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LONG-TERM OUTCOME OF EARLY RHEUMATOID ARTHRITIS

with special interest in comorbidity and permanent consequences of the disease

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ACADEMIC DISSERTATION

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LIST OF ORIGINAL PUBLICATIONS

I   Tiippana-Kinnunen T, Paimela L, Kautiainen H, Laasonen L, Leirisalo-Repo M: Can disease-modifying anti-rheumatic drugs be discontinued in long-standing rheumatoid arthritis? A 15-year follow-up. Scand.J.Rheumatol. 2010; 39: 12–8.

II   Tiippana-Kinnunen T, Laasonen L, Kautiainen H, Paimela L, Leirisalo-Repo M: Impact of early radiographic remission on the 15-year radiographic outcome in patients with rheumatoid arthritis. Scand.J.Rheumatol. 2011; 40: 263–8.

III Tiippana-Kinnunen T, Kautiainen H, Paimela L, Leirisalo-Repo M: Co-morbidities in Finnish patients with rheumatoid arthritis: 15-year follow-up. Scand.J.Rheumatol. 2013; 42: 451–6.

IV Tiippana-Kinnunen T, Paimela L, Peltomaa R, Kautiainen H, Laasonen L, Leirisalo-Repo M: Work disability in Finnish patients with rheumatoid arthritis: a 15-year follow-up. Clin.Exp.Rheumatol. 2014; 32: 88–94

ABBREVIATIONS

ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
ARA	American Rheumatism Association
AUC	Area-under-the curve
CCI	Charlson comorbidity index
CDAI	Clinical Disease Activity Index
CRP	C-reactive protein
CS	Cross-sectional
CTD	Connective-tissue disease
CVD	Cardiovascular disease
DAS	Disease Activity Score
DAS28	Disease Activity Score based on assessment of 28 joints
DEXA	Dual-energy X-ray absorptiometry
DMARD	Disease-modifying antirheumatic drug
ERR	Early radiographic remission
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FIN-RACo	Finnish Rheumatoid Arthritis Combination Therapy trial
GC	Glucocorticoid
GH	Global health
HAQ	Health Assessment Questionnaire
HCQ	Hydroxychloroquine
HLA	Human leukocyte antigen
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-17	Interleukin-17
IP	Interphalangeal
IQR	Interquartile range
LJR	Large joint replacement
LS	Larsen Score
LU	Larsen unit
MCP	Metacarpophalangeal
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
MTP	Metatarsophalangeal

MTX	Methotrexate
NSAID	Nonsteroidal anti-inflammatory drug
PIP	Proximal interphalangeal
RA	Rheumatoid arthritis
RF	Rheumatoid factor
RR	Relative risk
SASP	Sulphasalazine
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SE	Shared epitope
SHS	Sharp/van der Heijde Score
SMR	Standardized mortality ratio
TJR	Total joint replacement
TNF-α	Tumour necrosis factor α
US	Ultrasound
U.S.	United States
VAS	Visual Analogue Scale

ABSTRACT

The natural course of rheumatoid arthritis (RA) is currently regarded as varying inflammation of joints, which leads to progressive joint damage, reduction of functional capacity and of work capacity. In the early phase of the disease, functional disability and decreased work capacity are mostly attributed to the inflammation and may be suppressed with early-initiated, intensive disease-modifying antirheumatic drug (DMARD) therapy. In established RA, the functional disability is more related to progressive radiographic joint damage and reduced joint mobility.

This 15-year follow-up study focused on the permanent consequences of RA: radiographic outcome, functional capacity and permanent work disability in 86 patients with early RA (≤ 12 months of disease duration, age 18–65 years), collected between 1986 and 1989 in the Helsinki area and treated with early-initiated DMARD therapy. The outcome was determined in relation to DMARD treatment continuity, early disease activity, early radiographic progression and comorbidity. All patients, initially DMARD-naive, were treated with DMARD from the time of diagnosis starting with intramuscular gold, hydroxychloroquine (HCQ) or sulphasalazine (SASP). During the first 3 years, the DMARD treatment was changed and intensified according to the sawtooth strategy. The DMARD treatments of each patient over the 15-year follow-up were recorded in detail, which made it possible to examine the long-term outcome in relation to DMARD therapy continuity.

Most (71%) of the 70 patients who were evaluated at the 15-year follow-up needed continuous DMARD therapy (group A, 50 patients). In 20 patients (29%), the DMARDs were discontinued, due to clinical remission or to the symptom-free period of the disease. Of these patients, 9 (45%) experienced a flare-up of RA (group B) and 11 (55%) remained in remission (group C). For the patients whose disease flared up, DMARDs were restarted as soon as possible. At the 15-year examination, 64% of the patients in group C were in remission, according to the American Collage of Rheumatology (ACR) criteria, compared with 6% of the patients in A and 0% in B. The final functional capacity assessed with the mean Health Assessment Questionnaire (HAQ) was 0.60 in A compared with 0.38 in B and 0.24 in C. The patients in group A also had poorer 15-year radiographic outcomes with mean Larsen score (LS) of 54, compared with 25 in B and 12 in C. These results showed that few patients with RA achieved sustained drug-free clinical remission. If a patient's DMARD therapy is discontinued due to remission, the patient should be followed up carefully for a flare-up of disease, and DMARDs should be reinitiated immediately after a flare-up.

Radiographs of the small joints were taken at baseline, year 1, 2, 3, 5, 7, 10 and 15 and of the large joints at the 15-year visit and assessed with LS in 69 patients

(with full sets of radiographs). The final radiographic outcome was evaluated in relation to early radiographic remission [(ERR), an increase of LS ≤ 1 Larsen unit between two sequential sets of small joint radiographs during the first 2 years of RA]. The mean LS of the small joints (14) and LS of the large joints (0.8) remained substantially lower in 18 patients with sustained ERR (both year 1 and year 2), compared with 33 and 1.9 in 20 patients with temporary ERR (either at year 1 or year 2) or with 67 and 6.3 in 31 patients with no ERR (progression of LS ≥ 2 Larsen units during both first years). Considering these results, we postulated that radiographic remission should be one of the treatment goals in RA.

Comorbidity in RA, especially the relationship of RA to cardiovascular diseases (CVDs), has been recently discussed by several authors. In the present study of 80 patients with adequate data, 20% had at least one comorbid condition at baseline. At the 15-year visit or at time of death, 60% of the patients showed comorbidity, most commonly hypertension (30%), followed by CVDs (14%), malignancies (11%) and osteoporosis (11%). A striking finding was the relationship of comorbidity to disease activity during the first year of RA and still at the endpoint. The total load of baseline comorbidity in each patient was assessed with a modification of the Charlson comorbidity index (CCIa). The area-under-the curve of the Disease Activity Score based on 28 joints (DAS28 AUC) during the first 12 months and final DAS28 were higher in patients with baseline comorbidity (CCI_a 1–2 or CCI_a ≥ 3) than in the younger patients without comorbidity (CCIa 0). A similar trend was found in the 15-year HAQ.

Permanent loss of work ability has major economic and social influence, both on individual patients and on society. Of the 86 patients, of whom all were working or available for the labour force at baseline, 42 (49%) retired due to work disability during the 15-year follow-up or before death. Of the patients receiving a full-time work disability pension, 89% retired due to RA. The Kaplan-Meier estimated cumulative RA-related permanent work disability over 15 years was less frequent (3% at year 5, 10% at year 10 and 22% at year 15) in the 33 patients with low early disease activity (DAS28 AUC ≤ 3.2 during the first 12 months) than in the 53 patients with moderate or high disease activity (28%, 55% and 64%, respectively). Early radiographic remission (ERR) during the first year of RA showed a similar reduction in impact on RA-related retirement. The cumulative RA-related retirement in the 28 patients with ERR was 12% at year 5, 28% at year 10 and 33% at year 15 and in the 58 patients with early radiographic progression 25%, 43% and 54%, respectively. These findings highlight the importance of aiming for clinical remission or at least for low disease activity and of halting early radiographic progression for favourable long-term outcome in RA.

1. INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease affecting predominantly the synovial joints of the hands and feet. It was still considered a benign disease in the early 1980s (McCarty 1985, Kelley et al. 1989). Its chronic and progressive natural course with more or less continuous inflammatory activity, increasing damage of the joints, declining functional capacity, work capacity and increased mortality of patients was not precisely realized until the 1990s (Pincus and Callahan 1993, Wolfe 1996).

Due to misunderstanding of the true nature of RA and to the only few available, often toxic and less effective disease-modifying antirheumatic drugs (DMARDs), the treatment of RA was in the 1970s limited to regularly administered aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), rest and physical therapy (Sokka et al. 2008a). In the 1980s, increasing knowledge of the chronic inflammatory activity of RA and growing evidence of progressive joint damage encouraged the rheumatologists to use the DMARDs available earlier and more actively than before. Finnish rheumatologists were among the first to demonstrate the favourable effect of early-initiated DMARD therapy on long-term outcome in RA (Sievers et al. 1963, Luukkainen et al. 1977). The idea of continuous DMARD therapy was adapted in Finnish rheumatologic centres in the late 1980s (Möttönen et al. 1996) and was also part of the treatment strategy used in the present study.

In the early 1990s, the need for more effective drug treatments and the desire to control the inflammatory activity of RA more completely directed Finnish rheumatologists to undertake the Finnish Rheumatoid Arthritis Combination Therapy (FIN-RACo) trial, one of the first studies aiming at remission as the main goal of the study (Möttönen et al. 1999). The superior results of the FIN-RACo study regarding clinical outcomes (Möttönen et al. 1999), decrease in radiographic progression (Korpela et al. 2004) and favourable impact on work ability (Puolakka et al. 2004) resulted in formulating of the Finnish Current Care Guideline of RA (Hakala et al. 2009).

In the present study, the long-term outcome of RA was studied in a cohort of patients with early RA, recruited between 1986 and 1989 in the Helsinki area and treated initially according to the sawtooth strategy. The study focused particularly on the permanent consequences of RA: radiographic damage, functional capacity and work disability. Secondly the impacts of early disease activity, early radiographic progression and the patients' initial comorbidity on the outcomes and clinical disease activity at endpoint were evaluated.

2. REVIEW OF THE LITERATURE

2.1 RHEUMATOID ARTHRITIS

2.1.1 DEFINITION OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune disease affecting mainly the synovial joints. The clinical phenotype of RA varies from mild, self-limiting inflammation of a few joints to chronic extended and aggressive polyarthritis leading to progressive joint destruction. The clinical diagnosis of RA is based on the patient's symptoms and on the clinical signs of the synovitis and is often supported by the family history and laboratory or radiological findings of RA. The classification criteria for RA were originally designed for scientific purposes to differentiate RA from other arthritides and rheumatic diseases. The first diagnostic criteria for RA were introduced in 1956 and revised in 1958 by the American Rheumatism Association (ARA) (Ropes et al. 1958). The ARA 1958 criteria specify that at least 5 of the 11 possible criteria presented in Table 1 should be fulfilled for diagnosis of definite RA and at least 7 of the 11 criteria for the diagnosis of classical RA. These criteria were widely used in clinical studies until the next revised classification criteria for RA were published in 1987 by the American College of Rheumatology (ACR) (Arnett et al. 1988). In the ACR 1987 criteria, arthritis of the hand joints [proximal interphalangeal (PIP) and metacarpophalangeal (MCP) joints and wrists] and radiological changes of the hands were emphasized. If at least 4 of the 7 criteria presented in Table 1 are fulfilled, the arthritis could be classified as RA.

Table 1. Classification criteria for definite RA according to the American Rheumatism Association (ARA) 1958 and to the American College of Rheumatology (ACR) 1987.

ARA 1958 criteria	ACR 1987 criteria
1. Morning stiffness	1. Morning stiffness of > 1 hour
2. Tenderness or pain on motion in at least one joint	2. Arthritis in 3 or more joint areas*
3. Swelling in at least one joint	3. Arthritis in hand joint (PIP, MCP, wrist)
4. Swelling in at least one other joint	4. Symmetric swelling of 1 joint area
5. Symmetric joint swelling	5. Rheumatoid nodules
6. Rheumatoid nodules	6. Positive rheumatoid factor
7. Radiographic changes; erosions or periarticular osteopenia	7. Radiographic changes in hand and/or wrist joint
8. Positive rheumatoid factor	
9. Poor synovial fluid mucin precipitate	
10. Positive synovial biopsy	
11. Positive nodule biopsy	

*Right or left proximal interphalangeal (PIP), metacarpophalangeal (MCP) joints, wrist, elbow, ankle, knee and metatarsophalangeal (MTP) joints.

To be classified as definite RA, the 1958 ARA criteria specify that 5 of the 11 criteria from the left column should be fulfilled and criteria 1-5 must have been present for at least 6 weeks.

