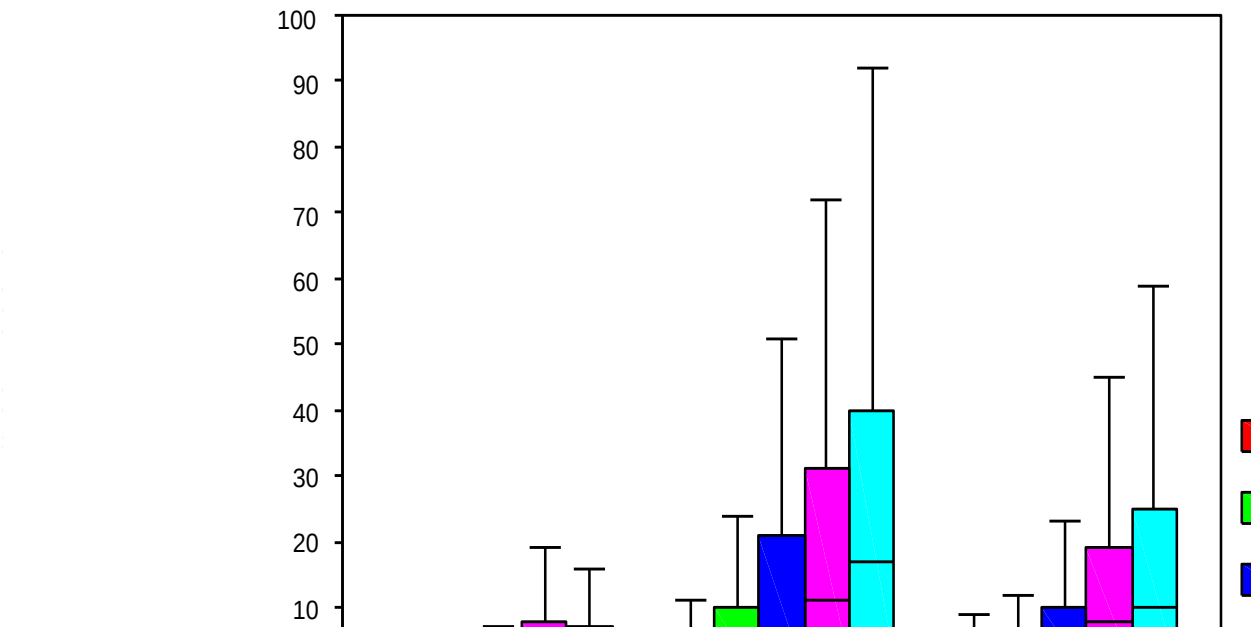
Radiographic progression

X-ray progression between baseline and year 5 is shown in table 7.3 and fig 7.1

Table 7.3 Radiographic progression in relation to clinical disease activity

Disease activity	Larsen score				
	Baseline	**Year1**	**Year2**	**Year3**	**Year5**
Low disease (Gr1)					
Mean (SD)	2.0 (4.3)	1.9 (3.9)	2.9 (5.5)	5.8 (7.9)	7 (10.2)
Median (IQR)	0 (0-2)	0 (0-2.25)	0 (0-3.50)	2 (0-8)	3 (0-7)
Mod/High (Gr2)					
Mean (SD)	5.6 (12.3)	7.3 (13.7)	12 (15.5)	19.3 (21)	23.4 (24)
Median (IQR)	0.5 (0-5)	1 (0-10)	5.5 (0-21)	11 (2-31)	17 (3-40)
Fluctuating (Gr3)					
Mean (SD)	4.2 (9.8)	5 (9.7)	8 (12.8)	13.6 (17)	16 (18.8)
Median (IQR)	0 (0-4)	1 (0-5)	3 (0-10)	8 (1-19)	10 (1-25)

Figure 7.1 Larsen score progression between baseline and year 5 in all the study groups



Legend for figure 7.1

LAR0 = Larsen score at baseline

LAR1 = Larsen score at year 1

LAR2 = Larsen score at year 2

LAR3 = Larsen score at year 3

LAR5 = Larsen score at year 5

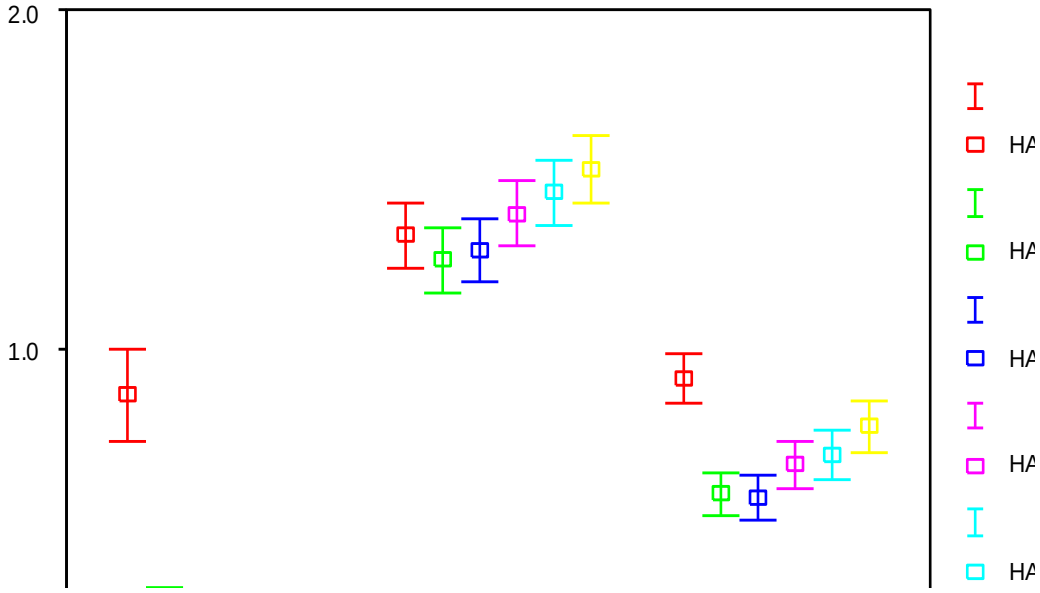
It is clear from the above tables and graphs that patients with persistently high or fluctuating disease activity showed increased x-ray damage progression, compared to patients with low disease during the study period.

Functional progression

Table 7.4 Functional (HAQ) progression in relation to clinical disease activity

Disease activity	Health assessment questionnaire (HAQ) score					
	Baseline	**Year1**	**Year2**	**Year3**	**Year4**	**Year5**
Low (Gr1) Mean (SD)	0.8 (0.7)	0.2 (0.4)	0.2 (0.4)	0.2 (0.4)	0.1 (0.3)	0.2 (0.4)
Mod/High (Gr2) Mean (SD)	1.3 (0.7)	1.2 (0.7)	1.3 (0.7)	1.4 (0.7)	1.4 (0.7)	1.5 (0.7)
Fluctuating (Gr3) Mean (SD)	0.9 (0.6)	0.5 (0.6)	0.5 (0.6)	0.6 (0.6)	0.7 (0.6)	0.7 (0.7)

Figure 7.2 Health assessment questionnaire (HAQ) progression between baseline and year 5 in all the groups



Legend for figure 7.2

HAQ 0yr = HAQ score at baseline

HAQ 1yr = HAQ score at year 1

HAQ 2yr = HAQ score at year 2

HAQ 3yr = HAQ score at year 3

HAQ 4yr = HAQ score at year 4

HAQ 5yr = HAQ score at year 5

The above table and figure show that baseline HAQ scores were relatively lower in patients with persistently low disease, which then subsequently improved over the next 5 years. In patients with fluctuating disease, mean HAQ score has improved from baseline to year1, then stabilised until year2 after which, it showed gradual, but continued deterioration over the next 3 years. Patients in the active disease group had higher HAQ scores at the study start with little improvement over the next year and then progressive decline in functional ability.

Outcomes

Long-term outcomes were assessed at the end of 5 years in the study groups in relation to their preceding cumulative clinical disease activity.

Table 7.5 Outcomes in relation to cumulative clinical disease activity

Disease activity	**Erosive disease**	**Marked x-ray damage (Larsen > 10)**	**Functional disability (FG III & IV)**	**HAQ > 1.5**
Low (Group 1)	58 (57%)	16 (19%)	2 (2%)	1 (1%)
Mod / High (Group 2)	183 (83%)	105 (61%)	62 (28%)	106 (48%)
Fluctuating (Group 3)	257 (78%)	133 (49%)	24 (7%)	48 (14%)
p-value	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**

FG = Functional grade, HAQ = Health assessment questionnaire

Table 7.6 Other outcomes in relation to cumulative clinical disease activity

Disease activity	**Stopped working**	**Stopped working due to RA**	**Extra-articular disease**	**Major orthopaedic surgery**	**Mortality**
Low (Group 1)	10 (10%)	3 (37%)	23 (23%)	2 (2%)	13 (13%)
Mod/High (Group 2)	44 (20%)	35 (85%)	96 (43%)	25 (12%)	62 (28%)
Fluctuating (Group 3)	50 (16%)	33 (72%)	102 (31%)	19 (6%)	63 (19%)
p-value	**< 0.001**	**< 0.05**	**< 0.001**	**< 0.001**	**< 0.005**

The above tables show that patients with persistent low disease had better outcomes at 5 years, compared to other two groups with persistently high or fluctuating disease activity.

Subgroup analyses

1. Radiographic progression, using SvdH method in chronological order, in patients in persistent DAS remission from year 1 to year 5
2. Prognostic factors and outcomes in relation to radiological progression in patients in persistent DAS remission

A total of 37 patients from Group1 (persistent low disease), who had DAS < 1.6 at all the study points i.e. year1, 2, 3, 4 and 5 (persistent DAS remission) were analysed separately to study radiographic progression, prognostic factors and outcomes.

This subgroup analysis, to some extent, was similar to the methodology described previously in chapter 6. However in chapter 6, Larsen method in random order was used to study radiographic progression during sustained remission and the study duration was for 3 years. In this subgroup analysis though, SvdH method in chronological order was used to assess x-ray progression during sustained remission and the study period was extended up to 5 years.

Radiographic progression

Structural damage progression on x-rays from year1 to year 5 in patients in persistent DAS remission was measured using SvdH method in chronological order. X-ray progression was analysed both in terms of absolute scores and clinically meaningful

change, using smallest detectable difference (SDD = 5). 19 patients did not have erosions at year1and 13 of them remained non-erosive at 5 years.

Although, 28 out of 35 patients (80%; 2 missing) showed an increase in total SvdH score of ≥ 1 between the study start and end points, only 15 of them (43%) showed clinically meaningful x-ray progression i.e. increase in SvdH score of > 5 (SDD) between the study points. In those 15 patients with significant x-ray progression, only 2 were due to new erosions and the rest were mainly due to joint space narrowing (JSN).

In order to analyse outcomes and prognostic factors, the patients (n=35) were further subdivided into two groups, based on radiographic progression using SDD, Group1: DAS remission without significant x-ray progression (n=20) and Group 2: DAS remission with significant x-ray progression (n=15)

Baseline disease characteristics of this subgroup of patients are as shown below.

Table 7.7 Baseline demographics

Baseline variable	DAS remission without significant x-ray progression (n=20)	DAS remission with significant x-ray progression (n=15)	p-value
Women	14 (70%)	5 (33%)	< **0.05**
Age of onset (years)	47.1 (14.6)	58.2 (15.7)	<**0.01**
Duration of symptoms (months)[#]	6 (4-10.75)	6 (3-7)	0.38
RF positive	9 (45%)	12 (80%)	<**0.05**
SE positive	9 (64%)	9 (75%)	0.68
Erosions	4 (20%)	4 (27%)	0.70
ESR*	39 (24)	47 (22)	0.41
DAS*	3.3 (1.3)	4.2 (1.3)	0.07
HAQ*	0.9 (0.7)	1.0 (0.5)	0.56
SvdH[#]	1.5 (0-5.5)	6 (0.5-10.5)	0.08

Values are expressed as count with percentages unless specified otherwise

* Mean (SD)

[#]Median (IQR)

RF = Rheumatoid factor, SE = Shared epitope

ESR = Erythrocyte sedimentation rate

DAS = Disease activity score

HAQ = Health assessment questionnaire

SvdH = Sharp-van der Heijde score

Both groups were similar except that in patients with DAS remission but x-ray progression, there were more men with higher age of disease onset and more RF positivity at baseline.

There was no significant difference in DMARD use between the two groups, both at study start and at the end (both at year1 & year5 = 55% vs 87%, p =0.06) as was the use of steroids at 5 years (5% vs 7%, p =0.35).

Prognostic factors for radiographic progression despite DAS remission: Predictive value of baseline variables for subsequent x-ray progression in patients in persistent DAS remission was tested using univariate and multivariate analyses.

Table 7.8 Univariate analysis

Baseline variable	Odds ratio (OR)	95% CI
Men	4.7	1.1 - 19.6
Rheumatoid factor (RF)	4.9	1.0 - 22.8
Shared epitope (SE)	1.7	0.3 – 9.1
Erosive disease	1.5	0.3 – 7.0
Sharp-van der Heijde (SvdH) score > 5	4.8	1.1 – 21.7

Male sex, RF and SvdH score at baseline showed significant predictive value for radiographic progression despite persistent DAS remission on univariate analysis. However, none of the baseline variables showed any prognostic value on multivariate model using logistic regression.

Outcomes

Long-term outcomes at 5 years in patients in persistent DAS remission in relation to their x-ray progression were analysed. There was no significant difference in functional disability between the two groups at 5 years (mean HAQ 0.0 vs 0.1; p =0.69), but more patients stopped working by 5years in the DAS remission with x-ray progression group (20% vs 5%; p <0.05). Use of allowances was not significantly different between the two groups (n = 0 vs 2; p =0.22) and none of the patients in either group required home adaptations or major orthopaedic surgeries.

7.5 Discussion

This study results confirm previous findings that clinical disease activity is directly related to subsequent radiographic progression and long-term outcomes (55;57;69). It also showed that sustained disease inactivity is more important than intermittent remission or low disease state at individual time points as the former group achieved better outcomes.

Patients with persistent disease activity were treated with DMARDs more frequently than patients with low or inactive disease and this was an expected finding as clinicians usually make their treatment decisions depending upon the disease severity. Nonetheless, there was no significant difference in the choice of first line DMARD (SSZ) or the time to initiate first DMARD (median 2 months) in either of these groups. Therefore in general, this study cohort was treated with standard DMARD regime that was widely prevalent during that period of pre-biologic era in the UK i.e. between 1988 and 1998 (12).

Although several studies have reported on disease progression and outcomes in RA, there is only limited information on early RA patients who had persistent low disease and treated with traditional DMARDs in a 'real-life setting' like ERAS. Patients with fluctuating disease activity showed significant x-ray damage progression and poor outcomes compared to persistent low disease, emphasizing the benefits of sustained disease control.

Previous studies have shown that time-integrated measures of disease activity such as, area under the curve (AUC) for DAS and acute phase reactants correlate with radiological progression and treatments that control these measures lead to significant reduction in radiographic progression (138-140;242-244). Others, however, argued that time-averaged estimates for disease activity do not reflect individual variability within patients.

Welsing et al, studied the longitudinal relationship between disease activity and radiologic progression in two different early RA cohorts with a maximum follow-up of 9 years, by using a special regression technique called generalized estimating equations (GEE). They found that radiologic progression was not linear in individual patients and fluctuations in clinical disease activity (mean interval DAS and SD of the mean interval DAS) were directly related to changes in radiographic progression (245). Few other studies also confirmed that radiographic progression may be highly variable at individual level, particularly in early RA, although it is approximately linear at group level (90;100).

Functional disability can be labile in early RA with individual variation between patients, but it generally increases with disease duration at a fairly constant rate

(6;107). Patients in this study, who had fluctuating or persistent clinical disease activity showed continued worsening of the HAQ scores with progressive functional disability, particularly between year2 and year5.

Functional status of an individual is an important determinant of his or her employment and it is a good predictor of future work disability (56;57;109). Functional impairment due to active RA is associated with increased rates of work disability and has shown to be important predictor of employment outcome (56).

This study results show that persistent or fluctuating disease activity is associated with worse outcomes including increased work disability, higher frequency of extra-articular disease, more requirements for orthopaedic surgery and excess mortality compared to patients with sustained low or inactive disease throughout the study period.

It is reassuring to see that better outcomes can be achieved even in routine outpatient clinics with less aggressive use of DMARDs, as long as the disease is persistently low or inactive for a prolonged period. Several clinical trials, using various treatment strategies including biological agents, have demonstrated that more the improvement in disease activity less the joint damage and better the outcomes (233;234;236-241). Therefore, the ultimate goal of treatment in RA should be to control the inflammation as much as possible and to avoid structural damage in order to improve functional as well as socioeconomic outcomes.

Subgroup analyses in this study showed that nearly half of patients (43%) in persistent DAS remission developed significant x-ray progression (above SDD), based on SvdH method. However, clinically meaningful x-ray progression in patients in sustained

DAS remission appeared to be mainly due to JSN rather than new erosions in this study.

Other studies have also reported on significant x-ray progression despite clinical remission (243;288;289). However, no studies have looked at sustained remission in early RA for as long as 5 years and analysed prognostic value of baseline clinical variables for subsequent x-ray damage like this thesis. It is interesting to see that a previous analysis of sustained DAS remission between year1 and year3, as part of this thesis, also showed that male sex and baseline radiographic scores were predictive of x-ray progression.

None of the study patients with persistent low disease or remission received aggressive combination therapy or biological agents. This may partly explain the radiographic progression unrelated to clinical disease activity in this group, as previous studies using biological agents have shown that structural damage on x-rays could halt or improve even without significant clinical improvement, due to their novel mechanisms of action (247;248).

Functional ability of patients in persistent DAS remission with or without x-ray progression appeared to be good in this study cohort. Frequency of work disability was slightly more in patients in DAS remission with x-ray progression compared to those without x-ray progression, but the patient numbers were too small (3 vs 1) to derive any meaningful conclusion. Otherwise there was no difference in any other outcomes. However, long-term follow-up with large number of patients may be

required to analyse functional outcomes as the correlation between x-ray damage and HAQ is stronger late in the disease i.e. > 5 years after disease onset (107).

As far as is known, this thesis is the first to report on baseline disease variables, particularly male sex, as predictors of progressive structural damage despite DAS remission in early RA. However, a possible limiting factor is the low statistical power of the study as there were only few numbers of patients in each subgroup, limiting robust statistical analysis and so the results need to be validated in large cohorts.

In conclusion, this study confirms that persistent low disease state is associated with reduced radiographic progression. Furthermore, patients with sustained clinical disease inactivity achieved better functional, surgical and other long-term outcomes, compared to patients with fluctuating or relapsing-remitting disease activity.

Male sex, RF and x-ray scores at baseline may have predictive value on subsequent x-ray progression in patients in persistent DAS remission. Sustained DAS remission in the study cohort had led to better functional outcomes at 5 years, although some of these patients showed significant radiographic progression.

CHAPTER 8

GENERAL DISCUSSION AND FUTURE DIRECTIONS

8. GENERAL DISCUSSION AND FUTURE DIRECTIONS

Early diagnosis is crucial in the management of RA, a prerequisite for timely intervention with targeted treatment strategies in order to achieve better outcomes. The concept of a 'window of opportunity' has promoted the development of early arthritis clinics to initiate appropriate management early in the disease.

Disease progression and outcomes in RA can be assessed in different ways and the important aspects from patients and physicians' perspective are clinical, radiological and functional. Various standard measures have been introduced over the years to assess disease activity in RA and they have been widely used in clinical trials as well as in outpatient clinics. Over the last few decades, several clinical studies have been designed to examine the natural course of early RA, using validated measures, outside clinical trial settings. These longitudinal observational studies of inception cohorts provide valuable information on the natural (treated) history of early RA, outcomes and prognostic factors. The rationale for inception cohort studies with long-term follow-up in RA is that they reflect 'true-to-life' patient management in ordinary clinical settings, and if well designed, they can provide vital information on clinical effectiveness of RA management and often complement the results of randomised controlled trials (RCTs) (294).

The Early Rheumatoid Arthritis Study (ERAS) is an observational cohort of early RA and more than 1000 patients have now completed 5-year follow-ups. The ERAS inception cohort provides an ideal opportunity to study the natural disease progression, outcomes and prognostic factors in early RA. A number of reports have

already been published by the ERAS group on various outcomes and prognostic factors including radiographic damage, functional disability, orthopaedic surgery and mortality (9;12;68;99;295;296).

This thesis aimed to study both disease activity and radiological disease progression over 5 years in the ERAS cohort, and to examine the relationship between the two. There is only limited information on sustained remission in early RA, how this affects outcome, and prognostic factors for this.

Several drug trials using intensive treatment regime involving aggressive combination therapy with or without steroids and biological agents have shown higher frequency of remission ranging between 30 and 65%. However, observational cohorts, where conventional DMARDS have been used according to their physicians' choice in a routine clinical setting, have reported lower rates of remission varying between 7 and 30% depending upon the disease characteristics, remission criteria and treatment used (292).

In a study by Wolfe et al, 458 patients with at least 3 consecutive clinic visits were analysed to study remission using ARA criteria (116). A majority of the study patients had established disease (median disease duration > 7 years) and only 27% had disease duration of <1 years at study entry. 18% of the patients achieved ARA remission and only 15% of these remissions lasted for more than 24 months. Median duration of remission was 10 months. In another observational study of 227 early RA patients (disease duration < 1 year) with a median follow-up of 4 years (range 1-6 years), 25%

achieved modified ARA remission at one visit and only 15% on two consecutive visits (279).

A prospective, longitudinal study of 142 early RA patients (< 2years) with a mean follow-up of 6 years, treated according to 'saw tooth' strategy using traditional DMARDS and steroids showed that 20%, 27% and 32% of patients achieved ARA remission at 1st year, 2nd year and at last visit respectively. However, only 19% were in remission both at 2nd year and at last visit (238). In another prospective study of 191 early RA patients (< 1 year) with a maximum follow-up of 5 years, remission rates based on DAS (<1.6) were 25% and 20% at 3 and 5 years respectively. Nonetheless, only 15.7% maintained remission at both time points (223).

Makinen et al, reported 39% and 37% of clinical remission at 2 and 5 years respectively in their inception cohort of 111 early RA (median disease duration 5 months). Nevertheless, only 21% achieved remission at both 2 and 5 years (119).
In another multicenter, observational study of early RA patients (< 1 year) with a maximum follow-up of 5 years, frequency of point and period remission was assessed using DAS 28 criteria (< 2.6). Although, 34 to 38% of patients in this cohort achieved remission at individual time points (18, 24 and 60 months), only around 20 % maintained remission at all time points (285).

Mierau et al analysed frequency or remission using modified ACR, DAS 28, simplified disease activity index (SDAI $\leq$ 3.3) and clinical disease activity index (CDAI $\leq$ 2.8) in 621 RA patients with established disease (mean disease duration 10 years) in a routine clinical practice. In that study, frequency of point remission was

43% and 34% based on DAS 28 and SDAI & CDAI respectively. However, only 20% (DAS 28) and 17% (SDAI & CDAI) achieved sustained remission (297). In a similar clinical cohort of 115 patients, but with early disease (< 2 years), although 34 patients achieved DAS 28 remission at one time point, only 5 patients maintained remission at multiple study points (287).

This thesis has shown that, although about one fourth of the study patients fulfilled DAS remission criteria at individual time points (21 to 26%), only around 10% were in sustained remission for at least three consecutive annual visits. Among those patients who were in DAS remission at any given time point (point remission), disease inactivity persisted (period remission) for 12 months in around 60% and for 24 months in 40% of patients. These findings confirm previous reports that period remission is less frequent than point remission in RA.

A number of early RA studies have analysed prognostic factors for remission and they showed that the predictive value of baseline disease variables for subsequent remission could be variable and inconsistent. However, some baseline features such as male sex, low joint count or disease activity and low HAQ have consistently shown good prognostic value for remission in many observational cohorts (12;80;223;279;281;285;287).

Studies have shown that male patients with RA have less severe disease and higher chances of remission. This gender difference in RA can partly be explained by hormonal differences as the disease activity usually improves during pregnancy and in a majority of patients it can flare up after delivery (298). Studies have also shown the

beneficial effects of oral contraceptives and hormone replacement therapy on disease activity (299;300) and oestrogen seems to have a positive impact on the immune system by down-regulating inflammatory immune responses and up-regulating immunoglobulin production (301).

It has been argued recently that the positive predictive value of male sex for remission may in fact be due to a possible gender difference in reporting tender joint count (TJC) and global health (GH), as women apparently tend to report these symptoms more (302;303). This is supported by findings from Makinen et al, that the difference in disease activity in relation to sex difference was more pronounced in patients with 0 or 1 swollen joint count (SJC) compared to patients with > 1 SJC and this was because of relatively higher TJC and GH scores in women compared to men, particularly in patients with low disease activity (302).

It has also been suggested that the type of remission criteria used may influence the frequency of remission, in relation to gender difference (302;303). This is because DAS and DAS28 do not have separate ESR values for men and women like ARA criteria, and the normal range for ESR tends to be higher in women. Also, ESR and GH may have more influence on the total disease activity score based on DAS and DAS28, because of the weighting in the formulae.

Makinen and colleagues have recently reported that women had higher mean ESR values compared to men in their cohort, although CRP levels were the same in both sexes. Although men appeared to have higher frequency of DAS28 remission in their study, ARA criteria did not show any gender difference in the remission rate (302).

In this thesis a subgroup analysis was carried out of prognostic factors in patients with 0 or 1 SJC compared to patients with > 1 SJC. The predictive value of male sex for sustained DAS remission remained the same in the ERAS cohort despite different subgroup analyses. In a previous analysis of the ERAS cohort (n=732) using more stringent ARA criteria, remission was reported as 13% at 5 years and male sex and low HAQ at baseline showed predictive value for ARA remission (12). It is likely that the good prognostic value of male sex for DAS remission reported in this thesis is due to true disease characteristics rather than any reporting difference between men and women.

Remission rates and prognostic factors for remission were comparable in ERAS despite using two different remission criteria. Analysis of the ERAS patients, using sustained DMARD-free remission criteria (no current use of DMARDS or steroids, no swollen joints and clinical diagnosis of DMARD-free remission by the treating physician) also showed frequencies (9.4%) similar to that of sustained DAS remission (11%).

Baseline features such as duration of symptoms, RAI and HAQ showed prognostic value for subsequent remission irrespective of the remission criteria used. Interestingly, baseline variables such as age, acute onset of symptoms, absence of RF and shared epitope (SE) showed predictive value for DMARD-free remission, but they were not of any prognostic significance for remission based on DAS. This may be due to difference in the remission criteria used and/or difference in total number of patients (704 vs 895) between the analyses (293).

Although, a number of early RA studies have reported on RF and SE as prognostic factors for remission, the positive predictive value of these prognostic markers, particularly of SE, have not been consistent and reliable (80;118;223;281;285;287).

Radiographic progression in RA, particularly during the early stages (< 5 years) can be highly variable and unpredictable and different models of x-ray progression have been proposed (90;100). Quantification of structural damage, using Larsen method in random order in ERAS has showed that radiographic progression at group level was essentially linear over the first 5 years of disease presentation, except between year 2 and 3, where it was accelerated. However, in contrast to x-ray progression, clinical and laboratory measures such as, DAS, HAQ and ESR improved from baseline, stabilised, and then gradually deteriorated between 4 and 5 years. This accelerated x-ray damage between 2 and 3 years follow-up was considerably different from x-ray progression at any other time points and there was no significant correlation between x-ray scores and any of the clinical or laboratory disease measures throughout the study period to explain this unexpected finding.

This thesis has attempted to explore other possible reasons for this disproportionate increase in x-ray progression between 2 and 3 years such as, higher clinical disease activity preceding the x-ray assessment, treatment effect and scoring methodology. As described earlier, the results showed that the accelerated radiographic progression was not related to any difference in clinical disease activity both before and during the x-ray assessments or to treatment. However, a small subgroup analysis of x-ray progression using the same Larsen method, but in chronological order (reading with known sequence) showed that radiological progression was constant and linear

between baseline and 5 years, and did not show the accelerated phase using random Larsen scoring. Possible weaknesses in the argument that the scoring order of films influenced the nature of x-ray progression in this study include the smaller number of films in the subgroup analysis.

The influence of scoring methodology on longitudinal x-ray progression was explored further in this thesis by comparing different scoring methods (Larsen, SvdH and SENS) and scoring sequence (random and chronological) in subgroups of patients.
Larsen's method used in this study was a global scoring system, which incorporates soft tissue swelling, joint space narrowing (JSN) and erosions together and gives a unified score (172). Inclusion of soft tissue swelling in the Larsen's score may lead to a relatively high score at baseline, decreasing with response to treatment. This may reduce the total possible increased score due to progressive damage, contributing to low sensitivity to change (149). Also, scoring JSN and erosions separately may give more valuable information on disease heterogeneity and progression (189).

Each scoring method has its own strengths and limitations in terms of scoring technique, time and reliability. SvdH method has shown to be superior to others in relation to its sensitivity to change, smallest detectable difference and in detecting minimal clinically important difference (181;182). SENS, a simplification of the SvdH method, has shown to be quick and easily reproducible in the research as well as in the routine clinical setting (170).

For the above reasons, these three commonly used scoring methods were compared in this thesis. As described in chapter 5, the results showed that radiographic progression

at group level, based on all three (Larsen, SvdH and SENS) scoring methods was essentially linear and similar, provided the films were read in chronological order. However at individual level, SvdH method was more sensitive in detecting x-ray progression above measurement error i.e. clinically meaningful x-ray progression.

Scoring order of the films is more important in RA studies with radiographic outcome as one of the main objectives. In clinical trials studying treatment interventions, the films should ideally be read in paired order (reading films without known sequence) in order to assess the real difference in treatment outcome without introducing any bias (158). However, in longitudinal studies and observational clinical cohorts, chronological reading of x-rays is more useful to detect clinically meaningful x-ray progression above measurement error (160).

In this observational cohort of early RA, chronological reading of x-rays was more sensitive in assessing longitudinal x-ray progression than random reading. However, it is difficult to draw a definite conclusion as the films were read in random (observer CS) and chronological order (observer KJ) by two different observers, although reliability between the observers was very good. Chronological scoring of x-rays using SvdH method in these patients has been shown to be more reliable and meaningful in measuring significant x-ray progression, both at group and at individual level, particularly in patients with low disease activity or remission.

As described in the earlier chapters, another interesting and important finding from the radiographic analysis of the ERAS cohort was that a small proportion of patients (8%) showed marked progression in their x-ray (Larsen) scores despite low or minimal

clinical disease activity. This unexpected finding has prompted a study of radiographic progression in detail in patients in sustained DAS remission, as there is only limited information on this in early RA patients treated with conventional DMARDs in routine clinical setting. Although, x-ray damage is relatively less in patients with minimal or no clinical disease activity (80;239), it has also been shown to progress despite clinical improvement or remission (243;288;289).

Radiographic progression during sustained periods of clinical disease inactivity was analysed in detail for this thesis, both at group and at individual level, using absolute scores as well as smallest detectable difference (SDD). Two separate analyses of x-ray progression in the ERAS cohort during sustained DAS remission were analysed.

The first analysis was radiographic progression over 3 years, using Larsen scoring method in random order, in patients in sustained DAS remission at 1st, 2nd and 3rd year follow up assessments and with serial x-rays (n=78). In this group, 22% showed significant or clinically meaningful x-ray progression and in a majority of them (82%), the progression was noted between 2nd and 3rd year assessments. Nearly one quarter of the patients in sustained DAS remission (24%) developed new erosions during the study period, most of them (89%) at year 3.

A separate analysis of the ERAS patients, who were in sustained DAS remission from year 1 to 5 and had serial x-rays (n=35), revealed significant radiographic progression despite remission. The SvdH method was used in chronological order for this analysis, as previous studies including this thesis, have shown that this scoring methodology is more sensitive in detecting x-ray progression that is clinically important (160;182).

Although, 80% of patients in this group showed an increase in their total x-ray (SvdH) scores between year 1 and 5, only half of them (43%) showed clinically meaningful progression i.e. progression above measurement error. However in a majority of patients, JSN rather than erosions appeared to be the main reason for increase in total x-ray scores, and only in 13% of them the x-ray progression was due to new erosions.

Various hypotheses have been put forward over the years to explain radiological deterioration in spite of clinical improvement or disease inactivity. Disease heterogeneity including a difference in pathogenesis between synovial inflammation and joint damage has been proposed as one of the main reasons (251;254;255). Other causes such as, residual inflammation in the joints despite fulfilling the remission criteria, time lag between clinical disease activity and appearance of erosions on x-rays and presence of subclinical synovitis detectable only on US or MRI have also been suggested as possible underlying reasons for progressive x-ray damage despite remission (266;268;269;289).

Disease heterogeneity is the most likely explanation for the paradoxical relationship between clinical disease activity and radiological damage in the ERAS cohort, as attempts to test various other hypotheses have not revealed any positive results.

ERAS used more stringent remission criteria than described in recent publications. The original DAS assesses more joints for swelling (44) and tenderness (68), involving both hands and feet, compared to DAS28 which assesses only 28 joints and does not include the feet (264-266). DAS of < 1.6 correlates with the more rigorous ARA remission criteria (279) and this DAS cut-off value was used to define remission in this thesis.

Therefore, residual inflammation in the joints despite achieving DAS remission is less likely in this study cohort, although it is a possibility.

Conventional radiography, using x-rays, may be relatively insensitive in detecting early radiological changes due to RA and there may be a significant time lag between clinical disease activity and appearance of erosions on x-rays. Although, this time lag can be quite variable and unpredictable, it is usually up to 12 months (268;269).
Among patients showing significant x-ray progression despite DAS remission in this thesis, a majority progressed to develop radiological damage including new erosions after being in remission for at least 12 to 24 months. Therefore, time lag as a possible reason for progressive x-ray damage is less likely in this cohort.

New imaging techniques such as US and MRI are more sensitive in detecting subclinical inflammation in apparently 'normal looking joints' and there may be a significant time delay between appearance of erosions on MRI and on x-rays (101-104). Therefore, it is possible that some ERAS patients could have had subclinical inflammation and/or early radiological changes, detectable only on US and MRI, in spite of DAS remission. However, radiographic analysis in this thesis was in early RA patients in sustained DAS remission for up to 5 years and so the results from previous short-term studies in patients with established or active disease should be carefully interpreted in the right context.

Scoring methodology as a potential reason for unexplained x-ray progression in patients with sustained remission was also explored. This showed that a significant proportion of patients in sustained DAS remission developed progressive x-ray damage

irrespective of scoring methods or reading sequence of films. No significant difference between patients in sustained DAS remission with and without x-ray progression in terms of DMARD treatment was seen. Therefore, scoring methodology and treatment effects are unlikely explanations for progressive structural damage seen in patients with low or no clinical disease activity.

Although, several studies have reported on prognostic factors for radiological progression in RA (68;69;138), there is not much information on predictive value of standard disease measures in determining subsequent x-ray progression in patients with clinically inactive disease. In a recent imaging study by Brown et al in RA patients in clinical remission, positive power Doppler signal and synovial hypertrophy on US and synovitis on MRI showed predictive value for x-ray progression at 12 months (289).

In a subgroup analysis of this thesis, male sex, RF, erosions and x-ray scores at baseline have shown prognostic value for x-ray progression in patients in sustained DAS remission. However, only male sex showed independent predictive value in multivariate analysis and other studies have not reported on this. This is an interesting and unexpected finding as men in general have shown to be in good prognostic group in relation to their disease activity and progression (303). On the other hand, oestrogen may have a favourable influence on the immune system in women with protective effect on the bone (301;303).

Nevertheless, previous studies have not shown any significant difference in radiographic outcome between men and women, and gender was not of any prognostic value in predicting x-ray progression (7;283;304).

Patient numbers in this group reported for this thesis were small, so caution is needed for these conclusions. Future long-term studies of patients with persistently inactive disease should elucidate this further.

The results of this thesis are consistent with previous reports that RA patients with active disease have worse outcomes (55;57). In a previous analysis of ERAS patients (n=732), functional disability (Steinbrocker's functional grade FG III & IV) had progressed from 7% at study entry to 16% at 5 years and female sex, age of onset > 60 years and baseline HAQ >1 were associated with worse functional outcomes (12).

Although, several studies have reported on various disease and non-disease specific outcomes in RA (9;12;56;57), there is only limited information on long-term outcomes such as work disability, orthopaedic surgery and mortality in early RA patients with sustained low disease activity or remission, treated with traditional DMARDS in routine outpatient clinics. As far as is known, long-term functional outcomes in relation to x-ray progression in early RA patients in sustained DAS remission have not been reported before.

Patients in sustained DAS remission had better outcomes including reduced functional & work disability, less radiographic damage and fewer requirements for supportive aids and orthopaedic surgeries compared to patients with disease activity.

Although, patients in sustained DAS remission had relatively fewer deaths (15% vs 23%), the difference was not statistically significant (p=0.14). It was reassuring to see that patients in sustained DAS remission had better functional and other outcomes, although a significant proportion of them showed progressive x-ray damage.

Also, it was encouraging to note that there was no significant difference in 3 & 5-year outcomes between patients in sustained DAS remission with and without x-ray progression.