For the definite RA, the 1987 ACR criteria specify that 4 of the 7 criteria from the right column must be fulfilled, with criteria 1-4 being present for at least 6 weeks.

These two criteria are highly specific and sensitive in differentiating RA from other rheumatic diseases, but are seldom fulfilled in early RA (during the first 6 weeks following the onset of symptoms). The importance of early-initiated and active treatment for improved outcome of RA was shown in several studies and the need to identify and diagnose RA earlier became the key issue in the late 2000s (Cush 2007). New RA classification criteria were formulated and published by the ACR and the European League Against Rheumatism (EULAR) in 2010 (Aletaha et al. 2010). These criteria comprise the following clinical parameters: the number and size of the joints involved and the duration of symptoms, and results of laboratory tests for serology and the acute phase reactants, which are scored as presented in Table 2. For definite RA, a score ≥ 6 is needed in a patient with at least one swollen joint that is not better explained by another disease. In patients with erosion typical of RA, the diagnosis can be confirmed, even if they do not fulfil the criteria. These criteria detect sensitively early, newly presenting arthritis, but leave the responsibility for differential diagnosis to the rheumatologist.

Table 2. The 2010 ACR/EULAR classification criteria and the scoring system for rheumatoid arthritis.

Target population to be tested 1. Patients who have at least one joint with definitive clinical synovitis (swelling) 2. Patients with synovitis not better explained by other disease	
A. Joint involvement	**Score**
1 large joint	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints)	2
4–10 small joints (with or without involvement of large joints)	3
> 10 joints (at least 1 small joint)	5
B. Serology (at least one test is needed for classification)	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute phase reactants	
(at least one test result is needed for classification)	
Normal CRP and ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	
< 6 weeks	0
≥ 6 weeks	1

RF = rheumatoid factor, ACPA = anti-citrullinated protein antibodies, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate.
A score ≥ 6 is needed for classification of definite RA.

2.1.2   EPIDEMIOLOGY OF RHEUMATOID ARTHRITIS

The prevalence of RA in adults varies between 0.3% and 1% in European and North American populations, being lower in the Southern European countries (0.3%) than in Northern Europe (0.5%) and in North America (1.1%). The annual incidence rates are estimated to be 16/100 000 for Southern Europe, 29/100 000 for Northern Europe and 38/100 000 for North America. Women are affected about three times more often than men (Bijlsma et al. 2012).

In studies done in Finland the prevalence of RA in the 1980s was 0.8% and the annual incidence 39/100 000 (Kaipiainen-Seppänen 2004). Between 1980 and 2000 the incidence apparently declined to 29/100 000 in 2000: 37/100 000 among women and 21/100 000 among men (Kaipiainen-Seppänen and Kautiainen 2006). A later register study showed that the annual incidence between 2000 and 2007 was 44.5/100 000: 58.9/100 000 in women and 29.5/100 000 in men (Puolakka et al. 2010). Over the 8-year period, the incidence for RF-positive RA remained stable in both sexes, while that of RF-negative RA decreased in women (Puolakka et al.

2010). The mean age at disease onset tended to increase between 1975 and 1995 (Kaipiainen-Seppänen et al. 1996). Between 2000 and 2007, about two thirds of the patients with newly diagnosed RA were of working age (Puolakka et al. 2010).

2.1.3 AETIOLOGY OF RHEUMATOID ARTHRITIS

During recent decades, knowledge of the aetiological factors and pathologic pathways in RA has increased widely. However, we still lack a complete understanding of the pathogenesis of this chronic autoimmune disease, characterized by synovial inflammation and hyperplasia, autoantibody production, cartilage and bone destruction and systemic features. The current understanding is that genetic predisposition, together with triggering environmental factors, induces the onset of RA (McInnes and Schett 2011).

2.1.3.1 Genetic factors

Twin studies indicate the role of genetic factors in the development of RA, with concordance rates of 15-30% among monozygotic twins and 5% among dizygotic twins (McInnes and Schett 2011). The most relevant and strongest genetic risk factor is the so-called shared epitope (SE). This consists of an identical sequence of amino acids (glutamine-leucine-arginine-alanine-alanine) in certain human leucocyte antigen (HLA)-DRB1 alleles (*0101, *0102, *0401, *0404, *0405, *0408, *1001 and *1402) in the major histocompatibility complex (MHC) class II molecules (Bijlsma et al. 2012). More than 80% of RA patients carry the epitope of HLA-DRB1*04, which shows a strong association both with the development of RA and with the severity of the disease (Choy 2012). Recent studies have indicated that the SE rather represents a risk factor for the development of anti-citrullinated protein antibodies (ACPAs) than a primary risk factor for RA (Huizinga et al. 2005). Within recent years, whole-genome association scans performed in large RA cohorts have identified more than 30 additional genetic risk factors outside the MHC locus (Scott et al. 2011). Most of these factors are located in the genes that are linked to immunological pathways in the pathogenesis of RA.

2.1.3.2 Environmental factors

Of the environmental factors, cigarette smoking predisposes the development of RA and is associated with more severe disease (Heliövaara et al. 1993, Klareskog et al. 2006, Scott et al. 2011). Smoking and concurrent presence of SE increases the risk of RA up to an estimated 21-fold, compared with SE-negative nonsmokers

(Klareskog et al. 2006). Cigarette smoking has been shown to reduce the response to both traditional DMARDs and to biological treatments (Hyrich et al. 2006, Saevarsdottir et al. 2011). Several infections have been suspected as triggers of the initial immune response necessary for RA development. One of the latest candidates has been periodontal disease caused by Porphyromonas gingivalis (Hitchon and El-Gabalawy 2011). To date no infectious pathogen has been clearly associated with RA pathogenesis. Due to female predominance in RA, sex hormones and other reproductive factors (age at menarche, pregnancies, breastfeeding, menopause and use of oral contraceptives) have been considered as influencing both the development and severity of RA (Oliver and Silman 2009, Scott et al. 2011).

2.1.4 PATHOGENESIS OF RHEUMATOID ARTHRITIS

Knowledge of the immunological mechanisms in RA has increased considerably during the last two decades and several major components of the pathogenesis are well-known. The key role of synovial inflammation in the pathogenesis of RA is commonly acknowledged. Accordingly, the current understanding is that breaking of immunological tolerance is required for the initiation of this autoimmune disease. The involvement of both the innate and the adaptive immune systems has become evident and the essential cells and other key factors (e.g. cytokines) in the pathogenesis of RA have been identified (McInnes and Schett 2011, Choy 2012). The predisposing factors of this phenomenon, particularly autoantibodies, have long been known but the actual trigger of this process is still unknown.

2.1.4.1 Cells and cytokines involved in rheumatoid arthritis

The earliest event in RA pathogenesis is activation of the innate immune response, primarily the activation of dendritic cells by exogenous and autologous antigens. Dendritic cells, macrophages and activated B cells present the antigens to naive T cells, which differentiate in to different helper T-cell subtypes. Type 1 helper T (Th1) cells and the recently described type 17 helper T (Th17) cells produce several cytokines involved in the pathogenesis of RA. Some of these cytokines lead to the recruitment of T cells, as well as macrophages and neutrophils in the joints. Other cytokines activate B cells to differentiate into plasma cells. The plasma cells produce autoantibodies, such as RF and ACPA, which generate inflammation via immune complex formation and complement activation. T-cell and B-cell activation results in the production of proinflammatory cytokines such as tumour necrosis factor α (TNF-α), interleukin-6 (IL-6) and chemokines, macrophage and B-cell interactions, thus increasing the production of cytokines and chemokines by synovial macrophages and other cell types. Currently TNF-α and IL-6 are regarded as the

predominant cytokines in RA. TNF-α activates leukocytes, endothelial cells and synovial fibroblasts, inducing production of other cytokines, chemokines, adhesion molecules and matrix metalloproteinases. In addition, TNF-α suppresses the function of regulatory T cells. It decreases synovial fibroblast proliferation and collagen synthesis and activates osteoclasts, leading to destruction of cartilage and bone. IL-6 activates leukocytes and osteoclasts and is involved both in T-cell proliferation and differentiation and in B-cell proliferation and antibody production. Besides these two cytokines interleukin-1 (IL-1) and interleukin-17 (IL-17) significantly impact the inflammatory process in RA. In addition to the cytokines, several chemokines, growth and differentiation factors, intracellular signalling molecules and transcription factors play a part in the pathogenesis of RA (McInnes and Schett 2011, Choy 2012).

2.1.4.2   Autoantibodies in rheumatoid arthritis

The identification and characterization of RF were the first suggestions of the autoimmune nature of RA in the 1940s and 1950s. RF is an autoantibody, presenting mainly as immunoglobulin M (IgM-RF) and targeting the Fc-part of human immunoglobulin G (IgG). RF is discovered in the sera of patients with RA more often (60-70%) than in healthy individuals (5%). The occurrence of RF increases in elderly individuals (15%) and it is also present in many other autoimmune and infectious diseases. In population studies its sensitivity for RA is 60-70% and specificity 50-90%. The role of RF in the pathogenesis of RA is not entirely understood. RF is thought to form immune complexes that activate complement in the joint. This leads to increase in capillary permeability and release of chemotactic factors, thus recruiting inflammatory cells to the joint (Bijlsma et al. 2012).

Other autoantibodies found in RA, such as antiperinuclear factors and antikeratin antibodies, were described in 1964 and 1979 (Nienhuis and Mandema 1964, Young et al. 1979). These antibodies were found targeting a common antigen, citrullinated fillagrin in 1995 (Sebbag et al. 1995). Later additional antibodies targeting citrullinated peptides were identified. In the early 2000s, a commercial application using synthetic cyclic citrullinated peptides (CCPs) to detect ACPA was developed for clinical use. ACPAs are found in 60–70% of RA patients and are seldom present in other diseases, being thus more specific for RA than RF. The ACPAs are associated both with the risk for development of RA and with a more severe disease course. The extent to which ACPAs are directly involved in the pathogenesis of RA and their mechanisms of action are unknown. Nevertheless, their presence years before the onset of RA and both in early and in longstanding RA strongly support their crucial role in RA pathogenesis (Willemze et al. 2012).

2.1.5   NATURAL COURSE OF RHEUMATOID ARTHRITIS

The inflammation in RA commonly affects the small peripheral joints and middle-sized joints, favouring the PIP joints, MCP joints and wrists of the hands and the MTP joints and ankles of the feet. The clinical signs of inflammation include swelling, tenderness and stiffness of the affected joints. The onset of disease is in most patients gradual and insidious, affecting first only a few, usually the small joints. Morning stiffness and symmetric arthritis are features of classical RA. Occasionally, RA may present as acute systemic disease with active polyarthritis, fever and extra-articular manifestations. A special entity of RA is palindromic rheumatism, in which suddenly appearing, from hours to days lasting and spontaneously improving episodes of mono- or polyarthritis alternate with symptom-free periods. One third of these patients descend later into typical RA (Bijlsma et al. 2012).

Later, the clinical course of RA varies from mild self-limiting arthritis of a few joints to continuously active and progressive polyarthritis (Pincus and Callahan 1993, Wolfe 1996, Ollier et al. 2001). If untreated, the disease is in most cases progressive and the inflammation expands to other joints. Continuous inflammation of the joints causes destruction of the cartilage and underlying bone. These changes detected by radiographics are usually permanent and several phenotypes of radiographic progression have been described (Graudal 2004). Both the inflammation in the early phase of RA and the increasing radiographic joint damage in the later phase of the disease impair the functional ability of patients (Drossaers-Bakker et al. 1999, Kirwan 2001, Welsing et al. 2001). The loss of functional capacity leads to difficulties in managing daily activities and in reduced working ability.

The extra-articular manifestations in RA may affect a specific organ or organ system, such as the eye (episcleritis or scleritis), skin (subcutaneous nodules), lungs (pleuritis, interstitial pneumonitis, pulmonary nodules or pulmonary fibrosis) or heart (pericarditis). Other extra-articular manifestations cause more systemic disease, such as Felty's syndrome, secondary Sjögren's syndrome or vasculitis. Most of these conditions manifest themselves in established RA, but rheumatic nodules and pleuritis may be present at the onset of the disease (Young and Koduri 2007, Prete et al. 2011). The rheumatic nodules are the most common extra-articular phenomenon being present in 30% of patients, followed by Sjögrens syndrome (10-25%), Raynaud's phenomenon (5-17%) and interstitial lung disease (5-10%). Chronic, systemic inflammation with elevated acute phase proteins, especially overproduction of serum amyloid A, increases the risk for secondary amyloidosis. The most severe manifestation of amyloidosis is renal disease, presenting first as proteinuria and later progressing to renal failure (Prete et al. 2011).