A separate analysis was carried out to study 5-year outcomes in relation to cumulative clinical disease activity (from initial disease presentation up to 5 years) in the ERAS cohort. The main objective was to analyse long-term outcomes in patients with persistently low or no disease activity (DAS $\leq$ 2.4) from year 1 to 5, compared to other patients with either persistently high or fluctuating (relapsing-remitting) disease activity. This showed that patients with persistent clinical disease inactivity had better radiographic and functional outcomes compared to patients with active or fluctuating disease.

Also, other outcomes such as, work disability, orthopaedic surgery and mortality were significantly less in the low or inactive disease group. It is important to note that patients with fluctuating or relapsing-remitting disease also had poor outcomes, although it was relatively better compared to patients with persistent disease activity. Previous studies have also shown that fluctuating clinical disease activity could have an independent effect on x-ray damage with worse radiographic outcome (243;245).

The strength of ERAS includes large number of early RA patients with long-term follow up in a 'real-life setting'. Longitudinal analyses of this traditional pre-biologic cohort provide valuable information on natural disease course, outcomes and prognostic factors in RA. Furthermore, no previous studies have reported on

radiographic progression, outcomes and prognostic factors in detail in early RA patients with sustained remission or low disease activity for up to 5 years.

However, there are some limitations. There is a possibility of bias in this type of hospital-based observational studies, as they may not include patients who go into remission early and not attend hospital (left censoring) and also it may not include patients who either die or become too unwell to attend (right censoring). The other common and unavoidable problem with such longitudinal studies is the missing data. Nonetheless, on separate analyses, there was no significant difference between the study patients and those with missing data in relation to most of the disease characteristics.

A further limitation, particularly with regard to sustained DAS remission is that the DAS were recorded only at yearly intervals and so there was a possibility of disease exacerbations between the study assessments. However, study patients were assessed by their treating physicians every 3 to 6 months and no treatment change was noted to suggest any flare ups.

In conclusion, sustained DAS remission is less frequent than point remission in this early RA cohort and baseline variables such as, gender, duration of symptoms, disease activity and HAQ showed prognostic value for sustained DAS remission.
The link between clinical disease activity and radiological damage may be variable and unpredictable and structural damage on x-rays can progress despite clinical disease inactivity or remission in early RA.

Male sex, RF, erosions and x-ray scores at baseline have shown modest prognostic value in predicting radiographic progression during sustained DAS remission in this study. Therefore, x-rays at regular intervals, even during clinical disease inactivity, may give valuable information on true disease progression in early RA.

Scoring methodology may have an influence on radiographic disease progression in RA, particularly at individual patient level, and so it is important to choose the appropriate method depending upon the type and purpose of the study.

Patients with persistently inactive disease had better outcomes compared to patients with relapsing-remitting or persistent disease activity. No significant difference was seen in functional and other outcomes between patients in DAS remission with x-ray progression and those in DAS remission without x-ray progression. Therefore, maintaining a state of disease inactivity is probably as important as achieving remission to have a favourable influence on subsequent disease progression and outcomes in RA.

FUTURE DIRECTIONS

The findings reported in this thesis has strengthened the resolve for a detailed analysis of ERAS patients who have completed at least 10-year follow up in order to study disease progression over a longer period. ERAS recruited patients in the pre-biologic era between 1988 and 1998 and management of RA has been revolutionized by the introduction of biological agents over the last decade.

Current evidence supports the use of targeted treatment strategy involving DMARDs, high dose steroids and/or biological agents as early as possible in the disease course to have a positive impact on disease progression and outcomes. Therefore, it will be interesting to see how these newer agents or other forms of intensive treatment influence long-term disease progression, particularly in relation to their effect on the link between clinical disease activity and radiological progression and other outcomes.

Future randomised studies of patients with different levels of clinical disease activity including low disease or remission and with long-term follow up may provide valuable information on the treatment effect, which is difficult to explore in detail without any bias in observational studies like ERAS.

Use of conventional radiography to assess disease progression in RA has several advantages, because performing x-rays of hands and feet is readily available, rapid, relatively cheap, and scoring methods are reproducible and validated. However, newer musculoskeletal imaging techniques such as US and MRI have shown to be excellent diagnostic as well as prognostic tools in the management of RA, both in the research

and clinical setting. X-rays can be relatively insensitive, particularly in the early disease and in patients with low or no clinical disease activity, whereas US and MRI can be very sensitive in detecting subclinical inflammation as well as early radiological damage in RA.

In addition, US and MRI findings appear to correlate with structural damage on x-rays and these imaging modalities have been shown to have good predictive value for subsequent development of erosive changes on x-rays. Therefore, future studies, using these newer imaging techniques, particularly in patients with inactive disease, may provide some vital information on the link between clinical disease activity and radiological damage in RA.

APPENDICES

APPENDIX 1. CRITICAL APPRAISAL

1. Critical Appraisal
Clinical and radiological disease progression in RA

NO	Study title	Objectives	Methodology	Results	Strengths	Limitations
1	Progression of radiological changes in RA. Scott D L, et al. Ann Rheum Dis 1984;43:8-17	To study the interrelationship between radiological changes and clinical and laboratory variables in RA, in relation to treatment with second line drugs	Prospective study of pts with active RA. Two different F/U periods – short term study = 1 yr F/U long term study = 10 yrs F/U Short term study = 64 pts with established RA and mean disease duration – 6 yrs. Clinical and lab variables used – grip strength, RAI, pain score, ESR/CRP, Hb, RF & Igs X-rays were scored using Larsen's (mean score of 2 observers were used) DMARDs used – IM Gold, auranofin, penicillamine, clobuzarit and no steroids. Long term study = 112 pts with established RA and mean disease duration – 5 yrs. Clinical and lab variables were same as above. Functional ability and x-rays were reported using steinbrocker grading (2 observers) DMARDs used – HCQ, IM Gold, penicillamine, AZA, chlorambucil, CYC and steroids (91%)	No correlation between radiological damage and clinical and lab variables (radiological damage occurred in all cases). Good correlation between clinical and lab variables	Prospective study using conventional DMARDs Analysis of clinical, lab and radiological disease status	Clinical disease activity and radiological damage was assessed/scored using non validated/non specific methods except Larsen's. Feet not included in Larsen's scoring. X-ray progression criteria not clearly stated. Radiological progression before the study entry was considered as linear, which is not true in all cases (as in ERAS study)
2	Remission in rheumatoid arthritis. Wolfe F et al. J Rheumatol 1985;12:245-252	To assess the frequency and duration of remission	Observational study a) database with details prospectively entered was analysed – 458 pts with atleast 3 clinic visits were included & only 27% of pts had < 1 yr disease at the initial visit b) parallel chart review by an independent observer was also done. F/U – up to 30 months (1131 pt year) ARA remission criteria used – either 5 /6 or 4/5 (excluding	Remission rate - 18.1%(ARA) & 18.8%(chart) Only 15% of these remissions lasted for more than 24 months. Median duration of remission 10 months. Female sex, onset < 60 yrs & early erosions –reduced rate of remission	Prospective analysis. Large no of pts. All pts met ARA criteria for RA. Spontaneous Vs drug induced remission was also analysed	Too many subgroup analysis. Chart review was not validated for assessing remission. Small no of pts (16) in the remittive, non-treated group. Patients with established RA (median disease duration >7 yrs).

			fatigue) Chart review – clinical remission or inactive disease noted by the clinician			F/U visits were not standardised
3	Remission of rheumatoid arthritis – myth or reality? Piai et al. Revmatologira (Mosk) 1990 Apr-Jun;(2):68-72	To study different types of remission ie. Drug induced Vs spontaneous	Observational (5 yrs) 956 pts	Lengthy remission (1-5 yrs) was attained in 14% of pts	Long term observational data with a large no of pts	Frequency of F/U & type of remission criteria not stated. Only abstract available
4	Frequency and prognostic features of rheumatoid patients with remission inducing agents – a comparison of different kinds of medication. Kutsuma et al. Ryumachi 1990 Oct;30(5): 336-42	To study the frequency of complete remission in RA & their special features with different treatment	Observational (2 yrs) 466 pts (90 male, 376 female) ARA remission criteria used	7.1% achieved remission. High remission rates in pts who had no F/H of RA, no rheumatoid nodules or hip contracture	Observational data with a large no of pts	Frequency of F/U not stated Only abstract available
5	Radiologic progression during intramuscular methotrexate treatment of rheumatoid arthritis. Sany J et al. J Rheumatol 1990;17:1636-41	To study whether treatment with IM MTX in patients with established RA could reduce the radiological progression	Prospective controlled study 41 pts with established RA (mean disease duration 13 yrs) F/U – 2 years (mean 31 months) Mean MTX dose:10 mg Clinical remission criteria – not stated Radiological remission – Larsen's index of <5 over the 2 yrs study period	Clinical improvement in all 41 cases with IM MTX. Radiological deterioration occurred in >83% of pts(hands& wrists), >76% of pts(hands, wrists & feet). No predictive factor for radiographic	Prospective study. Validated x-ray scoring method used and read by two independent observers in random order.	Patients with established RA and radiological damage (baseline Larsen score was high-mean 84). Clinical remission criteria not stated. Small no of pts and low dose of MTX. No control group. All the x-ray films

				evolution		were available in only 25 pts.
6	Studies on clinical remission of rheumatoid arthritis. Itoh I et al. Ryumachi 1992 Feb;32(1):47-51	To study the frequency of remission	276 pts and duration of F/U – 17 months	19 out of 276 pts were in clinical remission. All 19 pts remained in remission for 17 months. Remission rate higher in male pts. Erosive changes developed even after clinical remission.	Looked at both clinical and radiological disease status.	Only abstract available. No details on study design, pt characteristics, remission criteria used and x-ray scoring methods. No details on statistical analysis.
7	Clinical improvement and radiological deterioration in rheumatoid arthritis: Evidence that the pathogenesis of synovial inflammation and articular erosions may differ. Mulherin D et al. Br J Rheumatol 1996;35:1263-1268	To assess the relationship between clinical and laboratory measures of disease activity and the radiological course in a cohort of RA pts.	Patients with active RA entered a prospective study. 1958 diagnostic criteria for RA used. No previous DMARDs or steroids. 40 pts included and the mean duration of F/U 6yrs. Clinical assessment – EMS, pain (VAS), grip strength, RAI, Hb, ESR Radiological - Larsen	Significant improvement in clinical & lab measures of disease activity (RAI, Hb, ESR) but marked radiological deterioration. Measures of disease activity at enrolment did not predict the radiological course. Correlation between RAI, Hb, ESR and x-rays at review was found.	Prospective study. Validated x-ray scoring method. Duration of F/U 6 yrs. Correlation between clinical, laboratory variables and radiological course & outcome were analysed.	Small no of pts and no details of F/U(frequency, no of study points). All pts had established RA with active disease. SJC not included in the analysis and HAQ not available. Radiological deterioration may be due to the active disease at the study entry rather than at the study point.
8	Remission in a prospective study of	To evaluate the prevalence of	Observational study with an inception cohort of early RA pts (<1 yr disease duration since diagnosis) with a maximum F/U of 6 yrs and no previous	69 pts(37%) fulfilled the remission criteria	Prospective study with a long F/U.	Variable F/U duration. TJC was

	patients with rheumatoid arthritis. ARA preliminary remission criteria in relation to the disease activity score(DAS). Prevoo M, et al. Br J Rheumatol 1996 Nov;35(11):1039-40	remission according to the ARA criteria and to investigate the relationship of the ARA remission criteria with the DAS	DMARDs. 227 patients were included, median age – 55 yrs and median duration of F/U 3.9 yrs. F/U visits were every 3 months. Modified ARA remission criteria was used –4/5	at least once and 39 pts(21%) on at least two consecutive visits. Because of variable F/U duration pts fulfilling remission criteria/ follow up yr was calculated: 25% at one visit & 15% on two consecutive visits. DAS of 1.6 correlated with ARA criteria for remission.	Validated remission criteria used. Standardised F/U system. DAS was compared with ARA remission criteria for the first time to get a cut-off point for remission using DAS. SJC was the most influential and EMS, ESR were the least influential factors in deciding remission	assessed in only 53 joints and SJC was assessed in only 44 joints and so the remission rate could have been lower if more joints were included.
9	Evaluation of the ARA preliminary remission criteria in rheumatoid arthritis: a prospective study. Alarcon G, et al. J Rheumatol 1987;14:93-6	To study the frequency of remission using ARA remission criteria	Cross sectional study, which included two different populations of patients with established RA from two different countries. ARA remission criteria used.	Prevalence of remission –1% and 30% at one visit in two populations respectively		Pts with established RA and pts were selected during a visit at the clinic.
10	Outcome in patients with early rheumatoid arthritis treated according to the 'sawtooth' strategy. Mottonen T, et al. Arthritis & rheumatism June 1996;39(6): 996-1005	To investigate the outcome of early RA when treated according to the 'sawtooth' strategy	Prospective, longitudinal study including 2 cohorts of patients from 2 centres with early RA (<2 yrs) and no previous DMARDs. All pts met the 1987 ACR diagnostic criteria at some point of the study. Total no of pts –142, mean disease duration 7.9 months and mean time from the onset of symptoms and start of DMARDs was 7.9 months. Most common first DMARD was IM gold (82%) followed by SZZ (10%) and HCQ (7%). 92% of pts were symptomatic for <12 months at study entry. F/U every 3-6/12 for 3 yrs and then yearly. Mean duration of F/U 6.2 yrs (range 18-111 months). ARA remission criteria used. x-rays – Larsen's(0,1,2 & at last visit) Outcome measure- functional grade (Steinbrocker & MHAQ)	All pts had atleast 1 DMARD. Mean ± SD cumulative time of DMARD treatment was 60 ± 24 months (or 81% of the mean F/U) and mean cumulative no of DMARDs used by all pts was 3.3 (1-8). 49 pts received steroids (<10 mg)	Prospective study with early RA pts. Low drop out rate-only 3 pts. Long duration of F/U. Inefficacy was the most frequent cause for discontinuing DMARDs rather than advers events	Clinical and radiological disease status was reported only for year 0, 1, 2 & last visits. Radiological progression despite clinical remission at the last visit could be due to fluctuating disease in the preceding years and

				Remission –20% (year 1), 27% (2nd yr) and 32% (last visit). Only 19% of pts were in remission both at 2 yrs and at the last visit. 94% of pts who were in remission at their last visit had erosive disease. Only 24% progressed to functional grade III-IV		it was not the primary outcome measure. Absolute Larsen's scores in pts in remission Vs non-remission were not reported, so difficult to comment on the significance of radiological progression. Prognostic/ predictive factors not studied.

11	Clinical course and remission rate in patients with early rheumatoid arthritis: Relationship to outcome after 5 years. Eberhardt K, et al. Br J Rheumatol 1998;37:1324-1329	To investigate the clinical course in early RA pts and to assess the outcome after 5 yrs and to identify prognostic factors.	Prospective study of definite RA pts with disease duration of <24 months. Total no of pts-183, mean age-51.4 yrs and mean duration of symptoms-11.1 months. F/U – every 6months for 5 yrs. 1.Modified ARA remission criteria - 4/5 on at least two consecutive visits (6 months apart) 2.Clinical remission criteria -'no arthritis at least at one F/U visit' X-rays – Larsen's at baseline & then yearly. Patients with active disease received DMARDs and 62% of pts received DMARD some time during F/U. Most common DMARD was HCQ. 29 pts (16%) had oral steroids.	37 pts (20%) achieved ARA remission periods of at least 6 months duration. 21 were spontaneous and 18 drug induced. Mean duration of remission = 20.5 months. 36% of pts were in remission according to the clinical remission criteria. 56% had a relapsing-remitting disease and 44% had a persistent disease	Prospective study with a F/U of 5 yrs. Low drop out rate-only 7 pts(4%). Standardised F/U. Remission assessed at two study points	Radiological progression not analysed / reported at regular intervals in relation to the clinical disease activity. No prognostic model to predict remission using logistic regression analysis
12	The relationship between synovitis and erosions in rheumatoid arthritis. Kirwan J, et al. Br J Rheumatol	To study the correlation between synovitis and erosions in individual joints	Analysis of data from a prospective multi-centre study of low-dose prednisolone. Total no of pts - 93 Clinical assessment every 3 months and the duration of F/U-2 yrs Clinical disease – soft tissue swelling + tenderness=synovitis.	216 joints (out of 2064) showed progressive x-ray damage and 44% of these had little or no	Prospective, multicentre study. X-ray scoring done by two observers. Pts with early RA	Clinical assessment not accurate. All pts had active disease. No details on

	1997;36:225-228	in hands	X-ray – Larsen's (change in score over 2 yr period)	synovitis. Of the 12% of joints that were synovitic, 63% show no x-ray progression. In contrast to placebo, steroid treated pts did not have any increase in correlation between synovitis and erosions as progressively larger combinations of joints were considered together		DMARDs. Absolute change in Larsen score not mentioned and feet not included in the analysis. Acute phase reactants not analysed. Duration of F/U (2 yrs) probably not enough to assess structural damage on x-rays. Inter & intrarater reliability not reported
13	Utility of disease modifying antirheumatic drugs in 'sawtooth' strategy. A prospective study of early rheumatoid arthritis patients up to 15 years. Sokka T, Hannonen P. Ann Rheum Dis 1999;58:618-622	To study long term utility of early, continual, and serial use of DMARDs in early RA in clinical setting	Two cohorts (total=135 pts) of early RA pts who met the 1958 ARA criteria for RA. Cohort 1(1983) – 58 pts (observational) Cohort 2(1988) – 77 pts (case-control – SSZ vs placebo) Subsequently both cohorts were enrolled into this prospective study F/U every 3/12 for the first 2 years and at least yearly thereafter Maximum F/U duration- 15 yrs from disease onset. ARA remission criteria used. Criteria for early RA not reported. All pts were treated with DMARDs except one (self-limiting)	Most commonly used DMARD – GST & SSZ Median duration of DMARD period = 10 months (range 6-18) Reason for stopping DMARDs = inefficacy (51%), adverse reactions (28%), other reasons (15%), remission (n=32, 6%)	Prospective study with a maximum F/U of 15 yrs. Standardised F/U at regular intervals. Validated clinical remission criteria used	Small no of pts and some pts in cohort 2 had placebo before this study. Clinical remission was not studied as a primary outcome and it was rather reported as a reason for DMARD discontinuation So, patients in remission but staying on DMARDs were missed and so the actual remission rate may be higher than reported.

						Radiological assessment not explained
14	How does functional disability in early RA affect patients and their lives? Results of 5 yrs of follow up in 732 pts from the ERAS. Young A, et al. Rheumatology 2000;39:603-611	To assess the impact of RA on function and how this affects patients' lives	Inception cohort of early RA pts (disease duration < 2 yrs and no prior DMARD use). 732 patients who fulfilled the 1987 ACR criteria for RA and with a maximum F/U of 5 yrs were included. Clinical assessments at 0, 3, 6 months and then yearly. X-rays at 0,1,2,3,5 & 9 yrs and scored using Larsen's. ARA remission criteria used. Functional assessment using steinbrocker's functional grade and HAQ.	84% of pts received atleast one DMARD. NSAIDs and/or steroids were used in 16% Most commonly used first DMARD SSZ (73%) followed by Gold inj(10%). Remission by 5 yrs – n=94, 13% Predictive factors for remission – male sex & baseline HAQ of < 1 FG III,IV has increased from 7%(baseline) to 16% by 5 yrs- bad prognostic factors = female sex, age of onset >60 & baseline HAQ of >1	Large no of early RA pts with a F/U of 5 yrs. Regular F/U assessments were made and validated clinical remission criteria and x-ray scoring methods were used	Remission was not assessed as a primary outcome and the ARA remission criteria was probably not strictly followed (no report of either 5/6 or 4/5 ARA remission criteria and only one study point) Clinical disease activity and radiological progression were not analysed together
15	Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a review of	To examine disease outcome and predictors of prognosis among	All pts with a new onset of IP, who presented to primary care were recruited to NOAR. Median age – 55 yrs No of pts who completed 3 yrs F/U – 486 out of 579(84%)	6% fulfilled the remission criteria at 3 yrs and 11% fulfilled the criteria	Primary care based study with a large no of pts. Left censorship, which	Results of the study may not be generalizable to other populations.

	the literature. II. Outcome at 3 years. Harrison B, Symmons D. Rheumatology 2000;39:939-949	pts with new onset of IP/RA, referred to NOAR	Outcomes assessed = remission of synovitis, functional disability (HAQ) and radiological damage (Larsen) A subset of 231 pts (47%), who satisfied the 1987 ACR criteria for RA were also assessed separately Clinical assessments & HAQ at 0, 1, 2 ,& 3 yrs. X-rays were done only in pts ,who satisfied the study criteria(total no=390, x-rays available-only 335 pts) Median time from symptom onset to the latest available x-ray was 22 months Remission – 4/6 ARA criteria excluding ESR & fatigue Acute phase reactants were not measured in this study. Over the 3 yr F/U period, 357 pts (73%) were referred to hospital for arthritis.	cross-sectionally at any point during F/U. Significant association was found between remission and younger age at disease onset(16-25 yrs) and male sex. The median HAQ score was higher in RA subset at 3 yrs. Linear relationship between HAQ and age at disease onset. Women had higher HAQ scores. Baseline HAQ was the most important predictor of future disability Out of 335 pts ,who had x-ays, 61% fulfilled the criteria for RA and 38% had seropositive disease. Median Larsen score 4 (RA subset). Significant relationship was found between erosive disease and older age at disease onset, RF positivity and longer symptom duration before initial presentation. HLA-DRB1 was associated	is a major problem in hospital based studies can be minimised in this type of studies. Multiple logistic regression analysis was used to predict outcomes. Other related studies were compared in the discussion.	The proportion of true 'RA' pts is lower in NOAR than hospital based studies. X-rays were not taken in all pts and pts who did not meet the x-ray criteria initially went on to develop erosions at 5 yrs. Acute phase reactants were not measured. ARA remission criteria was not strictly applied. No details of remission rate in the subset of RA pts.

				with the development of erosions(only in seronegative pts). No positive correlation between erosive disease and disability.		
16	Remission and response to early treatment of RA assessed by the DAS. Svensson B, et al. Rheumatology 2000;39:1031-1036	To assess criteria for individual response and remission based on the DAS in RA pts participating in a long-term observational study	Open, controlled study within the observational study. Early RA pts (<1 yr) who fulfilled 1987 ACR criteria. Mean disease duration – 6/12. All pts had active disease with a mean DAS >4 (90% of pts had DAS > 2.4) No of pts – 90, duration of F/U – 2 yrs. Pts randomised to 2 strategy 1) Pred ± MTX 2) SZP/Gold ± Pred Clinical remission – DAS X-ray scoring – Larsen's (mean of the two independent observers values used)	No difference in the two treatment groups for responders and remission 36% (n=32) were in remission at 2 yrs. Significant radiological progression in moderate and non-responders. No radiological progression in good responders (DAS <2.4) and remission.	Prospective study of early RA pts. Validated clinical remission and x-ray scoring criteria used.	Small no of pts. All pts had active disease and all were on DMARDs and so no comparison can be made. Radiological progression not addressed in detail. No detailed comparison with other related studies. F/U not long enough to study the predictive factors, x-ray changes and other outcomes. Details of F/U, duration of remission not reported

17	Radiographic remission in seropositive RA. A 20-year follow-up study. Jantti J, et al. Clinical and Experimental Rheumatology 2001;19:573-576	To study the frequency of radiographic remission in pts with seropositive RA over 20 yrs of F/U	Prospective study of 117 pts with recent onset RA (< 6 months) Mean age 45 yrs F/U at 1,3,8,15 & 20 yrs. For this study 102 pts(out of 117) with seropositive and erosive RA who were seen at 8 and 20 yr check-ups were included. 82 out of 102 pts attended 15 yr F/U and 67 pts attended 20 yr F/U. Larsen's method was used to assess x-ray progression Radiographic remission criteria - no change or a change in score of ≤ 1 point between two study points	Radiographic remission = 27 out of 102 pts (26%) (at 1 yr - 3 pts, at 3yrs – 5 pts, at 8 yrs – 6 pts, at 15 yrs – 13). ESR and CRP at year 8 & year 20 F/Us were low in pts in remission. SJC at year 8 F/U was low in pts in remission. More pts in remission group had less DMARD and /or steroids treatment compared to progression group.	Prospective study with a long duration of F/U. First study to look at radiographic remission prospectively and to some extent clinical and lab measures of disease activity were compared with radiographic progression.	Small no of pts and the frequency of F/U was too long. Clinical & lab assessments were made only at 0, 8 & 20 yrs. Only pts with seropositive and erosive disease were included and so no comparison can be made. Intra/inter observer variability not reported and scoring methodology was not reported in detail.
18	How to diagnose RA early. A prediction Model for Persistent (Erosive)ArthritisVisser H, et al. Arthritis & Rheumatism. Feb 2002;46(2):357-365	To develop a clinical model for the prediction, at the first visit, of 3 forms of arthritis outcome: self-limiting (natural remission), persistent	Prospective study of pts with early arthritis (presence of arthritis in at least 1 joint and if the symptoms lasted <2 years) Total no of pts – 524 (23% were seropositive for RF) Median age – 49, median symptom duration – 2.7 months Clinical, lab and radiographic details were recorded at 0, 1 & 2 yrs. At 2 yrs F/U the pts were divided into 3 groups: 1.Self-limiting – no arthritis and no DMARDs or steroids in the last 3/12. 2.Persistent arthritis- arthritis in at least 1 joint and/or treatment with DMARDs or steroids in the last 3/12.	At 2 years – 156 pts (30%) fulfilled the criteria for RA and 137 pts (26%) had undifferentiated arthritis. 5% of these pts with RA had self-limiting arthritis (natural	Prospective study with large no of pts. Predictive value of the discriminative factors to identify different outcomes at 2 yrs were reported and it can be applied to day to day clinical practice.	Some of the pts were treated with DMARDs , which may have influenced the outcomes. The remission rate was lower in pts with RA as it

		nonerosive, and persistent erosive arthritis	3.Erosive arthritis- erosions	remission)and it was 33% in undifferentiated arthritis. Criteria to discriminate 3 types of arthritis , at the first visit –1) symptom duration, 2) EMS of at least 1 hr, 3) arthritis in ≥ 3 joints, 4) bilateral compression pain MTP joints, 5) RF, 6) anti CCPabs, 7) erosions Duration of symptoms, RF & anti CCP positivity and erosions were strongly associated with persistent arthritis. Bilateral compression pain in MTPs, RF and anti CCP positivity were strongly associated with erosive disease		included only natural remission and not drug induced remission. This study result (remission rate) may not be generalisable to the other early RA studies as the inclusion criteria and study design were completely different.
19	Ten year outcome in a cohort of patients with early RA: health status, disease process and damage. Lindqvist, et al. Ann Rheum Dis 2002;61:1055-9	To investigate outcome as measured by health status, disease process, damage in an unselected group of pts with early RA and search for prognostic features	Observational study of pts with early RA Total no of pts – 183 Duration of F/U - 10 yrs Modified ARA remission criteria used	Remission rate – 18% Health status was the only predictable outcome using HAQ		

20	Functional disability in relation to radiological damage and disease activity in patients with RA in remission. Molenaar E, et al. J Rheumatol 2002;29:267-70	To investigate the relationship between functional disability, radiographic joint damage, variables of disease activity and co-morbidity in patients with RA in remission	This study was part of a larger cohort observational study. Total no of pts-186 Median disease duration – 7 yrs Assessment was made at one study point Co-morbidity was considered to be present when the pt was medically treated for a disease. Clinical remission – modified ACR criteria - 4/5 (omitting fatigue) & DAS X-rays – SvdH method (mean of two observer scores were used)	Only 82% of pts (out of 186) fulfilling modified ACR remission criteria were in remission using DAS. Female = 65%, Ever RF + = 69% 92% of pts had joint erosions SvdH score = 52 (mean), 21 (median) – only few had significant joint damage. 70% of pts were on DMARDs. Significant correlation between HAQ and VAS, DAS, SvdH and disease duration. In pts with <7 yrs disease duration , significant correlation between HAQ & DAS and in pts with > 7 yrs disease, significant correlation between HAQ, DAS and SvdH.	Large no of pts and the inclusion criteria was that the pts should be in remission for the last 6/12. Validated remission criteria and x-ray scoring method used. First of it's kind to study this objective.	Cross-sectional study No direct assessment between clinical disease activity and radiological damage. Other reasons for functional disability i.e. co-morbidity and psychological factors were not studied in detail. No details on effect of clinical & radiological disease progression on functional disability.
21	Progression of radiologic damage in pts with RA in remission. Molenaar E, et al. Arthritis & Rheumatism vol 50(1); Jan 2004:36-42	To assess whether radiologic progression occurs during clinical remission in pts with RA	Prospective study of pts with established RA (median disease duration – 7 yrs) Only pts in clinical remission (should be in remission for 6/12 before the study entry) were included Pts on steroids were excluded Total no of pts – 187	Persistent remission = 59% (preliminary ACR), 52% (modified ACR) and 42% (DAS) Radiological progression was more in	Prospective study with large no of pts Frequent clinical assessment was done. Remission was assessed using 3 main types of	All pts with established RA. Pts on steroids were excluded, which could have influenced the

			Duration of F/U – 2 yrs Clinical assessment every 3/12 and x-rays were done at baseline, 1 & 2 yrs Clinical remission was based on preliminary ACR, modified ACR 4/5(omitting fatigue) and DAS X-rays were scored using SvdH method (progression of <5 after 2 yrs was considered not significant)	pts with disease exacerbation although a slight but statistically significant progression was also seen in pts in clinical remission DAS AUC (area under the curve) was a stronger predictor of radiologic progression than was the absence of persistent remission	validated criteria. X-ray progression was correlated with clinical disease progression.	results. X-rays were read in random order to assess radiologic progression (low sensitivity to change). No definite predictive factors
22	Value of DAS 28 and DAS 28-3 compared to ACR defined remission in RA. Balsa A, et al. J Rheumatol 2004 Jan;31(1):1-4	To assess criteria for remission based on DAS 28 and DAS 28-3 (excluding pt's global assessment of disease activity	Random sample of 788 pts with RA were selected from 34 Spanish centres. Clinical remission was based on both preliminary ACR and modified ACR (omitting fatigue)	Remission - 4% (7.9% if fatigue excluded) Positive predictive value for remission: ESR-6.5%, EMS <15 mins-8.4%, no tender joints -13%, no swollen joints-15.8%, no joint pain-27.7%, no fatigue-8.7% DAS 28 cut off value for ARA remission-2.81% and DAS 28-3 cut off value was 2.95% (if fatigue excluded)	Multi centre study with a large no of pts.	
23	Predictive factors in early arthritis: long term follow up. Schumacher et al. Semin Arthritis Rheum. Feb	To predict which pts with undifferentiated arthritis are likely to have a poor outcome (remission vs	Observational study of pts with early arthritis (symptom duration of <1 yr). Total no of pts – 121 and frequency of F/U was variable but at least once a year. Mean disease duration to the first evaluation was 3 months and median F/U was 5 yrs.	Remission rate – 52 % Pts meeting criteria for RA or spondylo arthropathies had more persistent disease and	Observational study of pts with recent onset arthritis and long duration of F/U. Prognostic factors were	Remission rate in this study can not be generalised to other RA studies because of

	2004;33(4):264-72	persistent disease)	Pts were assessed for either remission or persistent disease at the end of the study period.	pts with undifferentiated arthritis had better prognosis. Pts with poly articular and /or hand involvement had poor prognosis (less chances of achieving remission) Hand involvement was the strongest predictor of a poor outcome	analysed	different inclusion criteria and study design. Frequency of F/U was not standardised and clinical remission criteria not mentioned
24	Prognostic factors for remission in early RA: a multiparameter prospective study. Gossec L. et al. Ann Rheum Dis 2004;63:675-680	To determine prognostic factors for remission in early RA.	Prospective study of pts with early RA (disease duration of <1 yr and no prior DMARDs) Total no of pts – 191, mean age at diagnosis 50.5 and mean disease duration was 3.3 months 80% at baseline had seropositive disease and 45% had at least one SE. Six months after inclusion: 93% were on DMARDs (69% - monotherapy (mainly MTX/SZP) and 25% combination therapy (MTX+SZP) Mean DMARDs at 5 yrs – 1.95 33% received steroids at least once during F/U (5-15 mg/day) Duration of study – 5 yrs Clinical assessment by the same investigator at baseline, 6 months, 1 yr, 3 yrs and 5 yrs. X-rays of hands & feet were done at baseline, 3 & 5 yrs and scored using SvdH (films were read by 2 observers in chronological order and mean of two scores were used) Clinical remission based on DAS (<1.6) Remission was assessed at 3 yrs and both at 3 and 5 yrs (persistent remission)	Drop out rate - 7.3% (3 yrs) & 13.6%(5 yrs). Missing data at 5 yrs - 16% Remission rate at 3 yrs – 48 (25%), at 5 yrs – 38 (20%) and both at year 3 & 5 - 30 (15.7%) 79% of pts in remission at 3 yrs were also in remission at 5 yrs <u>Univariate analysis:</u> baseline DAS score of <4 (OR 3.2), HAQ <1.25, Ritchie <17 and CRP <14.5 were significantly correlated with remission at 3 yrs All the above variables and total Sharp score of <4, EMS <60 mins and RF negativity were	Prospective study with long duration of F/U. Pts were treated early with DMARDs. Standardised F/Us and detailed clinical, lab and radiological data were collected. Validated remission criteria and x-ray scoring method were used. Radiographic scores at baseline were assessed in relation to their predictive value for remission.	Clinical and lab variables were recorded only at 0, 6 months, 1, 3 & 5yrs and x-rays were only done at 0, 3 & 5 yrs. Role of DMARDs were not analysed in detail. Correlation between clinical disease activity/ remission and radiological disease progression and functional disability were not analysed

				correlated with persistent remission at 3 & 5 yrs Multivariate logistic regression : low DAS, baseline total radiographic score and Ritchie score were important predictors for both remission at 3 yr & persistent remission at year 3 & 5. Low HAQ and short duration of morning stiffness were predictive of remission at 3 years. Low baseline CRP was predictive of persistent remission		

25	The influence of sex on RA: A prospective study of onset and outcome after 2 yrs. Tengstrand B et al. J Rheumatol 2004;31:214-22	To analyse the influence of patient's sex on early RA within 1 yr of disease onset and after 2 yrs F/U	Prospective, multicenter observational study of early RA pts (disease duration of <12 months) Total no of pts - 844 (1987 ACR criteria for RA) Mainly 3 outcome variables were analysed in relation to sex: DAS28, HAQ and radiological damage/Larsen's score. Clinical disease activity was assessed using DAS 28 (remission <2.6). DAS 28 and x-rays were recorded at baseline and at 2 yrs. In a subgroup of pts (n=329) Larsen's method was used to quantify damage and the drop out rate at 2 yrs was 30%, mainly due to lost films. x-ray films were read by 1 or 2 observers and the mean score was used.	At study entry: significant difference in mean age of disease onset (men-62, women-54) and age distribution (incidence of RA = 1:5 M/F for age between 20 and 30 yrs and 1:1 for age between 60 and 70 yrs). Women had more hands & feet involvement with high DAS 28 and HAQ scores at presentation. More men with younger age of disease onset had seropositive disease and positive family history of RA. In women, CRP, DAS 28, radiological changes and Larsen's score were all correlated significantly with higher age at disease onset. Remission at 2 yrs-40% (men) & 28% (women). In men, significant correlation was found between disease duration before study entry, RF positivity, DAS 28 at baseline , HAQ and DAS 28 at 2 yrs. In men, presence of SE, initial DAS28	Prospective, multicenter study with a large no of pts with early RA. More detailed analysis of clinical, functional, lab and radiological disease status between men and women. Validated remission criteria was used.	Larsen's score was used only in a subgroup of pts. Duration of F/U (2 yrs) was probably too short to assess the functional and radiological outcome. Subgroup of pts in remission were not analysed in detail in relation to predictive factors for remission.

				and HAQ correlated with HAQ at 2 yrs. No significant difference in Larsen's score at 2 yrs between men and women. In men, RF and Larsen score at baseline correlated with Larsen score at 2 yrs. In women apart from above variables, age, CRP and DAS28 at baseline also correlated with Larsen score at 2 yrs . Multiple linear regression analysis showed that in men, RF and DAS28 at baseline correlated with DAS28 at 2yrs , whereas in women, age, HAQ, and DAS28 at baseline correlated with DAS28 at 2 yrs. Significant correlation between RF at baseline and Larsen score at 2 yrs in men and between RF,CRP at baseline and Larsen score at 2 yrs in women. Women switched DMARD more frequently than men during the first study year (42% vs 31%) Start of steroids at study entry – 53% (men) & 44% (women)		