The division between the extra-articular manifestations and comorbidities of RA varies among the studies. Malignancies (both haematological and solid cancers) and cardiovascular diseases (CVDs), with the exception of pericarditis and vasculitis are generally classified as comorbidities (Prete et al. 2011). The CVDs are currently

considered the most common and important comorbidities in RA (John et al. 2009, Gullick and Scott 2011). The incidence of CVD events in patients with RA is more than three times higher than that in the general population, and this increase is not explained by the traditional risk factors of CVD (Choy 2012). Recent data suggest that chronic systemic inflammation accelerates atherogenesis and thus impacts cardiovascular morbidity and mortality. Increased mortality in RA was also mainly attributed to CVDs in studies done in Finland (Sihvonen et al. 2004, Koivuniemi et al. 2009).

2.2   OUTCOME IN RHEUMATOID ARTHRITIS

2.2.1   CLINICAL OUTCOME

The outcome of RA can be measured by assessment of disease activity, remission and functional capacity. In investigating the efficacy of a certain drug or benefits of a treatment strategy, use of similar, internationally accepted quantitative methods is essential to improve the quality of the studies and enable comparison among the various studies. In addition to research, quantitative measuring of these outcome assessments is useful in clinical practice when the current status and treatment response of an individual patient are evaluated. Use of one single clinical parameter, e.g. acute phase reactants or joint count, is in general inadequate and results in incomplete information. To determine and measure the outcome more validly and reproducibly, core sets of several estimates have been developed.

2.2.1.1.   Joint assessment

In clinically examining the patient's joints, the swelling and tenderness in palpation and in motion are assessed. In addition, possible limitation of motion and deformity of the joints are observed. The number of joints assessed varies for swollen joints from 28 to 66 joints and for tender joints from 28 to 68. Both swelling and tenderness are in most joint counts scored as 1 when present and as 0 when not found. In the Ritchie articular index for joint tenderness, the peripheral joints of each hand (PIP and MCP) and feet (MTP) are assessed as one unit and the temporomandibular, sternoclavicular and acromioclavicular joints of both sides are assessed together. The degree of tenderness is scored on a 0–3 scale (Ritchie et al. 1968). The assessed joints of different joint counts are presented in Table 3 (Sokka and Pincus 2005).

Table 3. Joints assessed in different joint counts (Sokka and Pincus 2005).

Joint	66/68 joints	Ritchie index	44 joints	42 joints	28 joints
Atlantoaxial		+			
Temporomandibular	+	+			
Sternoclavicular	+	+	+		
Acromioclavicular	+	+	+		
Shoulder	+	+	+	+	+
Elbow	+	+	+	+	+
Wrist	+	+	+	+	+
Metacarpophalangeal	+	+	+	+	+
Proximal interphalangeal	+	+	+	+	+
Distal interphalangeal	+				
Hip (only tenderness)	+	+		+	
Knee	+	+	+	+	+
Talocrural	+	+	+	+	
Subtalar		+			
Midtarsal	+	+			
Metatarsophalangeal	+	+	+	+	
Proximal interphalangeal	+				

2.2.1.2   Visual Analogue Scale

The patient's assessment of pain, global disease activity and global health are estimated with the Visual Analogue Scale (VAS) ranging from 0 to 100 millimetres (Scott et Huskinsson 1976). The physician's assessment of global disease activity is measured with a similar scale. These scales are easy to use and serve as part of several composite indices.

2.2.1.3   Acute phase reactants

The systemic inflammation in RA is assessed with the erythrocyte sedimentation rate (ESR), measured according to the Westergren method, and C-reactive protein (CRP), is currently measured most often with nephelometry. The acute phase reactants are normal in about 40% of patients with RA (Sokka et al. 2012). They are nonspecific markers of inflammation, being often elevated in other autoimmune diseases and infections.

2.2.1.4   Composite indices of disease activity

The joint counts and the patients' self-evaluations alone are poorly reproducible and not precise enough to quantify the disease activity, as are the acute phase reactants, in a single assessment (Sokka et al. 2012). To avoid constricted impression of the disease activity, several composite indices have been created (Table 4). The first Disease Activity Score (DAS) based on the Ritchie index and the 44 swollen joint count, was described by van der Heijde et al. (1990). Currently the most often used composite index is modified Disease Activity Score based on assessment of 28 joints (DAS28) (Prevoo et al. 1995). Originally, the DAS28 (DAS28-ESR) was calculated with the ESR, later a modification using CRP (DAS28-CRP) was introduced.

Table 4. Composite indices for disease activity in rheumatoid arthritis (Anderson et al. 2011, Sokka et al 2012).

Index	Formula	Range
1.	Indices including physician's joint assessment	
DAS	$0.55938 \times \sqrt{(RAI)} + 0.06465 \times \sqrt{(SJC44)} + 0.330 \times \ln(ESR) + 0.00722 \times (GH)$	0–10
DAS28	$0.56 \times \sqrt{(TJC28)} + 0.28 \times \sqrt{(SJC28)} + 0.70 \times \ln(ESR) + 0.014 \times (GH)$	0–9.4
SDAI	TJC28 + SJC28 + CRP + MDGL + PTGL	0.1–86
CDAI	TJC28 + SJC28 + MDGL + PTGL	0–76
2.	Patient-reported indices	
RAPID3	MDHAQ x 3.3 + Pain + PTGL	0–30
PAS	(HAQ x 3.3 + Pain + PTGL)/3	0–10
RADAI*	self-reported questionnaire on 5 items	0–10

Scores/indices: DAS, disease activity score; DAS28, disease activity score based on assessment of 28 joints; SDAI, simplified disease activity index; CDAI, clinical disease activity index; RAPID3, routine assessment of patient index data; PAS, patient activity score; RADAI, rheumatoid arthritis disease activity index.

Abbreviations: CRP, C-reactive protein (mg/dl); ESR, erythrocyte sedimentation rate; GH, patient's assessment of global health (scored on a 0 to 10 scale); HAQ, health assessment questionnaire; MDHAQ, multidimensional health assessment questionnaire; MDGL, physician's global assessment of disease activity (scored on a 0 to 10 scale); PTGL, patient's global assessment of disease activity (scored on a 0 to 10 scale); RAI, Ritchie articular index; SJC28, swollen joint count on 28 joint evaluation; TJC28, tender joint count on 28 joint evaluation.

*RADAI is self-reported questionnaire on 5 items: disease activity in the last 6 months, current disease activity with respect to joint tenderness and swelling, arthritis pain, duration of morning stiffness (scored as 0 = none, 1 = < 30 minutes, 2 = 30 minutes to 1 hour, 3 = 1–2 hours, 4 = 2–4 hours, 5 = > 4 hours, and 6 = all day) and perceived joint pain in 16 joint areas (scored from 0 indicating no pain to 3 indicating severe pain). The first three items are scored from 0 (not at all) to 10 (extremely/very severe), last two components are transformed to a 0 to 10 scale and the sum of these component scores is divided by 5 to get the RADAI score.

2.2.2 REMISSION

In previous clinical studies remission was seldom assessed as an outcome measurement, and later several different definitions of clinical remission have been used (Shammas et al. 2010, Felson 2012). For the patients' asymptomatic status, absence of pain, tenderness and swelling of joints represent the condition that physicians refer to as remission. In the routine clinic, the absence of tender and swollen joints together with normal ESR and CRP is a practical and valid definition for remission (Mäkinen et al. 2005a). Currently authorities debate on whether to include radiographic remission in the criteria of remission and on which imaging method should in that case be used (Brown et al. 2008, van der Heijde 2012).

In clinical studies the most often used criteria for remission have been the ARA (later ACR) published in 1981 preliminary criteria (Pinals et al. 1981) and the remission criteria based on the DAS and DAS28 scores, proposed by EULAR in the early 1990s (van der Heijde et al. 1990, Prevoo et al. 1995). Table 5 presents the limits of the disease activity indices, which indicate remission and different states of disease activity. The limitation of the DAS28 and other disease activity indices based on assessment of 28 joints is that they ignore the MTP and tarsal joints and may consider patients with active arthritis in the feet to be in remission (Mäkinen et al 2005b).

Table 5. Definitions of remission and of various disease activity states of clinical composite disease activity indices (Anderson et al. 2011, Sokka et al. 2012).

Index	Remission	Low	Moderate	High
DAS	< 1.6	1.6 to < 2.4	2.4 to ≤ 3.7	> 3.7
DAS28-ESR	< 2.6	2.6 to < 3.2	≥ 3.2 to ≤ 5.1	> 5.1
DAS28-CRP	< 2.3	2.3 to < 2.7	≥ 2.7 to ≤ 4.1	> 4.1
SDAI	≤ 3.3	> 3.3 to ≤ 11	> 11 to ≤ 26	> 26
CDAI	≤ 2.8	> 2.8 to ≤ 10	> 10 to ≤ 22	> 22

For the definition of ARA preliminary remission, five of six criteria presented in Table 6 must be fulfilled. In many studies, the condition of fatigue is omitted, as in the modified ACR criteria (Table 6). The ACR criteria are regard by many authorities as the golden standard for clinical remission.

Table 6. Preliminary ARA criteria (Pinals et al. 1981) and modified ACR criteria for remission in RA.

Preliminary ARA criteria	Modified ACR criteria
1. Morning stiffness < 15 minutes	1. Morning stiffness < 15 minutes
2. No joint pain by history	2. No joint pain by history
3. No joint tenderness on examination	3. No joint tenderness on examination
4. No joint or tendon sheath swelling	4. No joint or tendon sheath swelling
5. ESR < 30 mmHg (women) or < 20 (men)	5. ESR < 30 mmHg (women) or < 20 (men)
6. No fatigue	
At least 5 of 6 over 2 months	At least 4 of 5 over 3 months

After 30 years of publishing the ARA criteria, new common criteria for remission were formulated by the ACR and EULAR (Table 7) to be used in clinical trials (Felson et al. 2011). The index-based definition of remission shares the limitations of the other criteria, which are based on disease activity indices with assessment of 28 joint counts (Mäkinen et al. 2005b, Landewe et al. 2006). When using the boolean-based definition, more inclusive joint counts can be evaluated.

Table 7. The 2011 ACR and EULAR criteria for remission in RA (Felson et al. 2011).

Boolean-based definition:

At any time-point, patient must satisfy all of the following:

  Tender joint count ≤ 1

  Swollen joint count ≤ 1

  CRP ≤ 1 mg/dl

  Patient global assessment ≤ 1 (on a 0-10 scale)

Index-based definition:

At any time-point, patient must have a

  Simplified Disease Activity Index (SDAI) score of ≤ 3.3

SDAI is defined as the simple sum of the tender joint count (28 joints), swollen joint count (28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale) and CRP level (mg/dl).

2.2.3   FUNCTIONAL CAPACITY

In RA, both the acute inflammation and the long-term damage in the joints reduce the patient's functional ability (Drossaers-Bakker et al. 1999, Welsing et al. 2001). The functional capacity in RA is most often evaluated with the Health Assessment Questionnaire (HAQ). This questionnaire consists of eight sections concerned with functioning: dressing, arising, eating, walking, hygiene, reaching, gripping

and performing tasks assessed with 20 questions (Fries et al. 1980). The answers to each question are scored from 0 to 3, the score 0 representing the activity that can be performed without difficulty, 1 with some difficulty, 2 with much difficulty or the patient needs help or devices, and 3 means that the patient is unable to perform the activity. The HAQ score is calculated by summing the highest scores of each of the 8 sections and dividing the sum by 8. If the HAQ score is 0, patient's functional capacity is normal; the score of 0.13–1 represent mild or moderate disability, 1–2 severe disability and 2–3 very severe disability (Bruce and Fries 2003). The Finnish version of the HAQ score was formulated in the early 1990s (Hakala et al. 1994). The HAQ score has proved to have good correlation with other health status measures and has showed to be a predictor for long-term outcome in several studies (Bruce and Fries 2003).

2.2.4   RADIOGRAPHIC OUTCOME
2.2.4.1   *Radiographic progression of the small joints*

The inflammatory process in RA favours the small joints (the PIP joints, MCP joint and wrists in the hands and the MTP joints in the feet), and thus the radiographic changes, narrowing of the joint space and erosions usually manifest first in these joints. In routine practice radiographs of the hands and feet are taken at the time of RA diagnosis to determine the erosiveness of the disease and often after one or two years' duration of the disease to evaluate the radiographic progression and adequate efficacy of treatment. The EULAR recommendations for the use of imaging of the joints in the clinical management of RA were published in 2013 (Colebatch et al. 2013). These specify that radiographs of the hands and feet should be used as the initial imaging technique to detect damage, but, particularly in early RA, ultrasound (US) and magnetic resonance imaging (MRI) can be used to confirm the diagnosis of RA. These imaging methods may detect active inflammation not found with clinical examination and are thus helpful in monitoring disease activity. Strict recommendations for later evaluation of joint damage with conventional radiographs were not given, but radiographs of the hands and feet should be considered after the first 12 months of the disease (or during the first 2 years) to detect changes in previous erosions or the appearance of new erosions.

In clinical studies, precise methods that enable extensive evaluation of joint damage are needed to assess the amount and severity of the joint damage. When conventional radiographs are used, the Larsen scoring (LS) method and the Sharp/van der Heijde scoring (SHS) method (van der Heijde 1996, Boini and Guillemin 2001) are the recommended methods for evaluating radiographic progression. Currently some studies have used MRI to detect early erosive changes and signs of inflammation in early RA (Haavardsholm et al. 2008). However, this imaging method is expensive and less available in the routine

clinic and thus a less proper tool in clinical practice and in large or long-term follow-up studies.

In the LS method (Larsen et al. 1977, Boini and Guillemin 2001) the radiographs of the MCP I–V, interphalangeal (IP) I, and PIP II–V of the hands and wrists and the MTP II–V and IP I of the feet are evaluated. Each joint is graded from 0 to 5: 0 = normal; 1 = soft-tissue swelling, periarticular osteoporosis or narrowing of the joint space; 2–5 = increasing degrees of erosion and destruction, using a set of reference radiographs. Joints that have undergone surgery are scored as grade 5. The total LS is calculated by summing all the scores with wrists multiplied by 5, thus resulting in a scale from 0 to 200. If at least one joint of a patient has an LS grade of 2 or more, his/her RA is defined as erosive.

The SHS method assesses and grades both the erosions of 16 joints and joint space narrowing (JSN) of 15 joints in the wrists, hands and feet (van der Heijde 2000, Boini and Guillemin 2001). This method emphasizes changes in the wrists. In the erosion score, the joint surfaces of the first metacarpal base, radius, ulna, navicular and lunate of each hand are assessed separately; the trapezium and trapezoid are assessed as single unit, as are the IP joints of the thumbs, four PIP joints and five MCP joints of both hands. In the feet, the five MTP joints and first IP joints are assessed. The erosions in each joint are graded from 0 to 5, depending on the amount of the surface area affected. The score for JSN combines the assessment of subluxation/luxation and of narrowing of the joint space assessed in five MCP joints, four PIP joints, multiangular navicular-lunate, radiocarpal and carpometacarpal (CMC) III and V joints of the hands and the five MTP and first IP joints of the feet. The changes are graded from 0 to 4, depending on the proportion of the narrowing in the percentage and grade of subluxation. The maximum total score for erosions is 280 and for JSN 168, giving a maximum total score of 448.

Of these two scoring systems the LS seems to be more specific, especially when the radiographs are scored chronologically. The advantage of the SHS is its sensitivity and ability to detect small changes earlier than the LS (Boini and Guillemin 2001, Bruynesteyn et al 2002).

2.2.4.2   Large joint damage

Even if RA affects mainly the wrists and small joints of the hands and feet, the inflammation may spread to the large joints or in some patients manifest first as monoarthritis or oligoarthritis of the large joints. In clinical practice, imaging of the large joints is performed based on constant joint involvement or if there is suspicion of the need for operative treatment. In clinical studies, large joint damage is assessed either with the amount of total joint replacements (TJRs) or radiographic assessment. Most follow-up studies have reported the amount of arthroplasties needed instead of radiographic evaluation.

A more exact method for evaluating large joint damage in RA is a systematic evaluation of large joint radiographs at a certain time point in the disease. In addition to the number of damaged large joints, the severity of the joints can be evaluated, by using a scoring system such as the LS for large joints. In the LS radiographs of the shoulders, elbows, hips, knees and ankles (both talocrural and subtalar joints) are assessed and each joint is scored from 0 to 5 points, 1 representing slight joint space narrowing and 2–5 increasing grades of erosions, giving a scale from 0 to 60. Joint replacement and arthrodesis are scored as 5 (Larsen et al. 1977).

2.2.5 COMORBIDITY

The incidence and importance of comorbidities on later outcome in RA have been highlighted in several studies (Michaud and Wolfe 2007, Radner et al. 2010, Gullick and Scott 2011). The high incidence of the CVDs in RA and their relationship to mortality has become evident (Young et al. 2007, Turesson et al. 2008, John et al. 2009, Radovits et al. 2010). The incidence of CVD events in patients with RA is more than three times higher than that in the general population, and this increase is not explained by the traditional risk factors of CVD (Choy 2012). Some studies have considered RA to be as a important risk factor for CVD as diabetes (Peters et al. 2009, Lindhardsen et al. 2011). Evaluation of the traditional cardiovascular risk factors is currently included in good clinical care of patients with RA (Charles-Schoeman 2012).

Some malignancies, such as lung cancer and skin cancers, seem to be more common in RA patients than in the population in general (Michaud and Wolfe 2007). The elevated risk of RA patients for lymphomas and the relationship of this risk to disease activity has been determined in several studies (Baecklund et al. 2006, Kaiser 2008). The increased risk for lymphomas was also indicated in Finnish patients with RA in the 1970s (Isomäki et al. 1979).

Some of the comorbidities, such as infections, gastrointestinal ulcerations, osteoporosis and cataract are linked to the medications for RA, especially to the use of oral corticosteroids. In addition to these conditions interstitial lung disease and CVDs are often related to both the disease itself and to the medications taken for it (Gullick and Scott 2011).

2.2.6 WORK DISABILITY

Both inflammatory activity and progressing joint damage impair the functional capacity of patients with RA and may cause work disability. Early-initiated, intensive treatment targeting remission in the early phase of the disease can restore patients' functional and working capacity and prevent later loss of these capacities, due to

permanent joint damage (Puolakka et al. 2005). In addition to the disease-related factors, working ability is determined by patient-related factors, including age, education and psychosocial status and by the physical demands of work and the working circumstances. Depending on the weight of these factors, the patient's experienced work disability may differ from the degree of disability defined by the treating physician. National definitions of work disability are set by social security legislation and by conditions of pension insurance. The definitions and criteria for work disability vary widely among countries and also in society over time, which complicates the comparison between different countries and studies (de Croon et al. 2004, Verstappen et al. 2004).

In general, work disability rates are higher in studies done in Europe than in the United States (U.S.). This difference was also found in a study that compared the probability to continue working during the first 4 years after RA diagnosis in a Finnish cohort of 364 RA patients who were of working age and working with a similar cohort of 269 patients from the U.S. (Chung et al. 2006). The probability of working after the first year of RA diagnosis was similar (92%) in both cohorts. The difference between the cohorts began to present itself after 2, 3 and 4 years with 86%, 84% and 80% probability in the Finnish cohort and 89%, 89% and 84% probability in the U.S. cohort. Similar differences were evident in two studies with a long follow-up period: in a 15-year follow-up of a Swedish cohort with 183 RA patients enrolled between 1985 and 1989 (Eberhardt et al. 2007) and a cross-sectional (CS) study collecting data from a large national databank in the U.S. between 2002 and 2005 that concerned 4385 RA patients' working ability with a mean disease duration of 14 years (Allaire et al. 2008). In the Swedish cohort, the prevalence of work disability was 28% at the time of RA diagnosis and 44% after 15 years of disease duration. In the U.S. study all patients were employed at the onset of RA and the prevalence of arthritis-attributed work cessation was 28% with 14–16 years of disease duration.

2.2.7   MORTALITY

Increased mortality in patients with RA compared with the general population has been observed both in clinical follow-up studies and in population-based studies (Sokka et al. 2008b, Gabriel and Michaud 2009). The reported standardized mortality ratios (SMRs) have varied from 0.87 to 2.98. Two population-based studies done in Finland have reported SMRs of 1.37 and 1.78 for RA patients compared with the general population (Myllykangas-Luosujärvi et al. 1995, Sihvonen et al. 2004), while in two early RA cohorts from Jyväskylä (Sokka et al. 1999a) and from Helsinki (Peltomaa et al. 2002) the SMRs were 1.28 and 1.33. The most common causes of death in patients with RA have been CVDs, followed by malignancies, infections, gastrointestinal, respiratory and renal diseases (Sokka et al. 2008b, Gabriel and

Michaud 2009). A recent meta-analysis emphasized the importance of CVDs as a cause of mortality accounting for 40% of all deaths in RA patients (Meune et al. 2009). This meta-analysis showed that RA is associated with a 60% increased risk of cardiovascular death compared with the general population. The most significant disease-related predictors of mortality in RA are functional status measured by the HAQ and comorbidity (Sokka et al. 2008b, Carmona et al. 2010).

Treatments for RA have improved greatly in recent decades: however, the excess mortality has not declined until recently. A study from the Netherlands compared the mortality rates in three RA cohorts with the general Dutch population in the periods 1993–1995, 1996–1998 and 1999–2006. The patients of the first cohort were treated mainly with NSAIDs, in the second cohort with hydroxychloroquine (HCQ) and sulphasalazine (SASP) and in the latest cohort with methotrexate (MTX) or biological drugs. The SMR of the latest cohort with a more aggressive treatment strategy was 0.49 compared with 1.35 and 1.23 of the first two cohorts (van Nies et al. 2010).

2.3   DRUG TREATMENT OF RHEUMATOID ARTHRITIS

The treatment of RA has advanced outstandingly during the recent decades. Previous treatments have been based on clinical experience in the efficacy and benefits of antirheumatic drugs. Recent knowledge of the pathogenesis of RA, particularly of the role of cytokines and inflammatory cells, has led to development of new biological drugs, such as TNF-α inhibitors. In addition to the introduction of biological drugs, the introduction of novel treatment strategies has made it possible to treat RA more successfully.

2.3.1   SYNTHETIC DISEASE-MODIFYING ANTIRHEUMATIC DRUGS (DMARDS)
2.3.1.1   *Gold compounds*

Gold compounds, although originally developed for the treatment of tuberculosis, can be regarded as the first true DMARDs. The beneficial clinical effects of gold compounds were shown in the 1930s (Forestier 1935) and the retardation of radiographic progression in the 1970s (Sigler et al. 1974). Intramuscular gold (aurothiomalate) was the drug of choice in RA for decades, before the modern synthetic DMARDs were developed. Later, it was revealed that gold compounds have several different modes of activity in RA (Kean and Kean 2008). The use of intramuscular gold is often limited, due to its adverse effects such as stomatitis, skin rash, proteinuria, cytopenias, elevated liver enzymes or pulmonary reactions. Oral gold preparation (auranofin) has fewer substantial adverse effects, but also a weaker antirheumatic effect than aurothiomalate. However, intramuscular gold

can still be used in case of treatment failure with other DMARDs or when DMARD options are limited, due to reduced liver function or allergy (Cheung et al. 2012).

2.3.1.2 Sulphasalazine

Sulfasalazine (SASP) was introduced for the first time for the treatment of RA already in the 1940s by Svartz, but became rediscovered internationally in the late 1970s and established as a DMARD in early the 1980s (Box and Pullar 1997). The efficacy of SASP in RA has been shown both in placebo-controlled studies and in comparison to other synthetic DMARDs. Since the 1990s, SASP has been included in several combination treatment strategies. Even if some anti-inflammatory and immunomodulatory effects of SASP in RA have been identified, its mechanism of activity as a whole has remained unclear. Gastrointestinal symptoms, headache, dizziness, rash and elevation of liver enzymes are the most common adverse effects. Leucopenia or neutropenia due to myelosuppression occur in ≤ 3–4% of SASP recipients and requires discontinuation of the drug. Agranulocytosis or severe neutropenia have been reported in 0.6% of patients (Plosker and Croom 2005).

2.3.1.3 Hydroxychloroquine

Of the antimalarial drugs used since the 1950s, HCQ has established itself as an antirheumatic drug in RA and in various connective-tissue diseases (CTDs). In treating RA, its efficacy is moderate, and therefore it is currently used more often as part of DMARD combinations than as monotherapy. HCQ is generally well tolerated. The most common adverse events are solar rash, mild gastrointestinal discomfort and nightmares. Retinopathy is less common with HCQ than with the previously used chloroquine (Suarez-Almazor et al. 2000). Recent data suggest that HCQ may have a beneficial effect on lipid levels and thus reduce cardiovascular risk (Katz and Russell 2011).

2.3.1.4 D-penicillamine

Synthetic D-penicillamine has been a treatment option for RA since the 1960s. Its efficacy is equal to that of intramuscular gold, SASP and azathioprine; however, its common and often serious adverse effects, such as pemphigus, glomerulonephritis, and cytopenias restrict its use (Munro and Capell 1997).