26	Comparison of combination therapy with single-drug therapy in early rheumatoid arthritis: a randomised trial. FIN-RACo trial group. Mottonen T, et al. Lancet 1999;353:1568-73	To compare the efficacy and tolerability of combination therapy with monotherapy with or without prednisolone in early RA	Multicenter, randomised controlled trial. Patients with active RA (n=195)were randomised either to combination therapy (SZP=500 mg bd, MTX=7.5 mg/wk, HCQ=300 mg od, Pred=5 mg od) or monotherapy (SZP=2 gm od ± Pred ≤ 10 mg od) for 2 yrs and then they were treated according to the physician's choice. In the combination therapy arm, prednisolone could be tapered and stopped after 9 months if patients remained in remission. Clinical assessments were done at 1,3,4,5,6,9,12,18 and 24 months. Clinical remission (primary outcome measure) was assessed using modified ACR criteria (5/5 excluding fatigue) ACR 20, 50 and 70% responses were also analysed. X-rays of hands & feet at baseline, 6, 12 and 24 months and scored using Larsen method	97 pts received combination therapy and 98 received monotherapy in which MTX was substituted in 51 pts. At 2 yrs, 178 pts (combi-87, mono-91) completed the trial. At 2 years, more pts in monotherapy group used steroids than combination group (50 vs. 43) and cumulative no of steroid injections were higher in the monotherapy group. ACR remission was: 25%(yr 1) and 37%(y 2) in the combi group compared to 11% (yr 1) and 18% (yr 2) in the mono group. Early institution of DMARDs(< 4 months from disease onset) showed increase in remission rate in the mono group but not in the combi group. ACR 50% response	Randomised, controlled trial with standardised assessments and frequent F/Us. Good sample size with long duration of F/U (up to 5 yrs). First clinical trial to use clinical remission as a primary outcome measure. Clinical and radiological disease progression was analysed and was related to functional outcome after 5 years in another study from the same group. Radiological disease progression was studied prospectively in pts in persistent remission at 6, 12 and 24 months	Usual weaknesses of randomised trials as it does not reflect the 'real life' pts and clinical management. Relatively more pts received steroids both at study start (all in combi group and 64% in mono group) and after 2 years (49% in combi group and 55% in mono group), which could have influenced the results.

				was 75% (yr 1) and 71% (yr 2) in the combi group compared to 60%(yr 1) and 58% (yr 2) in the mono group. Frequency of adverse events were similar in both groups. Mean Larsen score did not increase significantly in pts in sustained remission at 6, 12 and 24 months.		
27	Retardation of joint damage in pts with early RA by initial aggressive treatment with DMARDs. Korpela M et al. Arthritis & Rheumatism. July 2004; vol50 (7):2072-2081	To evaluate the long-term frequency of disease remissions and the progression of joint damage in pts with early RA who were initially randomised to either monotherapy or combination therapy (3 DMARD) for 2 yrs. Frequency of remissions and the extent of radiological damage are the primary	Multicenter, randomised study of early RA pts (symptom duration of < 2 yrs; median 6 months) comparing the efficacy and tolerability of combination therapy (MTX+SZP+HCQ+Pred) with monotherapy (SZP ± Pred). IA steroids were allowed in all pts if necessary. A total of 199 pts (1987 ACR criteria) with active disease were included. After 2 years, the choice of DMARDs and Pred dose was unrestricted, but the aim was still to achieve remission. After the initial 2 yrs, clinical assessments were done at 30, 36, 42, 48, 54, and 60 months. Median no of DMARDs at 5 yr F/U in both groups was 3 (range 1-8 in monotherapy and 3-6 in combination therapy) Clinical remission was based on no swollen or tender joints and low ESR/CRP. X-rays were taken at baseline and then annually for 5 yrs (Larsen's method)	At 2 yrs, the frequency of remission was 37% (combi) & 18% (mono). At 3 yrs – 29% vs 21%, at 4 yrs – 34% vs 21% and at 5 yrs – 28% vs 22%. Radiologic progression was significantly low in combination therapy compared to monotherapy at both 2 and 5 yrs F/U (5yr median Larsen score 11 vs. 24). Logistic regression analysis showed that the extent of radiologic	Randomised study with long duration of F/U and standardised F/U assessments . Both clinical and radiological disease progression was analysed. Primary outcomes were remissions and extent of radiologic damage.	Usual weaknesses of randomised trials as it does not reflect the 'real life' pts and clinical management.

		outcome measures.		damage at 5 yrs was predicted by the presence of RF at baseline, single treatment strategy for the first 2 yrs, disease duration before diagnosis and ESR at baseline. Rate of permanent work disability at 5 yrs was nil in pts in remission at 6 months and pts in the initial combi group were more likely to maintain their capacity to continue in paid work over 5 yrs compared to mono group.		
28	The relationship between disease activity and radiologic progression in patients with RA. Welsing P, et al. Arthritis & Rheumatism. July 2004; 50(7):2082-2093	To study the longitudinal relationship between inflammatory disease activity and subsequent radiologic progression and to determine whether a change in disease activity is related to a change in radiologic progression in	Two prospective cohorts of early RA pts 1) <u>UMCN inception cohort :</u> disease duration of <1 yr and no prior DMARDs. For this study pts with at least 3 yrs F/U were included. A total of 185 pts with a maximum F/U of 9 yrs. Clinical assessment (DAS) was done every 3/12 and x-rays (SvdH-one observer) every 3 yrs. 2) <u>COBRA cohort:</u> 56-week, multicenter, randomised, double-blind, controlled trial to test the efficacy of SZP+MTX+Pred vs SZP alone (disease duration of < 2yrs and no prior DMARDs except HCQ or steroids). A total of 152 pts with active disease and a maximum F/U of 6 yrs. Clinical assessment (DAS28) at 0, 16, 28, 40 and 56 weeks and then at least once a yr and x-rays (SvdH-mean score of 2 observers) 6 monthly first yr and then annually.	Pts in the COBRA cohort had relatively high DAS and HAQ but less Sharp score (median) compared to UMCN cohort at study entry. In the UMCN cohort, RF positivity and Sharp score at baseline correlated significantly with radiologic damage. In the COBRA cohort, treatment allocation, RF	Prospective study of early RA pts with standardised and long duration of F/U. Longitudinal regression analysis (GEE) was used in this study to assess the relationship between clinical and radiologic disease progression. In other studies looking at relationship between disease activity and	Missing data. For 14 pts in UMCN cohort only one DAS was available. Radiographic scoring methodology (chronological order, interobserver variability and ceiling effect) could have introduced measurement error rather than true

		individual pts.		positivity and Sharp score at baseline were significantly related to radiologic damage. Fluctuations in disease activity had an independent effect on radiologic progrerssion and the strength of this association was dependent on RF status and/or baseline disease activity. Statistically a change in the mean interval DAS and/or SD of the mean interval DAS over time in the UMCN cohort or a change in the DAS28 over time in the COBRA cohort results in corresponding change in radiologic progression and this was only found in RF positive pts. The finding of RF positivity and baseline x-ray damage having an independent effect on radiologic progression in this study might explain the radiographic progression in pts in clinical remission, seen	radiologic progression, time- independent linear regression analysis were used , where within-patient variation in disease activity is not accounted for by AUC analysis and the correlation was only judged within one time interval. This study/statistical methods addressed the problems with other studies based on time-averaged estimates for disease activity to assess the interrelationship between disease activity and radiologic progression – time averaged estimates do not reflect the high variability of disease activity within pts and the ordinary regression methods used in these analyses assume a linear course of radiologic progression over time.	change in SvdH scores. Regression coefficients cannot be directly compared across both cohorts because of differences in inclusion criteria, treatment allocation, clinical assessment (DAS vs DAS28) and frequency & duration of F/U between two cohorts. X-rays were also done at different intervals in these two cohorts. .

				in other studies.		
29	A good response to early DMARD treatment of pts with RA in the first yr predicts remission during follow up. Verstappen S, et al. Ann Rheum Dis. Jan 2005;64(1):38-43	To describe the frequency and duration of remission in a cohort of pts with RA and to describe clinical and treatment characteristics of pts with remission vs pts without remission.	Randomised, prospective clinical trial of early RA pts (disease duration < 1 yr), who fulfilled 1987 ACR criteria. Pts were randomised into 4 treatment strategy groups: 1) HCQ, 2) IM Gold, 3) MTX, 4) pyramid (NSAIDs for at least a yr and then DMARDs if no response) After 2 yrs, the clinicians were allowed to use any other DMARDs. Total no of pts – 562 and the mean F/U duration was 62 months. Clinical assessment at baseline and every 3 months for the first 2 yrs and then 6monthly. For missing clinical data, the mean of the previous and next score was imputed. X-yays were taken at baseline and then yearly (SvdH). For missing data at the last visit, the slope of radiological progression of the previous yrs was used) Remission was defined as – EMS ≤ 15 mins, VAS pain sscore ≤ 10, Thompson joint score (a weighted joint score including both swollen and tender joint counts) ≤ 10 and ESR ≤ 30 for at least 6 months. Good response to initial DMARD (≥ 50% improvement from baseline on at least 3 of the following 4 parameters; VAS, Thompson joint score, EMS or ESR)was assessed at 1 yr after study entry	Baseline disease characteristics of the 4 treatment groups were similar. In the study cohort, 22% used oral steroids and 57% received IA steroids during F/U. A total of 144 pts dropped out during F/U (42 died, 13 in remission). 205 pts (36%) achieved at least one period of remission during F/U(57 pts had a second and 8 pts had a third period of remission). Of the 270 remission periods, 158 remission periods were followed by a flare up. Mean cumulative duration of all remission periods was 25 months , comprising 39% of total F/U time. Mean duration from study start until the first period of remission was 24 months. 16 pts (8%) did not receive any DMARDs	Prospective study of pts with early RA and long duration of F/U. More frequent clinical assessment. Effect of treatment on subsequent remission was analysed and predictive factors were looked at. Effect of different DMARDs on subsequent disease activity/ remission was analysed in detail. Both the frequency and duration of remission was looked at.	Missing data and large drop out rate. The results of this randomised, clinical trial may not be generalisable to the 'real-life' pts as we study in observational studies. Different treatment strategy could have influenced the results. Clinical remission criteria used in this study was not widely used and x-ray scoring methodology was not explained. Clinical disease was not correlated with functional and radiological disease progression.

				during the 6 months prior to first period of remission. At 4 yrs F/U, 142 out of 425 pts (33%) had at least one period of remission. Good responders at 1 yr F/U were found to achieve remission more likely in the subsequent yrs despite similar baseline characteristics and similar treatment. Baseline predictors of remission were good response to treatment, less pain, negative RF and lower joint score.		
30	Frequency of remissions in early RA defined by 3 sets of criteria. A 5 yr follow up study. Makinen H, et al. J Rheumatol 2005;32:796-800)	To study the frequency of remission using 3 sets of criteria in pts with RA at 5 yrs after the diagnosis.	Inception cohort of pts with early RA Inclusion criteria - pts > 16 yrs old with recent onset inflammatory arthritis who did not meet criteria or show clinical signs of other specific arthritides. Total no of pts – 127 at study entry and 111 pts completed the 5 yr F/U. Mean age – 56 yrs and median duration of symptoms before diagnosis was 5 months Clinical, lab measures of disease activity and x-ray findings (Larsen's – one observer) were recorded at baseline, 2 & 5 yrs. All pts but one had DMARDs. SZP followed by MTX were the two most commonly used first line DMARDs. During F/U 59% took MTX. 54% of pts used steroids at some time during F/U 3 types of remission criteria:	95 pts (75%) met ACR classification criteria for RA at baseline. cumulatively 96 out of 111 pts (87%) met ACR criteria for RA at 5 yrs and 9 pts fulfilled the ACR criteria for RA during the 5 yr F/U period. <u>Clinical remission</u>: 39% at 2 yrs, 37% at 5	Prospective study of pts with early RA and the aim of treatment was to achieve remission. Validated clinical remission criteria used and validated x-ray scoring method used. Both clinical and radiographic remission was studied. Other similar studies were discussed.	Relatively small no of pts. Classification criteria for RA was not met in all pts. Frequency of clinical and x-ray assessment was too long (0,2,5 yrs) X-ray scoring methodology was not discussed in detail. Predictive factors

			1) ACR remission criteria – fatigue excluded, 5/5 2) Clinical remission – no tender and no swollen joints and normal ESR 3) Radiographic remission – no worsening of erosions and/or no new erosions from baseline to 5 yrs.	yrs and 21% at both 2 & 5 yrs. ACR remission: 17% at 5 yrs Radiographic remission: 55% at 5 yrs. Only 13% met all 3 sets of remission criteria Less than 50 % of pts who were in clinical remission at 2 yrs were in remission also at 5 yrs. 22 pts with no swollen and no tender joints and normal ESR did not meet ACR criteria because of pain and/or EMS		not analysed. Clinical and radiographic disease was not correlated with function and/or other outcomes.
31	Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. van der Heijde D, et al. Ann Rheum Dis 2005;64:1582-1587	To assess methods to calculate achieving remission in a double blind randomised trial in pts with RA who received etanercept, MTX or the combination of both	TEMPO trial – multicenter, double blind, parallel design study active RA pts randomised to one of the 3 treatment groups. Total of 682 pts (MTX-228, Eta –223 & both – 231) Mean age – 52 yrs Duration of this study analysis – 1 yr. Clinical assessment using DAS, DAS28 and ACR 70.	DAS remission: 37%(eta+MTX), 18% (eta) & 14% (MTX). **DAS28 remission** 38% (eta+MTX) 18% (eta) & 17% (MTX) Concordance was greater between DAS and DAS28 but not between either of these and ACR70.	Prospective, randomised trial with large no of pts. Validated remission criteria used . Detailed statistical analysis to study sustained remission and to incorporate time factor. (ConRew scoring system and GEE)	Results of this study may not be generalisable to other remission studies because of different inclusion criteria, study design and treatment. Short duration of F/U and no correlation with radiographic and functional outcome.

32	Impact of age and co-morbidities on the criteria for remission and response in RA. Krishnan E, et al. Ann Rheum Dis 2005;64:1350-1352	To determine to what extent health status impairment in RA measured by self report of pain, global assessment and functional disability is attributable to age and other co-morbid conditions as opposed to the disease itself	Questionnaire survey of random sample of 1530 adults	As the no of co-morbidities increase, the no of subjects with increased pain, global health assessment and HAQ-D1 increase. When there are 3 or more co-morbidities 1 in 5 (20%) of the general population has 2 or more clearly abnormal measurements In median regressions, the only predictors of pain and global general health were age and co-morbidities.		
33	Is DAS28 an appropriate tool to assess remission in RA. Makinen H, et al. Ann Rheum Dis. June 2005;64:1410-1413	To study which cut off point of DAS28 corresponds to fulfilment of the ACR remission criteria and clinical remission criteria in patients with RA	Observational study of pts with RA. One off study point at 5 yr F/U. Remission at 5 yr was based on ARA remission (fatigue excluded, 5/5) and clinical remission (no swollen and no tender joints and normal ESR) Total no of pts – 161, mean age – 61 yrs 61% had seropositive disease and 32% had erosive disease.	12% met ACR remission criteria, 25% met the less vigorous ACR criteria (4/5) and 34% met clinical remission criteria. Cut off value of DAS28 was 2.32 for ACR remission criteria and 2.6 for the less vigorous ACR criteria.	Prospective study. ROC curve analysis was performed to calculate a cut off point of DAS28 that best corresponds to the ACR and clinical remission criteria.	Only abstract available. Clinical measures at baseline and at 5 yrs only.

				Cut off value of DAS28 was 2.68 for clinical remission criteria. In pts with DAS28 <2.32, 19% had tender joints, 11% had swollen joints and 7% had both swollen and tender joints. ESR had lowest positive predictive value and joint pain had highest positive predictive value		
34	Most patients receiving routine care for RA in 2001 did not meet inclusion criteria for most recent clinical trials or ACR criteria for remission. Sokka T, et al. J Rheumatol 2003 Jun;30(6):1135-7	To determine the proportion of 2 cohorts of pts with RA who met 4 common criteria for inclusion in clinical trials (SJC ≥ 6, TJC ≥ 6, ESR ≥ 28, EMS ≥ 45 mins)	Two cohorts of pts who met 1987 criteria for RA Cohort L (late): 146 pts with a mean disease duration of 14 yrs and a mean F/U of 6.2 yrs Cohort E (early): 232 pts with a mean disease duration of 1.8 yrs	Overall, 15.3% of cohort L and 34.1% of cohort E pts had ≥ 6 swollen and tender joints as well as an ESR of ≥ 28 or EMS of ≥ 45 mins. Only 4.1% of pts in cohort L and no pt in cohort E met ARA criteria for remission	Clinically relevant as it shows the 'real pts' that we see in clinics and the difficulty in recruiting pts for clinical trials with strict inclusion criteria	
35	The longitudinal evaluation of RA pts in clinical remission: Frequency of persistent remission, disease flare, structural and functional	To assess the longitudinal outcome of a cohort of pts in clinical remission and test the	Longitudinal study of 107 pts with RA, who were in clinical remission (absence of clinically significant synovitis with no disease flare or change in treatment for at least 6 months) Clinical, lab and imaging assessments at baseline and 12 months (MRI & US of the dominant hand and wrist)	At baseline, 55% pts satisfied criteria for ACR remission and 57% DAS28 remission. 79% had evidence of	Prospective study using x-rays, US and MRI to detect early radiological changes. Correlation between clinical, radiological	Pts with established RA. No details on DMARDs. Predictive value of baseline clinical

	status. Brown A, et al. [Abstract - ACR]	hypothesis that sub-clinical inflammation determines clinical, structural and functional outcome.		ongoing inflammation on US and 81% on MRI. By 12 months, 56% remained in ACR remission and 74% DAS28 remission. 79% had evidence of persistent inflammation on US and 77% on MRI. 28 out of 107 (26%) had a flare up, which required treatment change. Deterioration in erosion score in at least one joint was observed in 25% on x-rays, 34% on MRI and 38% on US. MRI total synovitis score at baseline was the best predictor of subsequent change in erosion score. Overall, 1 in 4 pts in clinical remission experienced disease flare and 1 in 3 had structural deterioration.	and functional parameters were analysed	and lab variables for remission not reported. Short duration of F/U to assess long term outcomes. These imaging techniques may not be easily accessible to many clinicians and difficult to organise in day to day clinical practice.
36	MRI and US may improve the accuracy of RA clinical remission assessment by identifying	To test the hypothesis that MRI and US would improve	Cross sectional study of 107 pts with RA who were in clinical remission (no swollen and no tender joints and normal ESR for at least 6 months) Clinical, lab and imaging (US & MRI) assessments. Mean age – 56 yrs and mean disease duration – 9 yrs	92% were on DMARDs 64% had seropositive disease and 83% had erosions.	This study revealed the problems with clinical remission criteria in assessing remission	Cross sectional study and no correlation with functional and