2.3.1.5   Methotrexate

Methotrexate (MTX) is a folic-acid antagonist inhibiting purine and pyrimidine synthesis and thus preventing cellular proliferation. It was originally introduced as a cancer therapy. MTX has been used since the late 1980s in the treatment of RA. Recent data suggest that MTX also has anti-inflammatory properties in RA (Chan and Cronstein 2010). Due to its favourable long-standing efficacy and safety profile, it is currently the anchor drug in RA (Gaujoux-Viala and al 2010). MTX is increasingly used as part of various DMARD combinations and together with biological agents (Braun and Rau 2009). MTX is initiated with a small dose (10–15 mg) once per week and elevated stepwise to up to 20–30 mg weekly. Complete blood count and liver enzymes are monitored for drug toxicity, and folic-acid supplementation is recommended to reduce toxicity. When the oral treatment appears insufficient, subcutaneous or intramuscular administration increases efficacy (Bijlsma and Jacobs 2009, Visser and van der Heijde 2009).

2.3.1.6   Azathioprine

Azathioprine is not as effective as MTX in treating RA. The use of azathioprine has decreased, because of its side effects: myelosuppression, increased risk of infections, hepatotoxicity and malignancies with long-term use. Currently azathioprine is used mostly in CTDs or in RA with clinical features of CTD (Gaffney and Scott 1998).

2.3.1.7   Cyclosporine

The main indication of cyclosporine is immunosuppression after organ transplantations. In RA, it was first tried in late the 1970s. Due to its moderate antirheumatic effect, cyclosporine is currently used in combination with other DMARDs or as a second-line DMARD. Hypertension and impairment of renal function are the main adverse effects of cyclosporine (Kitahara and Kawai 2007).

2.3.1.8   Podophyllotoxin

Semisynthetic podophyllotoxin (CPH 82), a vegetable compound of two benzylidated podophyllotoxin glycosides, has antirheumatic properties similar to those of SASP, auranofin, azathioprine and low-dose MTX (Martio 1998, Lerndal and Svensson 2000). It was a treatment option available until year 2013 for the patients with intolerance to several other DMARDs.

2.3.1.9　Leflunomide

Leflunomide is the first DMARD developed primarily for treatment of RA and has been available since the late 1990s. Leflunomide is as effective as MTX and SASP in RA (Nandi et al. 2008). Due to its side effects (gastrointestinal upset, oral ulcers, headache, hypertension, hepatotoxicity and predisposition for infections and peripheral neuropathy), leflunomide therapy is withdrawn more often than MTX therapy (Behrens et al. 2011).

2.3.2　GLUCOCORTICOIDS

Since their discovery in 1948, glucocorticoids (GCs) have been used widely in RA, due to their immediate and extensive anti-inflammatory and immunosuppressive effects. Most patients use oral GCs in some phase of the disease and a proportion of patients with active disease continuously. Due to the rapid anti-inflammatory effect, administration of oral GCs is useful in early RA as a bridging therapy, while waiting the effects of more slowly acting DMARDs. Disease-modifying effects and retardation of radiographic progression of GCs have been shown in several studies, and currently the use of GCs as a cotherapy with DMARDs has been recommended, especially in early RA (Gorter et al. 2010, Hoes et al. 2010).

Long-term use of oral GCs has several well-known adverse effects, such as osteoporosis, increased risk of infections, skin atrophy and cataract. In addition, the patients' cardiovascular risk may increase, due to some side effects such as weight gain, hyperglycaemia, hypertension and unfavourable effects on lipid profiles (Hoes et al 2010). Due to their unfavourable adverse effects, GCs are currently recommended to use only for short periods and with as low doses as possible.

In addition to oral GCs, intra-articular GC injections are effective in suppressing inflammation in the affected joints. The clinical benefit of frequently given intra-articular betamethasone injections in early RA was proved in the CIMESTRA (Cyclosporine, Methotrexate, Steroid in RA) trial (Hetland et al. 2006), which compared the clinical effects between combination of MTX and cyclosporine and MTX monotherapy. This study reported equal retardation of radiographic progression in both treatment groups at 5 years (Hetland et al. 2010). Intra-articular administration of GCs is a good alternative when only a few joints are affected or a comorbidity of the patient limits the use of oral GCs.

2.3.3　BIOLOGICAL TREATMENTS

The development of biological therapies has become possible by more precise understanding of the pathogenetic mechanisms in RA. These drugs target the

known key factors involved in the inflammatory pathways in RA, such as particular cytokines or cells.

2.3.3.1   TNF-α inhibitors

The first biological agents developed targeted TNF-α, a proinflammatory cytokine. The two first TNF-α inhibitors, infliximab and etanercept have been available in clinical use since 1999. Adalimumab was introduced next and golimumab and certolizumab-pegol in the late 2000s. Infliximab is administered intravenously and etanercept, adalimumab, certolizumab-pegol subcutaneously. Golimumab can be administered either subcutaneously or intravenously (Scott 2012). The clinical efficacy of all TNF-α inhibitors is quite similar and well documented, as is their impact on retardation of radiographic progression (Nam et al. 2010, Simsek 2010). Concurrent use of MTX improves the efficacy and is recommended. The clinical benefits of the TNF-α inhibitors were first proven in patients with established RA who showed inadequate response to DMARD treatment. Later studies confirmed their efficacy in early RA, and new EULAR recommendations for management of RA encourage earlier initiation of the TNF-α inhibitors in patients with active and DMARD resistant disease (Nam et al. 2010, Smolen et al. 2010).

The most essential adverse events of the TNF-α inhibitors (increased risk of infections and risk of tuberculosis reactivation) are associated with their impact on the host defence system. The bacterial infections most often reported are upper respiratory infections and pneumonias. The incidence of soft-tissue infections, skin infections and septic arthritis is increased, compared with the patients using conventional DMARDs. There are concerns that TNF-α- inhibitor therapy may induce activation of viral hepatitis B and C and predispose for herpes zoster infection (Thalayasingam and Isaacs 2011, Scott 2012).

2.3.3.2   Other biological treatments

In addition to TNF-α inhibitors, therapies targeting other cytokines or inflammatory cells have been developed for treatment of RA. The first of these drugs was an IL-1 receptor antagonist, anakinra, whose clinical efficacy is not as convincing as the efficacy of the TNF-α inhibitors (Scott 2012). Another, even more important proinflammatory cytokine in RA, IL-6, is inhibited by tocilizumab, a humanized monoclonal antibody targeting IL-6 receptors. Tocilizumab effectively suppresses clinical disease activity and improves possibility to achieve remission (Scott 2012). Rituximab is a B-cell-depleting, chimeric monoclonal CD20 antibody, whose efficacy is superior in seropositive patients (Scott 2012). Abatacept is a selective inhibitor of T-cell costimulation, necessary for T-cell activation. It thus reduces production

of the cytokines TNF, IL-1 and IL-6 (Scott 2012). In clinical practice, rituximab, abatacept and tocilizumab are mostly used as second-line biological treatments for patients failing the TNF-α inhibitor therapy.

2.3.4 TREATMENT STRATEGIES

2.3.4.1 Pyramid strategy

In the 1960s and 1970s, when gold salts, D-penicillamine, antimalarial drugs and GCs were available for antirheumatic treatment, the basis of therapy in RA was rest, physical therapy, splinting, regularly administered aspirin or other NSAIDs. Local, intra-articular injections of GCs were used to relieve joint pain and reduce inflammation. Systemic GCs were used in most severe cases and for short periods. The DMARD therapy in this pyramid strategy was initiated in a later disease course if the other treatments failed (Fries 2000).

2.3.4.2 Sawtooth strategy

In the 1980s, the use of DMARDs became more common, since the true nature of RA as a chronic and progressive disease was realized. A new more active treatment strategy was proposed by Fries (1990): the DMARD was administered early, as soon as possible in the disease (I). One or multiple DMARDs were used continuously throughout the entire disease course (II). The DMARD was replaced with another DMARD if no positive effect could be established, if the initial adequate effect was lost or if a clinically meaningful adverse effect occurred (III). In his original proposal, Fries advised that the disability and other outcome variables should be regularly monitored. A ceiling for disability should be set for each individual patient and exceeding of this limit indicated the need to change the DMARD treatment. Fries (1990) also mentioned DMARD combination as a treatment option.

2.3.4.3 Combination strategies

To increase the efficacy of the treatment, the idea of combination of several DMARDs was introduced in early the 1990s. The results of the first studies were not encouraging, due to several adverse effects and a marginally increased clinical efficacy (Felson et al. 1994). Several studies comparing combination treatments of MTX and SASP or of MTX, SASP and HCQ with DMARD monotherapy in early RA (O'Dell et al. 1996, Boers et al. 1997, Calguneri et al. 1999, Dougados et al. 1999,

Möttönen et al. 1999, Capell et al. 2007, Saunders et al. 2008) were published in late the 1990s and in the 2000s, showing much more promising clinical effects (Table 8).

Table 8. Clinical outcome in combination treatment studies based on methotrexate (MTX), sulphasalazine (SASP) and hydroxychloroquine (HCQ).

Author(s) Year	Inclusion criteria	Number of patients Mean disease duration	Follow-up time	Treatment arms	Outcome
O'Dell et al. 1996	Active RA, monotherapy failure	102 > 6 months	2 years		50% decrease in a pooled index of disease activity
				MTX + SASP + HCQ SASP + HCQ MTX	77% 40% 33%
Boers et al. 1997	Early RA, DMARD-naive	155 4 months	28 weeks		A pooled index of disease activity improved
				SASP + MTX + initial highdose prednisolone SASP monotherapy	72% 49%
Calguneri et al. 1999	Active RA, poor DMARD response	180 2.3 years	2 years		ACR remission
				MTX + SASP + HCQ MTX + SASP / MTX + HCQ MTX / SASP / HCQ	60% 45% 32%
Dougados et al. 1999	Active RA (DAS > 3.0), DMARD naive	205 < 1 year	1 year		Change in DAS
				SASP + MTX MTX SASP	- 1.26 - 0.87 - 1.15
Möttönen et al. 1999	Active RA, DMARD-naive	199 < 2 years	2 years		ACR remission
				MTX + SASP + HCQ monotherapy starting with SASP	37% 18%
Capell et al. 2007	SASP failure, DAS > 2.4	165 1 year	18 months		DAS remission
				MTX + SASP SASP MTX	10% 5% 3%
Saunders et al. 2008	Active RA, DMARD-naive	96 11.5 months	12 months		DAS28 remission
				SASP + MTX + HCQ step-up: SASP > MTX + SASP > MTX + SASP + HCQ	45% 33%

In addition to the more favourable clinical efficacy, the combination therapies decreased radiographic progression. This was shown in the early phase of RA in some of the studies presented in Table 8 (Boers et al. 1997, Calguneri et al. 1999, Dougados et al. 1999, Möttönen et al. 1999). Later, it became evident that long-term radiographic progression was also more moderate in patients treated

initially with combination therapy than in those treated with monotherapy, as shown both in the COBRA (Combinatietherapie Bij Rheumatoide Arthritis) study (Landewe et al. 2002, van Tuyl et al. 2010) and in the Fin-RACo study (Korpela et al. 2004, Rantalaiho et al. 2010). All these combination strategies emphasize the early initiation of effective DMARD therapy. Studies performed in the 2000s have also highlighted the importance of tight control of the treatment response and of intensive, according to disease activity modified antirheumatic therapy (Grigor et al. 2004, Goekoop-Ruiterman et al. 2005, Hetland et al. 2006, Verstappen et al. 2007).

2.4 TREATMENT PRACTICES AND TREATMENT RECOMMENDATIONS

2.4.1 EARLY TREATMENT PRACTICES IN FINLAND

From the 1950s to the 1980s, gold compounds, HCQ, SASP and GCs were available of those DMARDs that are used today. D-penicillamine was one option, but it often had to be discontinued, due to poor tolerability. Azathioprine, cyclophosphamide, chlorambucil and podophyllotoxin were used for selected patients with severe RA. Until the 1970s, treatment of RA was usually initiated with high doses of NSAIDs. In the pyramid strategy, synthetic DMARDs were used as a second-line treatment if the symptoms and inflammation were not controlled with NSAIDs, rest and physiotherapy. The favourable effect of gold on radiographic progression and importance of early initiation of DMARD therapy was shown first by Reijo Luukkainen et al. (1977). In the 1980s, first SASP and later MTX proved more effective and well-tolerated alternatives for medication in RA, and the idea of the continued DMARD therapy, sawtooth strategy was presented by Fries et al. (1990). This strategy was introduced in to clinical practice also in Finland since the 1980s (Möttönen et al. 1996).

2.4.2 CHANGES IN TREATMENT PRACTICE IN FINLAND DURING THE 1990S

During the 1990s, MTX was established in addition to SASP in the treatment of RA and initial combinations of these two or of other DMARDs were attempted for the treatment of patients who were resistant to DMARD monotherapy. In 1993, the FIN-RACo trial was initiated and late in the decade the superior results of the study (Möttönen et al. 1999, 2002) assured Finnish rheumatologists of the benefits of combination therapy and early initiation of DMARD therapy. This contributed to formulating Finnish guidelines for management of RA (Hakala et al. 1999). In the FIN-RACo study, 195 DMARD-naive patients with RA of recent onset (symptom duration < 2 years; median 6 months) were treated with either a combination of DMARDs (starting with MTX, SASP and HCQ with prednisolone; 97 patients) or

with a single DMARD (initially SASP, with or without prednisolone; 98 patients) for 2 years, targeting remission. After 1 year, ACR remission was achieved in 24 (25%) of the 97 patients with the combination treatment and in 11 (11%) of the 98 patients with the single DMARD therapy; after 2 years remission was achieved in 37% and 18% of the patients, respectively (Möttönen et al. 1999). In the single-DMARD therapy group, the frequency of remission was higher (35%) in those patients whose DMARD treatment was initiated within 4 months from the onset of RA than in those patients with after 4 months initiated treatment (11%)(Möttönen et al. 2002). After 2 years, the treatment strategy in both patient groups was unrestricted, but remission as a target was still kept valid. Later the 5-year data of the FIN-RACo study showed that patients in the combination treatment group had less radiographic progression and retained their ability to work better than patients in the initial monotherapy group (Korpela et al. 2004, Puolakka et al. 2004). Of the patients who were in remission at 6 months or at 12 months, none were permanently work-disabled over the 5-year follow-up (Puolakka et al. 2005).

2.4.3   FINNISH CURRENT CARE GUIDELINES

The national guidelines for treatment of RA in Finland were first published in 1999 and revised in 2003 and 2009. Based on the results of the FIN-RACo study, the authors of the Finnish Current Care guidelines for management of RA (Hakala et al. 2009) consider DMARD combination therapy to be more effective than DMARD monotherapy. The later guidelines specify that the aim of drug treatment is clinical remission, and early initiation of DMARD therapy results in increased remission and predicts more favourable long-term outcome. These guidelines recommend initiating treatment with a combination of MTX, SASP and HCQ plus low-dose prednisolone, at least if the disease is very active or if the initiation of drug treatment is delayed. TNF-α-inhibitors and other biological drugs are considered as second-line therapy in case that DMARD combination therapy fails.

2.4.4   INTERNATIONAL RECOMMENDATIONS

Finnish practice and guidelines differ from the recommendations published by EULAR for the management of RA (Smolen et al. 2010), which emphasize MTX as an anchor drug and advise switching or combination with other synthetic DMARDs only as a second option if the MTX therapy fails and the patients have no poor prognostic factors. For patients with poor prognostic factors and MTX failure, biological drugs are recommended as second-line therapy. These recommendations concluded that the benefits of DMARD combination therapies are not adequate enough and that the use of GCs in several studies may have had confounding effects

on the favourable results of these studies (Smolen et al. 2010). In a recently published update of EULAR recommendations for the management of RA (Smolen et al. 2014), combination therapy with conventional synthetic DMARDs was considered as an equal option as DMARD monotherapy for DMARD-naive patients with newly diagnosed RA. MTX should be part of the first treatment strategy in patients with active RA.

2.4.5   REDUCTION OR DISCONTINUATION OF DMARD TREATMENT

A controversial question is how to deal with patients who have been treated with continuous DMARD therapy and remain in sustained remission and whether to reduce or even discontinue their treatment. Small, short-term randomized and controlled studies from the 1970s and 1980s suggested that long-term maintenance treatment with azathioprine (Cade et al. 1976, De Silva and Hazleman 1981), with MTX (Szanto 1986, Kremer et al. 1987) or with intramuscular gold (Cats 1976) prevented flare-ups of the disease in RA. Some studies have indicated that the disease activity-controlling effect of parental gold may continue longer than the effect of other DMARDs after the treatment has been withdrawn (Van der Leeden et al. 1986, Sander et al. 1999).

In a randomized, double-blind, placebo-controlled study (ten Wolde et al. 1996), DMARD treatment was discontinued in 143 (placebo group) of 285 patients with RA who met modified ACR remission criteria, had stable disease for at least 1 year and were treated with one of the following DMARDs (HCQ, parental gold, D-penicillamine, SASP, azathioprine or MTX). The other 142 patients continued their current DMARD. During the 52-week follow-up, the disease flared in 53 patients (38%) of the placebo group and in 30 (22%) of those who continued DMARD therapy. The risk factors for a flare-up were randomization in the placebo group, a high maintenance dose of DMARDs [relative risk (RR) 1.8] and positive RF.

The 2010 EULAR recommendations for management of RA (Smolen et al. 2010) stated that it is still unclear how to continue or discontinue treatment in patients who had achieved remission. These recommendations suggested a gradual tapering at first and then a discontinuation of GCs. When remission persists after this (at least for several months), tapering of biological agents may be considered in those treated with these drugs. The opinion on tapering or discontinuation of synthetic DMARDs was more cautious, based on previous data showing that discontinuation of these drugs was associated with increased disease flare-up frequency (Smolen et al. 2010). The 2013 EULAR recommendations (Smolen et al. 2014) concluded that in patients with persistent remission after having tapered GCs, tapering of biological agents could be considered, especially in patients treated with a combination of biological agent and synthetic DMARD. In patients with sustained long-term remission, cautious reduction in the synthetic DMARD dose could be considered.

2.5.   LONG-TERM OUTCOME IN RHEUMATOID ARTHRITIS

2.5.1   CLINICAL OUTCOME ASSESSED WITH FOCUS ON REMISSION

Previous long-term follow-up studies have seldom reported clinical remission as an outcome measure in RA. Disease activity (number of swollen joints, number of tender joints, composite indices for disease activity as DAS or DAS28), functional capacity (commonly assessed with the HAQ score) and radiographic joint damage have been the most commonly used main outcome assessments. Scandinavian researchers were among the first ones to report remission as an outcome measure (Table 10). A cohort study done in Sweden reported 18% of patients with early RA diagnosed between 1985 and 1989 being in remission, according to the ACR criteria at 10 years (Lindqvist et al. 2002). The FIN-RACo study's 11-year results were reported in two initial treatment groups: 37% of the patients treated initially with DMARD combination and 19% of the patients treated with DMARD monotherapy were in ACR remission at endpoint (Rantalaiho et al. 2009). In the COBRA trial (van Tuyl et al. 2010), which initially compared MTX and SASP combination with high-dose prednisolone to SASP monotherapy, 39% of the patients in both groups were in DAS28 remission (DAS28 < 2.6) at 11 years. In the BeSt (Behandel Strategieen) study comparing four different treatment strategies, 48% of all patients were reported to be in DAS remission (DAS < 1.6) at 5 years; 14% of the patients were in drug-free DAS remission (Klarenbeek et al. 2011a). In the CIMESTRA study (Hetland et al. 2010), the patients with RA were treated initially either with a combination of MTX and cyclosporine or with MTX monotherapy supported with frequently given intra-articular GC injections; 56 % of those patients followed up to 5 years were in ACR remission at that point. A recent report of the Finnish Neo-RACo study showed that 60% of the patients treated with the FIN-RACo combination (MTX, SASP and HCQ) plus infliximab for 6 initial months of RA and 61% of the patients treated merely with the FIN-RACo combination, were in strict ACR remission at 5 years (Rantalaiho et al. 2013). The DAS28 remission rates were 84% and 89%, respectively.

Table 9. Long-term follow-up studies reporting clinical remission as an outcome measure in patients with RA diagnosed with the ACR criteria or former ARA criteria.

Study	Number of patients	Disease duration years	Follow-up period years	Remission criteria	Patients in remission (%)
Lindqvist et al. 2002	163/183	< 2	10	ACR	18
Rantalaiho et al. 2009	138/199	< 2	11	ACR	27
van Tuyl et al. 2010	134/155	≤ 2	11	DAS28*	39
Klarenbeek et al. 2011a	434/508	≤ 2	5	DAS**	48
Hetland et al. 2010	139/160	< 0.5	5	ACR DAS28*	56 78
Rantalaiho et al. 2013	91/99	≤ 1	5	ACR DAS28	60 87

* DAS28 score < 2.6

** DAS score < 1.6

At best, comparisons should be performed between such studies that share similar criteria for remission and are as similar as possible regarding the baseline demographics, baseline clinical variables and the period when the studies were completed.

2.5.2 RADIOGRAPHIC PROGRESSION OF THE SMALL JOINTS

Currently the radiographic scoring systems most often used for assessing damage in the small joints (hands, wrists and feet) are the Larsen method (LS) and the Sharp/van der Heijde method (SHS) with their modifications (Boini and Guillemin 2001). Comparison of the results of studies evaluating radiographic progression is challenging, due to the various scoring systems and differences in reporting the results. Several follow-up studies have reported the amount of progression at baseline and at endpoint or the change from baseline to endpoint (Table 10). Some studies have presented the proportions of patients having mild, moderate or severe radiographic progression. The different statistical methods further increase the difficulties in comparing the studies, as appears in Table 10.

Table 10. Radiographic progression in patients with RA diagnosed according to the ACR criteria in studies with follow-up time ≥ 10 years.

Study	Number of patients	Disease duration baseline, years	Mean follow-up time, years	Radio-graphic score, maximum	Median/mean change in score from baseline
Kaarela et al. 1997	66/103	< 0.5	20	LS 200	82 (mean)
Gordon et al. 2001	88/289	10	10	LS 200	21 (median)
Lindqvist et al. 2003	168/183	< 2	10	LS 200	48 (median)
Courvoisier et al. 2008	112/191	< 1	10	SHS 448	29 (mean)
Rantalaiho et al. 2010	130/195	< 2	11	LS 200	22 (mean)
Markatseli et al. 2011	144/407	< 5	10	LS* 140	20 (mean)

LS = Larsen score, SHS = Sharp/van der Heijde score

*only radiographs of hands and wrists were evaluated and scored

One method for comparing results of the radiographic progression assessed with various modifications of scores is to calculate and report the mean annual change in percentage of the maximum score (Paimela et al. 1998). Performing this calculation for the studies by Kaarela et al. (1997), by Rantalaiho et al. (2010) and by Markatseli et al. (2011) in table 10 gives a mean annual change (percentage of the maximum score) 4 Larsen units (LUs) (20%), 2 (10%) and 2 (14%), respectively.

Some researchers have evaluated different patterns of radiographic progression over time (Graudal et al. 1998, Plant et al. 1998). Five main types of radiographic progression were described in 109 RA patients whose radiographs were assessed with a modification of LS during follow-up periods varying between 10 and 22 years: (1) a rare (< 1% of patients) type with no radiographic progression, (2) a type with slow or moderate progression at onset, but an increasing progression rate (9% showing exponential growth type and 30% linear type), (3) a type with a moderate-to-fast onset and a stable progression rate (11%), (4) a type with rapid onset, but later decreasing progression rate (30%), (5) a type characterized by slow onset, then acceleration and later deceleration (20%) (Graudal et al. 1998).

2.5.3 LARGE JOINT DAMAGE

In previous studies large joint damage in RA has been commonly addressed with the requirement for large joint replacements (LJRs). In long-term follow-up studies (Drossaers-Bakker et al. 2000, Capell et al. 2002, Jäntti et al. 2002, Massardo et al. 2002, Kapetanovic et al. 2008) the number of patients with RA who had experienced at least one LJR varied between 15% and 50% within a mean 12–20-year follow-up periods (Table 11). The joints that were most often replaced were the hips and knees in the lower extremities and shoulders in the upper extremities.

Table 11. Large joint replacements (LJRs) in patients with RA in long-term follow-up studies.

Study	Number of patients	Time of collection	Duration of RA, years	Mean follow-up time, years	Number (%) of patients with LJR
Capell et al. 2002	52/123	1977–1979	5.5	20	(50%)
Jäntti et al. 2002	68/103	1973–1975	0.5	20	16 (24%)
Massardo et al. 2002	424	1955–1985	-	15	76 (18%)*
Kapetanovic et al. 2008	116/183	1985–1989	1.0	16	44 (24%)
Drossaers-Bakker et al. 2000	105/138	1982–1986	< 5	12	15 (14%)

*only RA-related LJR, in addition 34 (8%) patients with LJR for other reasons

Long-term radiographic large joint damage was evaluated with the LS in Dutch patients with RA (Drossaers-Bakker et al. 2000). Radiographs of the large joints were available in 103/138 patients at 12 years; 70% of these had LS ≥ 1 and 54% had erosive changes (LS ≥ 2) in at least one large joint. The median (range) LS of large joints for the entire cohort was 3 (0–55). Recent 8-year radiographic results in 290/347 Dutch patients in the BeSt study (Dirven et al. 2012) reported that 64% of the patients suffered damage in at least one large joint or the wrists, which were included in the analysis of this study. LJR was performed for 21 patients (7%). The mean [standard deviation (SD)] LS of the large joints was 2.7 (3.7) and median [interquartile range (IQR)] LS 1 (0–4) at endpoint.