	a high frequency of sub-clinical inflammation. Brown A, et al. [Abstract - ACR]	the precision of clinical remission assessment		Mean CRP – 5, mean duration of remission – 28 months. 55% of pts satisfied ACR remission criteria and 57% DAS28 remisssion. However, only 15% were in remission on US and 6.5% on MRI. 31% of joints on US and 44% of joints on MRI had evidence of synovitis despite no clinically detectable swelling.	more strictly. US and MRI were used to supplement the clinical parameters in assessing remission.	other long term outcomes. No detailed analysis of DMARDs. Predictive factors for remission not reported. These imaging techniques may not be easily accessible to many clinicians and difficult to organise in day to day clinical practice.
37	Clinical and radiographic outcomes of four different treatment strategies in patients with early RA (the BeSt Study). Goekoop-Ruiterman YPM, et al. Arthritis & Rheumatism vol.52, No.11, Nov 2005, pp 3381-3390	To compare clinical and radiographic outcomes of 4 different treatment strategies, with intense monitoring in pts with early RA.	Multicenter, randomised, controlled clinical trial with 4 different treatment arms: Group 1. sequential monotherapy (MTX→SZP →Lef→combi); Group 2. step-up combination therapy (MTX→MTX+SZP→MTX+SZP+HCQ→MTX+SZP+HCQ+Pred→other combi); Group 3. initial combination therapy (MTX+SZP+Pred 60 mg→other combi); Group 4. initial combination therapy with infliximab (up to 10 mg/kg every 8 wks) Patients with active RA and disease durarion of < 2yrs were included. Pts were assessed every 3 months for a year by a trained nurse who was blinded to treatment arm and therapy adjusted to keep DAS <=2.4. If DAS remained <2.4 for 6 months, drugs were tapered to monotherapy maintanence dose. <u>Primary end points</u>: functional (HAQ) and radiographic outcome (SvdH) from baseline upto yr 1. <u>Secondary end points</u>: ACR 20%, 50% and 70% response criteria and DAS remission (<1.6) x-rays of hands and feet were done at baseline and at yr 1 and scored by two	Total no of pts-508 (Group 1=126, Group 2=121, Group 3=133, and Group 4=128). 32% of all pts had DAS clinical remission at year 1. Low-disease activity (DAS <=2.4) at 1 year was 53%, 64%, 71%, 74% in Groups 1-4 respectively. 78% in group. 3 had stopped prednisolone and 50% in group.4 had stopped	Randomised clinical trial with large no of early RA pts. Validated clinical remission criteria and x-ray scoring method were used. Standardised F/U Correlation between clinical and radiological disease progression was analysed and related to functional ability. Detailed radiological assessments were done and the x-ray	All pts had active disease and the aggressive treatment strategy in this study makes it difficult to compare it with other remission studies. Short duration of F/U to assess the radiographic and functional outcomes. Quite high doses of steroids and infliximab were

			trained assessors and mean of the two scores were used. Radiographic progression was reported using mean, median and SDD	infliximab because of DAS persistently <=2.4. Mean HAQ scores were lower in groups 3 and 4 compared to groups 1 and 2 at 3 months but the difference was smaller at 1 yr. Radiographic progression was less in groups 3 and 4 compared to other groups and the median increase in total Sharp scores were 2.0, 2.5, 1.0 and 0.5 in groups 1-4 respectively. No progression of total Sharp scores were noted in 67%, 73%, 87% and 93% in groups 1-4 respectively. Of all pts with nonerosive disease at baseline, 29%, 53%, 38% and 15% of pts in groups 1-4 respectively progressed to erosive disease after 1 yr. Adverse events of >=1 was noted in 43%, 47%, 37% and	progression was reported both at group and individual level using SDD.	used in this study which have its own implications on cost and long term side effects. Still > 40% of pts in group 1 and 2 had a DAS of <= 2.4 at 1 yr and the difference in mean HAQ and radiographic progression between groups 3, 4 and 1, 2 was not very impressive at 1 yr considering the intensive treatment regime.

				39% of pts in groups 1-4 respectively No of serious AEs were, 8, 9, 17 and 6 in groups 1-4 respectively. No cases of TB or opportunistic infections.		
38	Clinical improvement in Early RA: Association with joint damage and benefit of initial combination therapy. De Vries-Bouwstra J, et al [Abstract - ACR]	To determine the association of clinical improvement with progression of joint damage for different treatment strategies in pts with early RA	BeSt-study – randomised clinical trial of 508 pts with early, active RA comparing 4 treatment strategies – 1. sequential monotherapy, 2. step-up therapy (both starting with MTX for 6 months) and initial combination therapy with 3. high dose prednisolone or 4. infliximab. Clinical assessment (DAS)every 3 months. For this study, all pts with continuous DAS <1.6 (remission) and pts with continuous DAS >2.4 (failure) between 6 and 24 months of F/U. Joint damage progression (SvdH) and functional ability for the subgroups of remission and failure between initial monotherapy (Groups 1+2) and initial combination therapy (Groups 3+4) were compared in this study.	61 pts (15, 6, 19 and 21 in Groups 1-4, respectively) achieved remission and 54 pts (19, 12, 12 and 11 in Groups in 1-4, respectively) were failures. Continuous remission was twice as frequent with initial combination therapy and was significantly associated with less radiographic progression and good functional ability. Within the remission group, the percentage of pts with radiographic progression was ten times higher with initial monotherapy as compared to initial combination therapy. For the failure group,	Randomised clinical trial with large no of early RA pts. Validated clinical remission criteria and x-ray scoring method were used. Standardised F/U Correlation between clinical and radiological disease progression was analysed and related to functional ability.	All pts had active disease and the aggressive treatment strategy in this study makes it difficult to compare it with other remission studies. Short duration of F/U to assess the radiographic and functional outcomes. Selection criteria for this study could have influenced the results.

				the percentage of pts with radiographic progression did not differ significantly between treatment groups; however for this group, the mean cumulative HAQ scores were significantly lower with initial combination therapy.		
39	Defining remission in RA using different instruments. Mierau M, et al. [Abstract - ACR]	To determine the frequency of remission in routine clinical care and to identify the potential remnant degree of disease activity, the frequencies of remissions using various criteria	Observational study of 757 RA pts. Clinical assessment every 3 months Mean age – 60.2 yrs Mean disease duration – 9 yrs. Remission criteria used were 1) modified ACR criteria (4/5, excluding fatigue), 2) DAS28 < 2.6, 3) DAS28≤ 2.4, 4) clinical disease activity index (CDAI) ≤ 2.8, and 5) simplified disease activity index (SDAI) ≤ 3.3	31% fulfilled modified ACR remission criteria at least once and 17% at least at 2 consecutive visits. 88 % of the visits in ACR remission criteria also fulfilled the DAS28 remission criteria (77% for modified DAS28, 64% for SDAI and 61% for CDAI). Modified ACR and DAS28 remission criteria allowed for higher joint counts and HAQ indices than SDAI and CDAI	Large no of pts. Comparison of different remission criteria and they are more easy to use in daily clinical practice. Correlation between different remission criteria was assessed.	Pts had established disease. Correlation with radiographic disease state/progression was not reported. Individual parameters of these remission criteria and their positive predictive value were not analysed/reported
40	Presence of significant	To test the	Prospective controlled cohort study	Study cohort was	Prospective cohort with	RA pts with

	synovitis in RA patients with DMARD induced clinical remission. Brown AK, et al. Arthritis & Rheumatism, vol.54, No.12, Dec 2006, PP 3761-3773	hypothesis that modern joint imaging (US & MRI) improves the accuracy of remission measurement in RA.	No of pts included – 107 RA pts with established disease (median disease duration = 7 yrs (2-38) No of controls – 17 (sex matched normal subjects) Inclusion criteria: physician determined remission, age > 18 yrs, at least 12 months disease duration, no disease flare or treatment change in the last 6 months. 3 different remission criteria were applied to the study cohort. 1) ACR remission at 0 & 2 months; 2) DAS 28 of <2.6; 3) Complete clinical remission ie,asymptomatic patients with no painful, tender, and swollen joints. Median duration of remission at study entry – 22 months (6-144) X-rays were scored using Genant method by one observer. US and MRI of the dominant hand & wrist (8 joint regions) were performed by a single observer.	predominantly female (66%) and the mean age was 56 yrs. 81% of pts had erosive disease. 99% of the study cohort had received DMARDs at some point during the course of their disease but only 92% were taking DMARDs at the study time and 2% were on steroids (<5 mg). 68% of pts were on monotherapy(most common – MTX, SZP), 24% were on combination therapy and 4 pts on biologics. Only 55% of study cohort fulfilled ACR remission and 57% fulfilled DAS 28 remission. Out of 31 pts (29%) who achieved complete clinical remission, 93% fulfilled ACR and DAS 28 remission. 85% of study cohort	sex matched controls. Sample size was good and reflect common clinical practice (physician determined remission). Established remission criteria were used as well as complete clinical remission. More sensitive imaging modalities with validated scoring systems were used to define the true disease status. Demonstrated that the day to day clinical assessment is insensitive in defining true disease inactivity and may explain the discrepancy between clinical and radiological disease progression in some cases. Appropriate statistical tools were used.	established disease. Study population was selected using non-validated remission criteria by different physicians which could have influenced the results. There were still significant no of pts with some form of disease activity (painful or tender joints and high CRP/ESR) which might explain some of the US or MRI findings. Expensive imaging modalities which require experienced readers and resources with financial implications particularly in a DGH setting. Very time consuming (US – 30 mins , MRI – 70 mins) and accessibility is a

				showed evidence of synovial hypertrophy (SH) on US and 60% had increased power Doppler signal. 36% of total joints examined (263 out of 725) on US showed SH despite normal clinical findings and increased power doppler signal was seen in one third of these joints. 92% of study cohort showed evidence of synovitis on MRI and 55% showed bone marrow edema. 52% of total joints examined (327 out of 627) showed synovitis on MRI despite normal clinical findings. 3 controls (18%) had evidence of synovitis on MRI but no bone marrow edema. 96% of pts in clinical remission according to all three remission criteria have infact showed synovitis on MRI. SH on US was seen		problem. Cost effectiveness of such approach is yet to be proven. Only long term studies of pts in clinical remission can show whether such expensive modalities have any influence on long term outcomes particularly in relation to treatment modification solely based on US or MRI findings. 3 out of 17 normal subjects (controls) had synovitis on MRI – Is it expected? Practically it is difficult to rely on US or MRI to define true remission and to justify any treatment change in asmptomatic pts with apparently .normal clinical findings.

				in 81% (ACR remission); 84% (DAS 28 remission) and 73% (complete clinical remission) of pts respectively.		
41	Sex: a major predictor of remission in early rheumatoid arthritis? Forslind K, et al. Ann Rheum Dis Jan 2007; 66:46-52	To determine the frequency of remission in early RA. Also to analyse predictive factors for remission with a detailed analysis on the influence of sex on future disease course/remission	BARFOT Study Group – multicentre, observational study of early RA pts (<= 12 months) No of pts at study entry and at 2 yrs – 698 No of pts at 5 yrs - 608 F/U visits at – 3 ,6, 12, 18, 24 and 60 months. Remission was assessed using DAS 28 (<2.6) and clinical remission criteria (no swollen or tender joints and normal ESR). Frequency of both point remission (at 18, 24 and 60 months) and period remission (18-24, 24-60, 18-24-60) were assessed. At baseline, > 80% received DMARD monotherapy (most common – MTX, SZP). After 2 years, 30% of pts were off DMARDS and some more after 5 years. At baseline, 42% of women and 41% of men were given prednisolone and at 2 years the corresponding figures were 35% and 33% and at 5 yrs- 23% and 17% respectively	Mean age of pts at baseline was 58 yrs, 64% were women and mean disease duration was 6.2 months. Most pts had moderate or severe disease activity at baseline (mean DAS 28– 5.27, mean HAQ- 1) 60% had seropositive disease and anti CCP was positive in 56% of pts. Remission rates: DAS 28 criteria – <u>Point remission:</u> 34.5% (at 18 months), 37.9% (at 24 months), 38.5% (at 60 months); <u>Period remission</u>: 26.3% (18 &24 months, 24 & 60 months) and 19.6% (18, 24 & 60	Multicentre inception cohort of early RA with large number of pts. Validated remission criteria used at specified time points. Low drop out rate. Both point and period remission rates were studied. Appropriate statistical methods were used. Detailed analysis of women and men separately and their influence on future disease course/ remission.	Long interval between 2nd (24 months)and 3rd (60 months) assessment during which time the disease could have fluctuated a lot and so reflected on the future disease course. Although overall physician assessment did not find higher baseline disease activity in women, the DAS28 scores were significantly higher in women at baseline which could have influenced the future disease course and results. Relatively more patients were on steroids at baseline

				months). For women the frequency of point remission at 18, 24 and 60 months were 30.4%, 32.1% and 30.8% respectively (42%, 48% and 52% for men) In women, frequency of period remission were 22%, 19% and 14% at 18+24 months, 24+60 months and 18+24+60 months respectively (34%, 39% and 30% for men). Using clinical remission criteria, 17.8% of women and 26.8% of men achieved remission at 24 months and the corresponding figures at 60 months were 21% and 28.5% respectively. Period remission (at 24+60 months) using above criteria was 9.5% in women and 16.4% in men. Univariate analysis showed sex, duration		and subsequently which may explain higher remission rate in this study Also it may be because the DAS28 is not as stringent as original DAS in assessing disease activity. Radiological data and long term outcome not reported. Odds ratio from univariate analysis were not reported and odds ratios from multivariate analysis were not that higher.

				of disease at baseline, anti-CCP, RF, DAS 28 and HAQ showing predictive value for remission. CRP did not show any predictive value. Multiple logistic regression analysis showed that male sex, short disease duration, low baseline DAS 28, low baseline HAQ score and RF negativity were independently associated with remission. Sex (male) seemed to be the major independent predictor of remission which was not influenced by age and disease duration at inclusion statistically. Disease progression was more noted in women at both 2 and 5 years compared to men. No difference in DMARD or steroid		

				treatment between women and men in relation to rate of remission		
42	Bone oedema predicts erosive progression on wrist MRI in early RA-a 2 yr observational MRI and NC scintigraphy study. Palosaari K, et al. Rheumatology 2006;45:1542-1548	To investigate if disease assessment by contrast-enhanced dynamic and static MRI and nanocolloid (NC) scintigraphy gives useful additional information in early RA	27 (21 women & 7 men) pts with early RA (<= 12 months) were prospectively assessed at baseline , 1 yr (1 pt dropped out) and at 2 yrs (further 3 pts dropped out). Median age – 51 yrs and median duration of symptoms - 5 months. Clinical (TJC, SJC, ESR/CRP) and functional assessment (HAQ) and MRI (wrist) & scintigraphy (hands) were done at 0, 1 & 2 yrs. Patients were classified as treatment responders if there was >= 50% improvement in the TJC, SJC, HAQ, with normal CRP/ESR at 1 or 2 yr F/U. Primary outcome measure was the progression of erosion score on wrist MRI.	9 out of 24 pts (38%) showed persistent clinical response throughout 2 yrs of F/U. At baseline, MRI detectable bone erosions were found in 21 pts (75%) and the corresponding figures at 1 yr and at 2 yrs were 81% and 83% respectively. 4 pts had no erosions in their baseline and F/U scans. Only 1 out of 9 responders developed new erosion during F/U. 13 out of 15 non-responders (87%) developed new /progressive erosions from baseline to 1 yr F/U. From 1 to 2 yrs F/U, 9 out of 15 non-responders (60%) had	Prospective, observational study of early RA pts. Sensitive and specific imaging study with F/U. Correlation was analysed between clinical, functional variables and erosive changes on MRI. Positive correlation between increased isotope uptake and development of new erosions on MRI as shown in this study was not reported before.	Small no of pts. X-rays of hands and feet were not done at any time point and so no information on correlation between x-ray and MRI findings and interrelationship between clinical, x-ray and MRI disease progression was not studied. Poor ICC (0.71) value for inter observer variability for reading erosions at 1 yr. Issues such as accessibility and cost effectiveness in relation to long term outcomes need to be addressed and evaluated before recommending the wider use of such expensive imaging

				progressive bone damage, while the remaining 6 pts (40%) had stopped erosive progression. Baseline variables such as bone oedema score, synovitis score, ESR, CRP and isotope uptake correlated with development of new erosions on MRI from baseline to 2 yrs and no correlation was found for age, sex, DMARDs, TJC, SJC, HAQ and RF. On multivariate analysis, bone marrow oedema was the only baseline variable, which showed predictive value (OR 4.2) for progression of erosions at 2 yrs F/U.		modalities in our routine clinical practice.
43	Low dose prednisolone in addition to the initial DMARDs in patients with early active RA reduces joint destruction	To assess the efficacy of low-dose prednisolone on joint damage and disease	Multicenter, open randomized trial comparing pred 7.5 mg + DMARD (n=119) vs DMARD (n=131) alone. Primary end point – difference in changes in radiographic damage scores after 2years. Secondary end points – remission rates and differences in disease activity	Remission rate after 1 yr: 51.3% (prednisolone) vs 39.2% (non-prednisolone) and after	Multicenter, randomized study. Patients were selected from a large observational cohort	Not' real life' pts as only pts with active disease were included and lot of pts were excluded

	and increases remission rate. Svensson B, et al. Arthritis& Rheumatism. Vol.52,No.11, Nov 2005, pp 3360-3370	activity in patients with early RA	and function. Inclusion criteria: early RA (<= 1 year), active disease (DAS 28 > 3.0) Exclusion criteria: earlier use of steroids, DMARDs or contraindication to steroids, patients with previous fragility fractures, pts aged < 65 years with a T score of < -2.5 and pts aged >= 65 years with a Z score of < -1 250 pts (all on DMARDs) were included and clinical & functional assessments at 0, 3, 6, 12, 18 and 24 months. X-rays of hands and feet at baseline, 1 yr and 2 yrs (SvdH). BMD (DEXA) was measured at baseline and after 2 yrs. Remission criteria – DAS 28 of < 2.6	2 yrs 55.5% and 32.8% respectively. group achieved remission. HAQ and SOFI index decreased significantly in the pred group than in the non-pred group. CRP fell rapidly in both treatment groups. Radiographic progression (change in total SvdH score) was less (erosion score more than JSN) after 1 and 2 yrs in the pred group compared to non-pred group. X-ray progression (total and erosion score) was less in pts in clinical remission at 2 yrs in the pred group but not in the non-pred group despite almost identical DAS 28. No of new erosions were also less in the pred than in the non-pred group. BMD at lum.spine and fem.neck did not differ significantly at baseline and after 2 yrs between the two treatment groups	(BARFOT). Large no of early RA pts and standardised follow-ups and radiographic assessment. Clearly shown that prednisolone reduces disease activity and radiographic progression over 2 yrs as there were no difference in DMARDs between two treatment groups and the baseline disease activity and radiographic scores were similar in both groups. Low drop out rates and 90% of randomized patients were eligible for radiographic evaluation.	because of various exclusion criteria. Not a double blind, placebo controlled study. Long term follow up needed to look for steroid induced adverse events like osteoporosis, diabetes and cardiovascular events. BP monitoring and the frequency of hypertension, cataract, glaucoma were not mentioned. Steroid as one of the risk factors for rheumatoid c.spine disease was not addressed and it will require long term F/U.