2.5.4   COMORBIDITY

The concept of comorbidity in RA has been rather complex and controversial. Some authors have included in comorbidities such conditions that are related to or causally associated with RA. Others have defined all of an individual's other diseases as comorbidities (Michaud and Wolfe 2007). Michaud and Wolfe divided the relationship of RA and comorbid conditions in the following way: In type I comorbidity, no relationship can be detected between RA and the comorbid condition. In type II comorbidity, a comorbid condition leads to an increase in some outcome parameter of RA. In type III comorbidity, an outcome parameter of RA leads to an increase in a comorbid condition. Type IV occurs if RA causes the comorbid condition (at least in part). Type V comorbidity occurs when treatment of RA causes or contributes to the development of a comorbidity. In type VI a common condition leads both to the RA and the comorbidity (Table 12).

Table 12. Types of comorbidity in RA (Michaud and Wolfe 2007).

Type	Cause	Direction	Example
I	Unrelated to RA or its treatment	Unrelated	Appendicitis, trauma
II	Comorbidity	From CC to RA outcome	Depression and work disability
III	RA consequences	From RA outcome to CC	Functional disability gastric ulceration
IV	RA itself	From RA to CC	Myocardial infarction, ILD
V	RA treatment	From RA to CC	Corticosteroids and infections, osteoporosis
VI	Common external Factor	From factor to RA From factor to CC	Smoking, RA Smoking, lung cancer

CC = comorbidity condition, ILD = interstitial lung disease

Most authors agree that comorbidity is an important issue in RA, due to its impact on the later outcome of both RA and of the individual patient as a whole (Michaud and Wolfe 2007, Gullick and Scott 2011, Norton et al. 2013, van den Hoek et al. 2013). Several comorbidities, such as CVDs or malignancies, increase both morbidity and mortality of patients with RA (Michaud and Wolfe 2007). In addition comorbidities, such as chronic liver disease or impairment renal function may restrict the treatment of RA.

During the last decade, the importance of CVDs and their impact on mortality in RA have been emphasized. Two meta-analyses (Avina-Zubieta et al. 2008, Meune et al. 2009) have reported a pooled SMR of CVD of 1.5-1.6 in patients with RA. Avina-Zubieta et al. reported the SMR separately for ischaemic heart disease (1.59) and for cerebrovascular accidents (1.52). In another meta-analysis (Meune et al. 2010),

a pooled estimate of myocardial infarction incidence risk ratio was 2.10 in patients with RA and 1.77 in the general population. In addition to the traditional risk factors of CVDs, the increased cardiovascular risk of RA patients has been related to the systemic inflammation present in RA (Turesson et al. 2008, Solomon et al. 2010).

A recent 5-year follow-up study reported the occurrence of cardiovascular events and risk factors for CVD in Swedish patients with early RA. In this cohort (collected from 1995), 48/442 of the patients (11%) experienced a new cardiovascular event; 15 had myocardial infarction, 4 patients were treated by coronary artery bypass, 23 had a stroke or a transient ischaemic attack, 5 had either deep-vein thrombosis or pulmonary embolism and one patient a rupture of an aortic aneurysm (Innala et al. 2011). The cardiovascular events were explained by traditional risk factors of CVDs and by high disease activity of RA. In a previous Swedish cohort study (Kapetanovic et al. 2010) with a 20-year follow-up of 183 patients with RA, 30 (16%) had CVD at the outset of the study and an additional 55 patients (30%) developed a new CVD during the follow-up.

In addition to CVDs, malignancies are comorbid conditions that have impact on later outcome in RA. The number of malignancies in patients with established RA varies quite widely in studies reporting comorbidities (Table 13). Both the risk of developing lung cancer (relative risk of 1.2–1.5) and the risk of mortality from lung cancer are increased in patients with RA (Michaud and Wolfe 2007). After lung cancer, breast cancer is the second most common malignancy in patients with RA. However, the risk of breast cancer seems to be slightly decreased among women with RA with a standardized incidence ratio (SIR) of 0.8 (Michaud and Wolfe 2007). Colon cancer has been found less frequently in patients with RA than in the general population (Kauppi et al. 1996). The risk of both Hodgkin's lymphoma and non-Hodgkin's lymphoma is elevated, with a risk ratio of 1.8–2.0 in patients with RA (Baecklund et al. 2006, Kaiser 2008). Lung cancer and lymphomas were also more frequently found in Finnish autopsy findings of 369 patients with RA than in patients without RA (Koivuniemi et al. 2011). Increase in both nonmelanoma skin cancer and melanoma has been described in association with biological treatments of RA (Wolfe and Michaud 2007).

Table 13. Occurrence of malignancies in RA patients with over 10 years' disease duration.

Study	Number of patients	Type of study	Mean age at end-point years	Mean disease duration years	Precentage of patients with malignancy
Kapetanovic et al. 2010	171/183	LO	-	20	24%*
Briggs et al. 2009	624	CS	57	16	4%
Radner et al. 2010	380	CS	61	12	11%
van Tuyl et al. 2010	133/155	LO	61	11	12%

LO = longitudinal follow-up study, CS = cross-sectional study

* 6% of patients with mean age of 51 years at baseline had malignancy at outset of the study; 18% developed new malignancy during the follow-up

RA-related interstitial lung disease and infections of patients with RA have been associated with increased mortality in RA. Both of these comorbid conditions could be related to treatments of RA. The occurrence of osteoporosis and gastrointestinal diseases are increased in patients with RA and these comorbidities cause increased morbidity in RA (Michaud and Wolfe 2007, Gullick and Scott 2011). Osteoporosis showed a two-fold increase in 394 Norwegian female patients with RA compared with the general population (Haugeberg et al. 2000). A follow-up study reported new vertebral fractures in 19% and new nonvertebral fractures in 16% of postmenopausal patients with RA during 5 years (Vis et al. 2011).

2.5.5   WORK DISABILITY

Loss of functional capacity or of work capacity are of great importance for both individual patients and for society, due to their economic and social consequences. A recent register study reported that early (during the first 2 years) work disability of patients with RA in Finland was less frequent in the later patient cohorts of the 2000s (2004–2005 and 2006–2007) than in the earlier cohorts (2000–2001 and 2002–2003). The incidence of RA-related work disability was nearly halved from 8.9% in 2000–2001 to 4.8% in 2006–2007 (Rantalaiho et al. 2012). Previous prospective studies from European countries have indicated that 20–30% of patients with early RA became work-disabled during first 3 years of RA (Sokka 2003a). Comparison among various studies is demanding and complicated, due to differences in the

study populations, study designs, the definition of work disability and divergences in the social security systems of various countries. The grounds for granting a work disability pension may also be changed over time.

Few longitudinal studies have investigated long-term work disability in RA. A follow-up study of 160 British patients with between 1989 and 1998 diagnosed RA reported that 33% of the patients became work-disabled during 5 years and 39% during 10 years (Barrett et al. 2000). A recently published study (Nikiphorou et al. 2012) evaluated the work disability rate in 647 patients with early RA (collected between 1986 and 1998), who were still working and ≤ 60 years of age. Within a median of 10 years follow-up, 49% of the patients had stopped working; 63% of these were work-disabled due to RA and 37% for other reasons. The estimated probability of work loss due to RA was highest in older patients (45–60 years) at onset of RA and in those who were recruited before 1992. The 5-year RA-related work disability rate in this British cohort was 29% (Young et al. 2002).

Work disability rates in Finnish studies (Mäkisara and Mäkisara 1982, Nissilä et.al. 1983, Kaarela et.al. 1987, Jäntti et al. 1999, Sokka et al. 1999b, Puolakka et al. 2004) and in Scandinavian studies (Ødegård et al. 2005, Eberhardt et al. 2007) varied between 25% and 40% after 5 years, 39% and 50% after 10 and 44% and 67% after 15 years of RA (Table 14). The work disability rates are in general higher in the European countries than in the U.S. (Verstappen et al. 2004, Chung et al. 2006). This difference was still evident among the studies in Table 14 and a study from the U.S. (Allaire et al. 2008) reporting premature work cessation in 35% of RA patients with 10 years' disease duration and 51% of patients with ≥ 25 years' disease duration.

Evaluation of the impact of various drug treatments or treatment strategies on work disability must be done with caution, due to the reasons described above. In assuming that the grounds for granting a work disability pension in Finland have not been substantially changed over recent decades, a positive influence of advanced drug treatment of RA may be observed in studies done in Finland.

Table 14. Work disability (WD) of patients with RA in Finnish and Scandinavian cohort studies and in cross-sectional studies (CS).

Cohort/study Authors, publication year	Time of collection Type of study	Number of patients	Mean disease duration, years	Rate of WD (%)
Mäkisara and Mäkisara 1982	CS	405	5 10 15	40 50 67

Heinola cohort
  Nissilä et al. 1983
  Kaarela et al. 1987
  Jäntti et al. 1999
	1973–75	107
		107
		103
		103
			
			3
			8
			20
				
				32
				43
				80

Jyväskylä cohort Sokka et al. 1999b	1983–85 1988–89	82*	2 10	19 44
FIN-RACo study Puolakka et al. 2004	1993–95	162*	5	25
Lund cohort Eberhardt et al. 2007	1985–89	148*	baseline 5 10 15	28 35 39 44
Oslo RA register Ødegård et al. 2005	CS	526	2.0 5.0 8.3 11.3 13.0 17.8 29.4	17 35.5 35.1 40.0 44.4 55.6 68.4

* all patients of working age

3.   AIMS OF THE STUDY

The main aim of this study was to evaluate the long-term outcome of RA patients, focusing on the permanent consequences of the disease: radiographic damage, functional disability and work disability, and comorbidities in a cohort of patients with early RA diagnosed between years 1986 and 1989.

The following items were examined:

1. The 15-year outcome of patients; disease activity, radiographic progression and functional capacity with focus on the continuity of antirheumatic treatment.

2. Long-term radiographic outcome of patients with early RA and impact of early radiographic remission (ERR) on 15-year joint damage.

3. The occurrence of comorbidities in RA and the relationship of comorbidity to disease activity and functional capacity.

4. Long-term work disability of early RA patients and the impact of early disease activity and of early radiographic progression on retirement due to RA.

4. PATIENTS AND METHODS

4.1 PATIENTS

A cohort of 87 patients with early RA was collected between 1986 and 1989 in the Helsinki area to study prospectively the course and outcome of early RA. The patients were referred from primary health care or private outpatient clinics to the Second Department of Medicine at Helsinki University Central Hospital or to the Department of Rheumatology at Helsinki City Hospital, due to recent onset of RA. To be included in the study, the patients had to fulfil the ARA 1958 criteria for definite RA (Ropes et al. 1958), the duration of their disease (defined as the time from the onset of symptoms) had to be ≤ 12 months and they had to be 18-65 years of age and DMARD-naive. Later during the follow-up, the patients were confirmed to fulfil also the ACR 1987 criteria (Arnett et al. 1988).

4.2 STUDY DESIGN

4.2.1 STUDY DESIGN DURING THE FIRST 3 YEARS

Antirheumatic therapy with DMARDs, was initiated immediately after the diagnosis of RA was confirmed for all patients, with the exception of one patient who initially refused to take any DMARDs. The initial DMARD could be intramuscular gold, SASP or HCQ. During the first 3 years, the patients were treated intensively and individually according to the sawtooth strategy (Fries 1990). The treatment with DMARD was administered early (I), one or multiple DMARDs were used continuously (II), the DMARD was replaced with another DMARD if no positive effect could be established, if the initial adequate effect was lost or if a clinically meaningful adverse effect occurred (III). If the initial treatments were ineffective or had to be discontinued due to adverse events, the patients could receive other DMARDs (oral gold, D-penicillamine, MTX, azathioprine, cyclosporine or podophyllotoxine). Combination therapy with various DMARDs could be used when DMARD monotherapy was ineffective. Low-dose oral GC treatment (≤ 10 mg prednisolone) was used in the active phase of the disease. Intra-articular GCs were used liberally.

4.2.2   LATER STUDY DESIGN: TREATMENTS AND FOLLOW-UP

After the intensive 3-year follow-up period, most of the patients were treated and followed up by the initial investigators or other rheumatologists at the Department of Rheumatology at Helsinki University Central Hospital or at Helsinki City Hospital. Some patients with long-lasting remission were later transferred to primary health care or occupational health services for follow-up. The DMARD treatments of individual patients were modified by the treating physicians, according to current Finnish practice and guidelines. During the 1990s, use of different combinations of DMARDs became more common if the disease was active. In addition to the DMARDs used in the earlier phase of the study, leflunomide became available in the late 1990s and biological agents since 1999. DMARD therapy could also be gradually reduced or discontinued in patients with long-standing clinical remission.