44	Very low-dose prednisolone in early RA retards radiographic progression over 2 years. Wassenberg S, et al. Arthritis & Rheumatism. Vol.52, No.11, Nov.2005, pp 3371-3380	To assess the effect of 5 mg/day of prednisolone on disease progression in patients with early RA receiving standard DMARD therapy	Double-blind, randomized, placebo-controlled trial. Inclusion criteria: disease duration < 2 yrs, at least 3 of 4 disease activity indices (6 tender joints, 3 swollen joints, EMS > 60 mins, ESR >= 28) Exclusion criteria: pts with steroid dependent disease, previous steroid use, previous use of or contraindications for MTX or IM Gold. 192 patients were enrolled but only 76 patients have completed the study after 2 yrs. Clinical and functional assessments at 0, 6, 12, 18 and 24 months. X-rays of hands and feet at 0, 6, 12 and 24 months (Ratingen and SvdH scoring). Lumbar spine x-rays at baseline and at 24 months. Primary outcome measure – changes in Ratingen score at 24 months compared with baseline. Secondary outcome measure – changes at 6 and 12 months, no of eroded joints, and changes in SvdH scores at each F/U visit compared with baseline Remission was assessed using ACR criteria at 2 yrs	Patients in the pred group were slightly older and more women. Clinical and functional improvement were only temporary in the pred group and failed to reach significance. Radiographic progression and no of new erosions were less in the pred group than in the non-pred group and this difference was less marked in the second year. Erosion scores showed more difference than JSN in assessing x-ray progression. ACR remission rate in pred group was 16% and in the non-pred group 9%.	Double-blind, randomized, placebo-controlled trial. Standardised F/U assessment and adverse events were recorded in detail	High drop out rate. BMD (DEXA) was not assessed for all the pts. Only MTX and IM Gold were used which might have influenced the results. Need long term F/U to look for steroid induced side effects
45	Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. Grigor C,	To test the hypothesis that an improved outcome can be achieved by intensive	Single-blind, randomised controlled trial. Inclusion criteria: RA pts with DAS of > 2.4 and with disease duration of < 5 yrs. Exclusion criteria: previous use of combination therapy with DMARDs, abnormal LFTs, FBC & creatinine. 110 pts were included and duration of study was 18 months.	Total no of pts – 110 (intensive-55, routine-55). 103 pts completed trial (intensive-53, routine-50). Baseline	Well designed, randomised controlled trial with standardised assessments. Treatment regime (step-up) is more practical and used by	Short/medium term improvement in clinical disease activity and functional outcome in this study could

	et al. Lancet 2004;364:263-69	management of RA pts in the out-patients compared with routine care	**Intensive group**: monthly F/U & DAS. In the first 3 months of starting a DMARD, if DAS remains > 2.4, IA/IM steroid were used. After 3 months of DMARD, if DAS remains > 2.4, then escalation of treatment with combination therapy including Pred 7.5 mg od (step-up) as per protocol were used. **Routine group**: 3 monthly F/U and no formal disease activity assessment. DMARD mono or combination therapy ± IA/IM steroids were used at the discretion of the treating physicians. Both groups had 3 monthly F/U with a metrologist (masked assessment) and had their clinical (EULAR, ACR) and functional (HAQ, SF 12) assessments done. Remission criteria - DAS < 1.6 X-rays of hands & feet done at 0 and 18 months and were scored (SvdH) by two radiologists in known order (Inter observer ICC= .84) Primary outcome: mean fall in DAS and proportion of pts with EULAR good response criteria. Secondary outcome: frequency of remission (EULAR), ACR response rates, EULAR core measures of disease activity and outcome including HAQ and SF 12. Cost benefits were also analysed.	characteristics were similar, although intensive group had slightly higher ESR (45 vs. 34) and CRP (44 vs. 38) but slightly less radiological damage/Sharp score (28 vs. 32) compared to routine group. Mean fall in DAS was significantly greater in the intensive group and this effect was seen within the first 3 months of study start and this effect lasted through out the study period. DAS remission at 18 months was 65% (n=36) in the intensive group and 16% (n=9) in the routine group. Significant improvement in all disease variables (except CRP), physical function (HAQ)and quality of life (SF 12) in the intensive group. Intensive group showed less progression of erosion and total sharp scores but not in joint space	many in a 'real life' situation. Low drop out rates and intention to treat analysis. Cost effective analysis was carried out	be attributed to increased use of steroids in the intensive group and long term F/U is needed to look for steroid induced side effects and to analyse the risk, benefit ratio. Study duration is not long enough to analyse the sustained improvement in radiographic and functional outcomes as previous studies (Kirwan) have shown that the benefits might be lost after stopping steroids. Monthly assessment of pts may not be practical.

				narrowing. In the intensive group, combination DMARDs were more frequent (67% vs. 11%) and mean MTX was higher. Drug related toxic effects were less frequent and fewer pts stopped DMARDs due to side effects in the intensive group. IA/IM steroid use (mean triamcinolone dose/month) was more in the intensive group (28 mg vs. 8 mg). Costs were lower in the intensive group but no significant difference in total hospital or community cost per patient between two groups		
46	Combination therapy with sulfasalazine and methotrexate is more effective than either drug alone in patients with rheumatoid arthritis with a suboptimal response to sulfasalazine: results from the double-blind	To establish whether a combination of SSZ and MTX is superior to either drug alone in pts with RA with a suboptimal responseto SSZ	Randomised, controlled study with active RA (DAS> 2.4) without prior MTX or SSZ. Phase I – 687 pts started on SSZ and assessed 6 months later. 165 pts entered phase II as suboptimal response to SSZ (MTX+SSZ=56 vs MTX=54 vs SSZ=55). Duration of F/U- 18 months and assessments were made at 6, 9, 12, 15 and 18 months. X-rays of hands and feet done at 6 and 18 months (scored by two observers in known order-SvdH).	Mean age – 55 yrs and mean duration of symptoms – 20 months. 77% female, 65% had sero positive disease. Mean DAS at baseline=4.0 Oral steroid not used.	Randomised , controlled study. True-to-life study recruitment protocol and most pts had early disease (70% < 1 yr).	24% of pts after phase I did not enter phase II even though eligible. Relatively large drop-out rate at study completion. (SSZ-25%, MTX-30%, combi-30%)

	placebo-controlled MASCOT study. Capell H, et al. Ann Rheum Dis 2007; 66: 235-241	(DAS > 2.4 after 6 months on SSZ)	Primary outcome: reduction in DAS Secondary outcome: EULAR and ACR response criteria	Improvement in DAS, ACR & EULAR response were better in combination arm than either treatment alone. No significant difference between MTX and SSZ arms. DAS remission = 10%(combi), 5%(SSZ), 3%(MTX)		Study was not powered to assess radiological progression. Better ACR response in combi arm was not statistically significant.
47	Radiological damage in patients with RA on sustained remission. Cohen G, et al. Ann Rheum Dis 2007;66:358-363	To assess the radiological damage progression in patients with recent RA in sustained remission	Prospective study of early RA pts (< 1 yr), some of whom already participated in a 52 week randomised controlled trial (SSZ vs,. MTX vs. SSZ+MTX). Clinical assessment at 0, 6, 12, 36 and 60 months by same observer. Remission – DAS < 1.6 and sustained remission – DAS < 1.6 at 3 and 5 yrs. Radiographic progression both at individual level (no of new erosions & progression above SDD) and at group level (mean & median) -rays of hands and feet at baseline, 3 and 5 yrs and were scored by two observers in chronological order (mean of the two scores were used; inter and intra observer ICC=>.85) Functional progression – HAQ at baseline, 3 and 5 yrs	Total no of pts = 191(women-140, men-51) 78.5% of these pts were already involved in a clinical trial. Mean age at diagnosis-50.5 yrs and mean duration of symptoms – 3.3 months. 81% were seropositive and 86% had atleast one shared epitope at baseline. 93% of pts were on DMARDs (68.6%-mono; 24.6%-combi) 6 months after inclusion. During the 5 yr FU, a mean of	Prospective, multicenter study with early RA. Clinical disease was correlated with radiographic and functional progression /outcomes. Validated remission criteria and x-ray scoring methods. Radiographic progression at individual and group level were analysed as recommended by OMERACT committee. Other similar studies discussed	Remission was assessed at only 3 and 5 years and pts could have had a disease flare in between, which might have accounted for new erosions and x-ray progression. No significant difference in functional (HAQ) progression was noted between 3 and 5 yrs in both groups.

				1.95 DMARDS (range 1-5) were used. 33% of pts received steroids atleast once during FU. <u>Remission rate:</u> 35.8%(n=48) at 3 yrs, 28.4%(38) at 5 yrs and 22.4% (n=30) at both visits. 80% of pts in remission at yr3 were also in remission at yr 5. Remission group had low baseline DAS, CRP, RF positivity, HAQ and a trend for a lower Sharp score. <u>Radiographic progression:</u> x-ray damage progression was significantly higher in pts with persistent disease activity. 5 pts (16.7%) in sustained remission had progression above SDD between 3 and 5 yrs (3 pts were not on treatment). Although no of pts with erosions remained the same		

				(n=16) at both 3 and 5 years in the remission group, 6 pts (20%) developed erosions in a previously unaffected joint between these time points. Functional progression: there was a significant difference between the two groups at 3 and 5 years but no difference between 3 and 5 years (progression in HAQ) in both groups.		
48	Assessing remission in clinical practice. Mierau M, et al. Rheumatology 2007;46:975-979	To study frequency of remission in routine clinical practice and to compare different	621 RA patients with complete data set for two consecutive visits over 12 months were included. Clinical remission criteria used: modified ACR (4 out of 5 excluding fatigue); DAS 28 (<2.6); SDAI (≤ 3.3); CDAI (≤ 2.8)	Mean age 61.4; mean disease duration 10 yrs and only 10% of pts with early RA (2 yrs). 78% female and 64%	Included large no of pts in a routine clinical setting. Validated remission criteria used and kappa statistics were used to	Cross-sectional study. Long disease duration. Median joint count was 0 at baseline.

		remission criteria		were seropositive. 93% were treated with DMARDs and 11% had biologics. At baseline: Median joint counts 0 (both SJC, TJC) and median ESR 22; median CRP 6. Remission at any one visit : 43% (DAS 28); 39% (mACR); 34% (SDAI, CDAI). Sustained remission: 16.7% (CDAI); 19.6% (DAS28). Agreement between remission criteria was best for CDAI and SDAI (κ=0.89) and good for DAS28 and SDAI or CDAI (κ=0.63 & 0.58) but only moderate between mACR and others ($\kappa \leq 0.40$). Residual swollen joints were seen in 13% of pts in DAS28 remission, 7% of pts in mACR remission and only 5% of pts in CDAI or SDAI remission.	compare between different criteria. Residual joint counts despite fulfilling remission were reported.	Short interval to assess sustained remission. Chances of observer error on assessing remission (it was not clear whether joints were scored by same observer) Only clinical remission was assessed and too short follow-up to report x-ray and HAQ details

49	Sustained remission and reduced radiographic progression with combination disease modifying anti-rheumatic drugs in early rheumatoid arthritis. Makinen H, et al. J Rheumatol 2007;34:316-21	To study frequency of sustained remission and good treatment response and the association of both with radiographic progression in early RA – FIN-RACo trial	195 pts with early RA (< 2 yrs duration) and with active disease were randomised to either combi (n=97) or monotherapy (n=98). Previous DMARD use or steroids 2 weeks before recruitment were excluded. COMBI ARM: SSZ+MTX+HCQ+Pred. MONO ARM: SSZ→MTX or other ± Pred. Clinical remission at 0, 6, 12 & 24 months (ACR -all 5 excluding fatigue, DAS28 < 2.6) and radiographs at 0, 6 & 24 months (Larsen score 0-200). Sustained remission – remission at 6, 12 & 24 months. Good treatment response – DAS28 < 3.2 and a decrease of > 1.2 from baseline	Total of 169 pts with complete data were included for final analysis. Mean age=47, female=63%, RF positive=71% and erosions at baseline 49%. Mean DAS28 at baseline=5.6. ACR remission at 6 months : 25% (combi), 12% (mono). Sustained ACR remission at 6,12 & 24 months: 14% (combi), 3% (mono). DAS28 remission at 6 months: 66% (combi), 37% (mono). Sustained DAS28 remission at 6,12 & 24 months: 51% (combi), 16% (mono). Good treatment response (EULAR) at 6 months: 75% (combi), 52% (mono). Sustained good response at 6,12 & 24 months:	Prospective study of early RA pts with 2 yrs follow-up and analysed frequency of sustained remission. Also analysed EULAR treatment response and correlation between clinical and radiographic disease progression was analysed. Mono and Combi DMARD therapy were compared in relation to clinical efficacy. X-ray progression over 2 yrs in pts in sustained clinical remission was studied.	All pts had active disease and a large proportion of pts received steroids (100% in combi group and 61% in mono group). Sustained remission was assessed only at 6, 12 & 24 months and pts could have had disease flare in between. Duration of follow-up was only 2 years to assess x-ray progression. X-ray progression in combi and mono groups separately were not reported and functional outcomes not studied.

				67% (combi), 27% (mono). Radiographic progression: Change of Larsen score from baseline to 24 months: 0 (sustained ACR remission), 1 (sustained DAS28 remission), 1 (sustained good response)		
50	Prognostic markers of clinical remission in early rheumatoid arthritis after 2 years of DMARDs in a clinical setting. Vazquez I, et al. Clinical and Experimental Rheumatology 2007;25:231-38	To analyse the frequency of clinical remission at 2yrs and to study prognostic factors for remission.	Open-label study of 115 pts with early RA (< 2 yrs duration) who were treated with standard treatment strategy using step-up approach (gold + MTX + Pred) for the first year and then according to clinician's discretion. No prior DMARDs but if pts were taking < 10 mg of pred, they were included for the study Clinical assessments were done at 0, 6, 12, 18 & 24 months (DAS28) and radiographs at 0, 12 & 24 months (Larsen score). Primary outcome: clinical remission = DAS28 < 2.6 Significant radiographic progression = ≥ 4 Larsen score between baseline and 24 months. ACR20 and 50 response criteria and EULAR response criteria were also analysed.	Total of 105 pts completed the study. Mean age=55, female=81, RF positive=74%, anti CCP=70% and mean DAS28 at baseline=5.7 No DMARD in 13 and 15 pts at 1 and 2 yrs respectively and 63% of pts were still on steroids after 2 yrs. DAS28 remission: 34 pts (32%) at 2 yrs but only 5 pts had sustained remission at 6, 12, 18 & 24	Study was conducted in a real out pt setting. Early RA pts with frequent follow-ups and standard treatment regime. Predictive factors for remission analysed and frequency of sustained remission reported.	Small no of pts and pts and some of them may have been on steroids already when they entered the study. Radiographic progression was not analysed properly and a cut off point was chosen to report significant progression without any explanation of how it was chosen. Follow-up not long enough for x-ray

				months and 15 pts had sustained remission at 3 out of 4 study points. X-ray progression was not statistically different between pts in remission and not in remission. DAS28 < 5.1, high Hb levels and male gender were baseline predictors for remission at 2 yrs on univariate analysis. On multiple regression analysis, DAS28 < 5.1 was the only independent factor associated with clinical remission. On multivariate analysis, ACR50 response and a good EULAR response emerged as independent factors associated with remission at 2 yrs.		progression and functional outcomes not analysed
51	An explanation for the apparent dissociation between clinical remission and continued	To evaluate the long-term significance of subclinical	Prospective study of 102 RA patients who were considered to be in remission by their treating physicians whilst on conventional DMARDs. Inclusion criteria: ACR criteria for RA, disease duration of atleast 12 months, no disease flare within the preceding 6 months, stable therapy for 6	90 patients with complete set of x-rays were included for final analysis.	Prospective study with standard follow-ups and assessments. Validated remission criteria and	Short term follow-up

	structural deterioration in rheumatoid arthritis. Brown AK et al. arthritis & Rheum vol. 58, No.10, Oct 2008, p 2958-2967	synovitis and its relationship to structural outcome	months and no clinical indication for a change in treatment. A control group of 17 sex-matched normal subjects was also studied. Clinical remission: no joint pain, swelling and tenderness Modified ACR remission criteria: 5 out of 6 criteria at 0 & 2 months DAS28 remission criteria: DAS28 < 2.6 Clinical assessments and blood tests were done at 0, 3, 6, 9 and 12 months x-rays of hands and feet were done at baseline and at 12 months and were scored by one observer (paired reading) using Genant-modified Sharp method. SDC was used to assess significant x-ray progression. US [for synovial hypertrophy(SH) and power Doppler (PD), erosions] and MRI [for bone marrow edema (BME) , synovitis and erosions] of the dominant hand and wrist was done at baseline and at 12 months	67% women; 64% RF positive; median disease duration 7 years. Median duration of remission at baseline was 2 years. 99% had DMARDs during the disease course (21% on combination therapy, 2 received biologics before). 54% fulfilled ACR remission criteria and 56% satisfied DAS28 remission criteria. At baseline, 60% had erosions on x-rays. On US, 68% had erosions, 89% had SH, 63% had increased PD signal. On MRI, 96% had erosions, 92% had synovitis and 53% had BME. 3 control subjects (18%) had synovitis on MRI but none had BME. At 12 months, 45% of pts fulfilled ACR remission criteria and 61% fulfilled DAS28 remission	radiographic assessments were performed. Compared x-rays with US and MRI and assessed the predictive ability of these modalities for subsequent erosions/radiographic progression. First to demonstrate a direct association between synovitis and radiographic progression in individual joints and first to assess the predictive ability of subclinical inflammation on US and MRI for subsequent radiographic progression.	

				criteria. In total, 19% of pts showed radiographic damage > SDC at 12 months. In the clinical remission group, 16% showed x-ray progression above SDC and the corresponding figures for ACR remission and DAS 28 remission groups were 11% and 12% respectively. Baseline predictive factors for x-ray progression: positive PD signal (OR 12.2), SH (OR 2.3) on US and synovitis (OR 2.9) on MRI		

APPENDIX 2. ERAS DATA FORMS

RCT 0

FIRST VISIT FORM

CARD 1 | HOSP | ID NUMBER | SEX | DOB (YEAR) | ETHNIC

1 = Caucasoid
2 = Asian
3 = Negroid
4 = Mongoloid
5 = Semitic
6 = Other

INITIAL DATA FORM

STICKY LABEL or

PATIENT's NAME

ONSET OF DISEASE MONTH | YEAR

HAND (R = 1, L = 2, Both = 3)

HEIGHT (CM)

SPEED
1 = Acute
2 = Insidious
3 = Episodic
4 = Other

PATTERN OF JOINT SYMPTOMS

	Small	Large	Both
Asymmetrical	1	2	3
Symmetrical	4	5	6
Neck	7		
Palindromic	8		
Soft Tissue	9		
Monoarticular	0		

PRODROME

Flu like	= 1
Weight loss	= 2
Malaise/Fatigue	= 3
Depression	= 4
Soft tissue	= 5
Rash	= 6
Myalgia	= 7
Other	= 0

TRIGGER

Illness	= 1
Infection	= 2
Trauma	= 3
Surgery	= 4
Drugs	= 5
Hormonal	= 6
Bereavement	= 7
Emotional	= 8
Pregnancy	= 9
Other	= 0

FAMILY HIST | PAST MED HIST

RA	= 1	Seroneg spond	= 6
Other CTD	= 2	Psoriasis	= 7
AI Thyroid	= 3	Inflam. Bowel	= 8
IDDM	= 4	Ocular	= 9
Other AID	= 5	Other	= 0

Drg 1 | Drg 2 | Crap

DATE OF VISIT MONTH | YEAR

TREATMENT CURRENT 1 2 | PREVIOUS 1 2

0= None
1= Analgesia
2= NSAIDS
3= 1+2
4= Short course Steroids
5= IA Cortisone
9= Other

EFFICACY 1 2 | SIDE EFFECTS 1 2

(See follow up form for codes)

ARA CRITERIA

EMS
0 = <1/5 hour
1 = <1 hour
2 = <2 hour
3 = <3 hour etc

JOINT SCORE (00-59)

JOINTS INVOLVED
1 = Hand/Wrists
2 = Feet
3 = Both
4 = Large Jts Only
5 = Small + Large Jts
6 = Mono Articular
7 = Soft Tissue Only
8 = Neck Only
9 = Other

SYMMETRY
1 = Symmetry
2 = Asymm

CLINICAL MEASUREMENTS

Nocturnal Waking No. times night | FUNCTIONAL GRADE (I-IV = 1 - 4)

GRIP (R) --0/30 | GRIP (L) --0/30 | RITCHIE 00-78 | PAIN SCORE 00-99mm | HAQ 00-24 | WEIGHT (KG)

CLINICAL SUBSETS

TYPE OF SYNOVITIS
0 = None
1 = Mild Proliferative
2 = Marked Proliferative
3 = Dry/Atrophic
4 = Soft Tissue
5 = Myalgic
6 = Tenderness Only
9 = Other

RA / Other

COURSE
0 = Too Early
1 = Episodic/Palin
2 = Nonrecurrent
3 = Relapse/Remit
4 = Chronic Persistent
5 = Transient Synovitis
6 = Other specific diagnosis
7 = Diagnosis not known
9 = Other

PAIN THRESHOLD
1 = Low
2 = Normal
3 = High

EXTRA ARTICULAR DISEASE 1 2 3
1 = Nodules
2 = Sjögren's
3 = Raynaud's
4 = Lung
5 = CNS/Muscle
6 = Non Specific
7 = Feltys
8 = Cut/Ocular Vasculitis
9 = Systemic Vasculitis
0 = Other

X-RAYS: HANDS | FEET | C/S
0=Normal 1=OA only 9=Not done
2 = Joint Space Loss
3 = Juxta OP
4 = Erosions
5 = Ankylosis
2 = AAS
3 = Subaxial Subluxation
4 = Both
5 = Ankylosis

LABORATORY

WCC /Cumm^2 | HB Gm/l | PLATELETS x10/l^9 | ESR mm/hr

LX | SCAT | ANA
0 = Negative
1 = Equivocal
2 = Low Positive
3 = High Positive
(or titre eg 1=1/10 2=1/20 3=1/40 etc)

LABORATORY STORAGE
0 = None
1 = Serum
2 = Cells
3 = Urine
4 = 1 + 2
5 = 1 + 3
6 = 2 + 3
7 = 1, 2, 3

FOLLOW UP FORM

CARD

HOSP ID NUMBER

DATE OR VISIT

DNA

IF DNA
1 = Moved
2=Can't
3=Won't
4=Remission
5=since died
6=Discharged
9=Don't know

CURRENT MEDS 1 2

0= NSAIDs only
1= Chloroquin
2= SZP
3=IM Gold
4=Oral G
5=DPM
6=AZA
7=CYCLO
8=MTX
9=Other

CURRENT STEROIDS

Dose Mgs
0= None
1=2.5
2=5
3=7.5
4=10
5=12-5
6=15
7=20
8=>20
9=Other

PREVIOUS STEROIDS

Dose Mgs

PREVIOUS MEDS (Since last visit)

1 DRUG 2

EFFICACY

TOXICITY

CODES FOR EFFICACY & SEVERITY OF TOXICITY

Effective — Ineffective

1.....No toxicity.....5
2.....Tolerable 6
3.....Intolerable 7
4.....Severe 8
9=fatal
0=don't know

CODES FOR TYPE OF TOXICITY

1= Skin rash
2=Mucocutaneous
3=Renal
4=Haematology
5=Dyspepsia
6=Peptic Ulcer
7=Hepatic
8=Ocular
9=CNS
10=Other

LIST NSAIDS
1
2
3

LIST TYPE
1
2
3

DETAILS
1
2
3

ARA CRITERIA

EMS

0=<1/5hour
1=<1hour
2=<2hour
3-3hour etc

JOINT SCORE

00 - 59

JOINTS INVOLVED

1= Hand/Wrist
2=Feet
3=Both
4=Large Jts only
5=Small&Large
6=Mono Articular
7=Soft Tissue only
8=Neck only
9=Other

SYMMETRY

1=Symmetry
2=Asymm

CLINICAL MEASUREMENTS

Nocturnal Waking — No. times night

Functional Grade (I-IV=1.4)

Grip(R) --0/30

Grip (R) --0/30

Ritchie 00 – 78

Pain Score 00 – 99mm

HAQ 00-24

Weight (KG)

CLINICAL SUBSETS

TYPE OF SYNOVITIS

0=None
1=Mild Proliferative
2=Marked Proliferative — RA
3=Dry/Atrophic
4=Soft Tissue
5=Myalgic — Other
6=Tenderness only
9=Other

COURSE

0=To early
1=Episodic/Palin
2=Nonrecurrent
3=Relapse/Remit
4=Chronic Persistent
5=Transient Synovitis
6=Other specific diagnosis
7=Diagnosis not known
9=Other

PAIN THRESHOLD

1=Low
2=Normal
3=High

EXTRA ARTICULAR DISEASE 1 2 3

1=Nodules
2=Sjögern's
3=Raynaud's
4=Lung
5=CNS/Muscle
6=Non Specific
7=Feltys
8=Cut/Ocular Vasculitis
9=Other

X-RAY

HANDS FEET C/S

0=Normal 1=OA only 9=Not done
2=Jt . space loss 2=AAS
3=Juxta OP 3=Subaxial Subluxation
4=Erosions 4=Both
5=Ankylosis 5=Ankylosis

LABORATORY

WCC /Cumm^2

HB Gm/l

PLATELETS x10/l /9

ESR mm/hr

LX **SCAT** **ANA**

LABORATORY STORAGE

0= None
1=Serum
2=Cells
3=Urine
4=1+2
5=1+3
6-2+3
7=1,2,3

0=Negative
1=Equicoxal
2=Low Positive
3=High Positive
(or titre eg 1=1/10, 2=1/20, 3=1/40)

HAD SCALE

A D

ERAS OUTCOME 3 / 5 OR 10YEAR FOLLOW UP

Eras ID number: ☐ **Date:** ☐

1. SOCIAL DETAILS – at time of entry to ERAS and yearly outcome visits
2. Visit date:

	Fup year	Fup year	Fup year
Fup year	☐	☐	☐
Tick if no change:			
1a. Occupation details reasons for change spouses occupation	☐	☐	☐
1b. Av. Hours per day	☐☐	☐☐	☐☐
1c. Months off (RA)	☐	☐	☐
1d. Marital status	☐	☐	☐
1e. Support FAMILY	☐	☐	☐
1f. Support LOCAL	☐	☐	☐
Accomodation 1g. Type	☐	☐	☐
1h. Numbers bedrooms	☐	☐	☐
Details & reason if different:-			
1i. Education	☐	☐	☐
1j. Social Class (1-5)	☐	☐	☐
1k Allowances:-	☐	☐	☐
1w. Other:-	☐	☐	☐

1x. Comorbid Conditions
1.
2.
3.
4.
5.
6.

Cause of Death:-

Current Medication:-

1.	2	3
4	5	6
7	8	9
10		

CODES

Occupation
1= manual
2= semi manual
3= semi sedentary
4= sedentary
5= housewife
6= employed
7= retired
8= student
9= other
0= none

If out of work at present put in code for normal job and in hours/day:98=redundant, 99=unemployed

Marital Status
1= married 2=cohabit
3=single 4= divorced
5=separated 6=widowed
7=single parent 8= other
9=don't know

Family & local support NONE = 0

NON PERSONAL	PERSONAL
1=< once a week	4=<once a week
2=>once a week	5=>once a week
3= daily	6 = daily

Acomodation

Owned	Rented
1 = Room	=5
2 = Flat	=6
3 = Bungalow	=7
4 = House	=8
Part III	=9
Institute	=10

Education
0=None 1=No CSE
2= CSE/O's 3=CSE/A's
4= Training 5= Nat.Diploma
6=University Degree 7= Other
8=Don't know

Social Class
1=Professional – Doctor etc
2=Professional – Teacher etc
3=Skilled
4=Semi-skilled
5=Unskilled

Enter details of comorbid conditions & medication in text, abbreviations or acronyms.

Smoking Data

Current smoker

Amount per day	Start date	Todays date

Ex-smoker

Amount per day	Start date	Stopped date

2. IN PATIENT EPISODES

Fup year _____

(please enter)	DATE	REASON	Number of days	Codes op'n	Codes jt/site
2l:				☐	☐
2m:				☐	☐
2n:				☐	☐
2o:				☐	☐
2p:				☐	☐
2q:				☐	☐
2r:				☐	☐
2s:				☐	☐

on W/List for:

Codes for med/orth IP

(Columns 1 & 2)
0 1 = RA medical
0 2 = iatrogenic
0 4 = non RA
0 5 = rehab
0 6 = other

OPERATION CODE
(Column 1)
1 = joint replacement
2 = revision replacement
3 = excision
4 = CT decompression
5 = surgical synovector
6 = soft tissue operation
7 = arthodesis
8 = medical synovector
9 = other

JOINT/SITE CODES
(Column 2)
See jt/site in sect. 4 ROM

3. OUT PATIENT EPISODES

Fup year:	____ year	____ year
3t. Endoscopies	☐	☐
3u. OT/PT/Hand Rx	☐	☐
3v. Chiropody	☐	☐
3w. Appliances	☐	☐
3x. shoe fitter	☐	☐
3y. Wheel chair	☐	☐
Home adapt	☐	☐

Codes for OP episodes

Write in number of episodes/ sessions (eg 0-8,9=9 ore more)

APPLIANCES
0 = none
1 = wrist splint/collars
2 = kitchen/home aids
3 = walking aids
4 = calipers etc
5 = hoists
6 = other

WHEEL CHAIR
0 = never 1 = > 1/year
2 = > 1/month 3 = >1/week
4 = daily 5 = constant

4. RANGE OF JOINT MOVEMENT (ROM)

Fup year:	____ year		____ year	
Joint site	R	L	R	L
1. Shoulder	____	____	____	____
2. Elbow	____	____	____	____
3. Wrist	____	____	____	____
4. MCP/PIP	____	____	____	____
5. Hip	____	____	____	____
6. Knee	____	____	____	____
7. Ankle	____	____	____	____
8. Hindfoot	____	____	____	____
9. MTP	____	____	____	____
0. Cervical spine	____	____	____	____

Codes for ROM

0 = Normal ROM

1 = up to 25% loss

2 = up to 50% loss

3= up to 75% loss

4 = up to 95% loss

5 = complete ankylosis

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ)

Name: ……. Date: …….

We are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments at the end of this form.

PLEASE TICK THE ONE RESPONSE WHICH BEST DESCRIBES YOUR USUAL ABILITIES OVER THE PAST WEEK

	Without **ANY** difficulty (0)	With **SOME** difficulty (1)	With **MUCH** difficulty (2)	**Unable** to do (3)
1. DRESSING & GROOMING Are you able to:				
Dress yourself, including tying shoelaces and doing buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
2. RISING Are you able to:				
Stand up from an armless straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
3. EATING Are you able to:				
Cut your meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new carton of milk (or soap powder)	☐	☐	☐	☐
4. WALKING Are you able to:				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES :

☐ Cane ☐ Walking frame ☐ Crutches ☐ Wheelchair

☐ Built up or special utensils ☐ Special or built-up chair

☐ Other (specify) ……...

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON :

☐ Dressing and Grooming ☐ Eating ☐ Rising ☐ Walking

PLEASE TICK THE ONE RESPONSE WHICH BEST DESCRIBES YOUR USUAL ABILITIES OVER THE PAST WEEK

	Without **ANY** difficulty (0)	With **SOME** difficulty (1)	With **MUCH** difficulty (2)	**Unable** to do (3)
5. HYGIENE Are you able to:				
Wash and dry entire body?	☐	☐	☐	☐
Take a bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
6. REACH Are you able to:				
Reach and get down a 5 lb object (e.g. a bag of potatoes) from just above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
7. GRIP Are you able to:				
Open a car door?	☐	☐	☐	☐
Open jars which have been previously opened?	☐	☐	☐	☐
Turn taps on and off?	☐	☐	☐	☐
8. ACTIVITIES Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of the car?	☐	☐	☐	☐
Do chores such as vacuuming, housework or light gardening?	☐	☐	☐	☐

PLEASE TICK ANY AIDS OR DEVICES THAT YOU USUALLY USE FOR ANY OF THESE ACTIVITIES :

☐ Raised toilet seat ☐ Bath rail ☐ Bath seat ☐ Jar opener (for jars previously opened)
☐ Long handled appliances for reach ☐ Other (specify) …….

PLEASE TICK ANY CATEGORIES FOR WHICH YOU USUALLY NEED HELP FROM ANOTHER PERSON :

☐ Hygiene ☐ Gripping and opening things ☐ Reach ☐ Errands and housework

We are also interested in learning whether or not you are affected by pain because of your illness.

HOW MUCH PAIN HAVE YOU HAD BECAUSE OF YOUR ILLNESS IN THE PAST WEEK ?

Place a mark on the line to indicate the severity of the pain

No pain _____ Very severe pain

APPENDIX 3. PAPERS & ABSTRACTS FROM THIS THESIS

3. List of Papers and Abstracts from this Thesis

Papers

1. van der Woude D, Young A, Jayakumar K, Toes REM, van der Heijde D, Huizinga TWJ and van der Helm-van Mil A. Prevalence and predictive factors for sustained DMARD-free remission in rheumatoid arthritis; results from two large early arthritis cohorts. Arthritis Rheum 2009 Aug;60(8):2262-71

2. Jayakumar K, Dixey J, Young A, Solymossy C, Emmett C, Jones P, Williams P, on behalf of ERAS. Evidence of an accelerated phase of structural damage in an early rheumatoid arthritis cohort from the pre-biologic drug era. (In preparation)

3. Jayakumar K, Young A, Norton S, Solymossy C, et al, on behalf of ERAS. Remission in early rheumatoid arthritis: results from an observational study. (In preparation)

4. Jayakumar K, Norton S, Young A, Solymossy C, Dixey J, et al, on behalf of ERAS. Structural damage on x-rays can progress despite DAS remission in early rheumatoid arthritis. (In preparation)

Abstracts

1. Jayakumar K, Boonen A, van der Heijde D, Solymossy C, Dixey J, Norton S, Young A. Evaluation of radiographic progression in RA using different scoring methods: Larsen, Sharp van der Heijde (SvdH) and simplified erosion narrowing score (SENS) [Abstract}. Ann Rheum Dis 2009; 68 (Suppl 3):401

2. Jayakumar K, Young A, Dixey J, Sollymosy C, Williams P, Norton S. Low disease activity in rheumatoid arthritis (RA) results in better clinical outcomes, but radiological damage in hands and feet can still progress [Abstract]. Rheumatology (Oxford) 2009; 48 (Suppl 1):i140

3. Dixey D, Jayakumar K, Koduri G, Williams P, Norton S, James D, Young A. Disease activity and five year outcome of early rheumatoid arthritis (RA) in a biologic drug free inception cohort [Abstract]. Rheumatology (Oxford) 2009; 48 (Suppl 1):i136

4. Ramabhadran B, Koduri G, Jayakumar K, Musa R, Winfield J, Williams P, Young A. Cervical spine instability in rheumatoid arthritis (RA) is more common in patients undergoing orthopaedic surgery [Abstract]. Rheumatology (Oxford) 2009; 48 (Suppl 1):i139

5. Jayakumar KS, Boonen A, van der Heijde D, Sollymosy C, Dixey J, Young A, et al. Disconnect between clinical disease activity and x-ray damage in early rheumatoid arthritis [Abstract]. Arthritis Rheum 2008; 58 (Suppl): S755

6. Williams P, Norton S, Jayakumar K, Seymour A, Devlin J, Prouse P, Young A. How long do patients with RA remain on their initial disease modifying therapy? Results from an inception cohort prior to the biological era [Abstract]. Ann Rheum Dis 2008; 67 (Suppl II): 206

7. Dixey J, Young A, Emmett C, Koduri G, Jones P, Jayakumar K, Sollymosy C. What factors at disease onset predict poor functional outcome in the first 9 years of rheumatoid arthritis? Results from the ERAS cohort [Abstract]. Rheumatology (Oxford) 2008; 47 (Suppl 2): ii109

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10. Jayakumar KS , Young A, et al. Influence of scoring methodology in assessing radiographic disease progression in early rheumatoid arthritis: random vs. chronological order [Abstract]. Ann Rheum Dis 2007; 66 (Suppl II):355-356

11. Jayakumar KS , Young A, et al. Analysis of radiological disease progression in early rheumatoid arthritis using two different scoring methods: Larsen vs. Sharp van der Heijde (SvdH) [Abstract]. Ann Rheum Dis 2007; 66 (Suppl II): 355

12. Jayakumar KS, Sollymossy C, Dixey J, Cox N, Young A. Frequency of clinical remission and radiographic progression in early rheumatoid arthritis (RA): results from an inception cohort of early RA patients [Abstract]. Rheumatology (Oxford) 2007; 46 (Suppl I):i100

13. Jayakumar KS, Sollymossy C, Dixey J, Stafford S, Young A. Radiographic disease progression despite clinical remission in early rheumatoid arthritis (RA): Early RA Study (ERAS) [Abstract]. Rheumatology (Oxford) 2007; 46 (Suppl I):i100

14. Jayakumar KS, Williams P, Gough A, Young A How many patients go into clinical remission by 5 years? Results from an inception cohort of early rheumatoid arthritis [Abstract]. Ann Rheum Dis 2006; 65 (Suppl II):114

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