The medication of each patient over the first 3 years was recorded at each study visits. Later data on patients' DMARD treatments were collected at each follow-up examination from patients' medical records. The treatment data of the patients followed up in primary care or occupational health care were collected by history and confirmed from medical records and prescriptions. Interruptions of DMARD treatment, due to adverse events, pregnancies or other illnesses, were recorded and taken into account in reporting the number and duration of the DMARD therapies.

4.3   ASSESSMENT OF CLINICAL OUTCOME

The study group was followed up by the initial investigators for up to 3 years: every 3 months for the first year and every 4 months during the last 2 years. All patients were invited for 5-, 7-, 10- and 15-year follow-up examinations. To evaluate the patients' clinical disease activity, joint counts for tender joints (53 joints and 28 joints) and for swollen joints (44 joints and 28 joints) and acute phase reactants were assessed at every study visit. Length of morning stiffness and joint pain by history were registered to determine if the patients were in remission according to the ACR criteria (Pinals et al. 1981).

The patient's self-reported assessment of global health (GH) was recorded from the third year of the study. As a result, DAS28 (Prevoo et al. 1995) was calculated with three parameters (tender joints, swollen joints and ESR) for the first 3 years of the study. At the endpoint, the DAS28 was calculated with four parameters (tender joints, swollen joints, ESR and patient's global assessment of disease activity). The patients' functional capacity was assessed with HAQ (Fries et al. 1980, Hakala et al. 1994) from the third year of the study.

4.4.   ASSESSMENT OF RADIOGRAPHIC DAMAGE

Plain radiographs of the hands, wrists and feet were examined at the outset of the study and at 1, 2, 3, 5, 7, 10 and 15 years. The radiographs of the hands, wrists and feet were evaluated according to Larsen's scoring system described earlier (Larsen et al. 1977) by an experienced radiologist blinded to the clinical information. A total LS was expressed on a scale from 0 to 200. The patient's RA was defined as erosive if she or he had at least one joint with LS grade ≥ 2 (Larsen and Thoen 1987).

The large joints were systematically examined at the 15-year follow-up. The total amount and severity of large joints damage was determined by evaluating the shoulders, elbows, hips, knees and ankles according to the Larsen large joint score (Larsen et al. 1977). In addition to the imaging, information of total joint replacements (TJRs) was collected longitudinally.

4.5   COMORBIDITY

Information on each patient's comorbidities was registered at the outset of the study and by interviewing the 70 patients who participated in the 15-year examination. The data received by history were confirmed from the patients' medical records. In the case of deceased patients, comorbidities were collected both from medical records and death certificates. For the patients participating in the 15-year study visit, bone mineral density assessed with dual-energy X-ray absorptiometry (DEXA) of lumbar spine and hips (Chun 2011) was performed to diagnose osteoporosis. The abdominal fat subcutaneous aspiration was taken to detect amyloidosis (Klemi et al. 1987). Lipid values and fasting blood glucose were studied to determine the cardiovascular risk factors. Smoking history of the patients was registered at the 15-year examination.

Patients' total comorbidity load at baseline was assessed with the Charlson comorbidity index (CCI), which is a validated and weighted score of 19 conditions that significantly influence the relative 1-year mortality risk (Charlson et al. 1987). The comorbid conditions of the CCI and their weights are presented in Table 15. The sum of all conditions with their weights can range from 0 to 33. In this study, we used a modification of the original CCI (CCIa), which considers the impact of ageing on mortality by adding an extra point for each decade of age above 50 years (Charlson et al. 1994).

Table 15. Comorbid conditions of Charlson comorbidity index with their weights.

Comorbid condition	Weight
Coronary artery disease	1
Congestive heart disease	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatoid disease	1
Peptic ulcer	1
Mild liver disease	1
Diabetes mellitus, no complications	1
Diabetes mellitus with complications	2
Hemiplegia or paraplegia	2
Renal disease	2
Solid tumour, nonmetastatic	2
Leukaemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumour	6
AIDS	6

4.6   WORK DISABILITY

Cumulative retirement due to RA was followed up longitudinally at each study visit. The date of retirement, type of disability pension (full-time or part-time disability pension) and the main cause for retirement were collected from the patient's work disability certificates and medical records. The judgement on heavy physical work was based on the patient's occupation. The physical demands of work were defined at the 15-year follow-up visit with a brief questionnaire evaluating following items: lifting and carrying heavy loads, continual manual labour, difficult working position or mainly standing work.

4.7 ETHICAL CONSIDERATIONS

The study design was approved by the Ethics Committee of the Helsinki University Central Hospital. Each patient gave a written consent to use his or her medical records for supplementary data collection. Statistics Finland permitted use of information on the causes of death and comorbidities.

4.8 STATISTICAL METHODS

Results of variables with normal distribution are presented as means or medians with standard deviation (SD), 95% confidence interval (95% CI) or interquartile range (IQR). Statistical comparison between the groups was performed with the T-test, analysis of variance (ANOVA) or bootstrap-type test. Variables with ordinal descriptive values were expressed as medians with IQRs and the differences between the groups were analysed by the Mann-Whitney U-test or the Kruskal-Wallis test. Measures with a discrete distribution were expressed as counts with percentages and analysed by the chi-square test, the Fisher-Freeman-Halton test or Cochran-Armitage trend test with Monte-Carlo P-value.

Repeated measures of continuous outcomes were evaluated, using generalized estimating equation (GEE) models with exchangeable correlation structure. These models do not require complete data and are appropriate for use when data at some time-point of longitudinal follow-up are not available. The normality of variables was evaluated by Shapiro-Wilk statistics. The 95% CIs were obtained with bias-corrected bootstrapping when the outcome variables' distribution was skewed. The STATA 12.1, StataCorp LP (College Sation, TX, USA) statistical package was used for the analyses.

An ordered logistic regression analysis was performed to estimate the impact of baseline variables and ERR on radiographic progression during 15-year follow-up. The relation between baseline comorbidity and later disease activity and functional capacity was evaluated in three groups, using the CCIa. The statistical significance for hypotheses of linearity was evaluated by ANOVA and Cochran-Armitage trend test with Monte-Carlo p-value.

The analysis of cumulative retirement due to RA-related work disability was based on the Kaplan-Meier estimation. The Cox hazard regression model was used to estimate the adjusted risk for RA-related retirement. The comparison of still working and the retired patients was evaluated with the chi-square test and the Fisher-Freeman–Halton test.

5.   RESULTS AND DISCUSSION

5.1   GENERAL RESULTS

5.1.1   BASELINE DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

The study group consisted of 87 patients [69 females (79%) and 18 males (21%)], who were diagnosed with early RA between 1986 and 1989. At the beginning of the study, the mean (range) age of the patients was 44 (18–65) years and the mean (range) disease duration (time from the first symptoms of RA) was 8 (2–12) months. The number of RF-positive patients was 57 (65%) and 45 (52%) of those who had erosive disease.

Seventy patients (80%) participated in the 15-year examination; 10 patients (11%) died during the follow-up and six (7%) were lost to follow-up (four of whom moved from the area and two of that no longer wanted to participate, due to old age and other diseases). One female patient was excluded from the final analysis, because of revised diagnosis (Behcet's disease). The baseline demographics and clinical characteristics of the patients who were evaluated at 15 years, those who died during the follow-up or dropped out from the study appear in Table 16. The baseline data of the RF-positive and RF-negative patients examined at 15 years is presented in Table 17.

Table 16. Baseline demographics and clinical characteristics of patients participating in the 15-year examination and those who died or were lost to follow-up.

	Patients examined at 15 years n = 70	Patients who died n = 10	Patiets lost to follow-up n = 6
Total follow-up time (years), mean	15.6	8.1	7.5
Demographics			
Age (years), mean (SD)	43 (12)	58 (4)	40 (14)
Female, n (%)	59 (84)	5 (50)	4 (67)
Duration of disease (months), mean (SD)	7.9 (3.6)	7.0 (3.2)	8.8 (2.1)
Rheumatoid factor present, n (%)	46 (66)	9 (90)	2 (33)
Clinical characteristics			
Tender joints, mean (SD)	14 (8)	20 (10)	16 (11)
Swollen joints, mean (SD)	5 (5)	7 (6)	4 (3)
ESR (mm/h), mean (SD)	31 (22)	51 (34)	43 (32)
Erosive disease, n (%)	35 (50)	6 (60)	4 (67)

Table 17. Baseline demographics and clinical characteristics of RF-positive and RF-negative patients examined at 15 years.

	RF-positive patients n = 46	RF-negative patients n = 24	P-value
Demographics			
Age (years), mean (SD)	46 (8)	36 (9)	0.002
Female, n (%)	37 (80)	22 (92)	0.21
Duration of disease (months), mean (SD)	8.1 (3.6)	7.6 (3.7)	0.62
Clinical characteristics			
Tender joints, mean (SD)	13 (9)	14 (8)	0.61
Swollen joints, mean (SD)	5 (5)	5 (5)	0.88
DAS28, mean (SD)	4.35 (1.16)	4.49 (1.03)	0.60
Larsen score, mean (SD)	5 (7)	3 (5)	0.08

5.1.2 TREATMENT DURING THE FIRST 3 YEARS OF THE STUDY

Antirheumatic therapy with DMARDs was initiated for all patients as soon as the diagnosis was confirmed. One patient initially refused to take any DMARD, but was willing to begin DMARD treatment later during the first year of RA. The initial DMARD was intramuscular gold for 67 patients, SASP for 14 patients and HCQ for 5 patients (Table 18). During the first 3 years of the study, the patients were treated according to the sawtooth strategy (Fries 1990). If several DMARDs as sequential monotherapy were ineffective or not tolerated, combination therapy with various DMARDs was already used during the first years of RA.

The first initiated DMARD was well tolerated and controlled the signs and symptoms of the disease in 28 (33%) of the 86 patients. The initial DMARD was changed to another DMARD, due to adverse effects in 32 patients (37%) and due to inefficiency in 26 patients (30%). The second DMARD was well tolerated and effective at controlling the clinical signs of RA for 16 (19%), the third DMARD for 14 (16%) and the fourth DMARD for 12 (14%) of the patients. In addition to intramuscular gold, SASP and HCQ, D-penicillamine and auranofin were often used during the first 3 years of the study. Of the remaining 16 patients not responding to the treatment, a tolerated and effective DMARD or DMARD combination (generally intramuscular gold in combination with SASP or with HCQ) was found for 8 patients during the first 3 years of the study. In general, combination therapy was used for 13 patients (15%) and MTX for 8 patients (9%) during the 3 three years of the study.

5.1.3 TREATMENT OVER THE 15-YEAR FOLLOW-UP

Of the 70 patients participating in the 15-year examination 55 (78%) used DMARDs during the visit: 30 (43%) were on monotherapy, 22 (31%) were on DMARD combinations and 3 (4%) were treated with biological agents (Table 18). There were 15 patients without any antirheumatic treatment; the DMARDs of 4 patients were discontinued due to adverse events and those of 11 patients (73%) due to clinical remission or a prolonged symptom-free phase with minor disease activity. Of the 55 patients who were treated with DMARDs, 32 (58%) used MTX, half of these as part of a DMARD combination. Twenty patients (29%) used low-dose oral GC as part of their treatment at the 15-year visit and 43 patients (61%) were treated with oral GC at some phase of the follow-up. The total time on DMARD treatment in percentages of the total follow-up period was calculated for each of the 70 patients participating in the 15-year examination. The mean total time on DMARD treatment was 73% of the mean follow-up time and the mean number of DMARDs or DMARD combinations was 5.1.

Table 18. Antirheumatic treatment of all 86 patients at the outset of the study and treatments of the 70 patients followed up over 15 years at the end-point.

	At outset of the study n = 86		At 15-year examination n = 70	
DMARD monotherapy	86	(100%)	30	(43%)
Intramuscular gold	67	(78%)	1	(1,4%)
Sulphasalazine	14	(16%)	3	(4,3%)
Hydroxychloroquine	5	(6%)	3	(4,3%)
Methotrexate			15	(21,4%)
Azathioprine			2	(2,9%)
Cyclosporine			0	(0%)
Podophyllotoxin			1	(1,4%)
Leflunomide			5	(7,1%)
DMARD combination			22	(31%)
Biological agents			3	(4%)
No DMARDs or biological agents			15	(21%)

5.2 CLINICAL OUTCOMES

5.2.1 DISEASE ACTIVITY AND REMISSIONS

At the 15-year follow-up visit, the disease activity according to the DAS28 criteria was low in 39 (56%) of the 70 patients and thus the mean (SD) DAS28 for the whole study group remained low [3.20 (1.14)]. In all, 26 patients (37%) were in DAS28 remission (DAS28 ≤ 2.6), but only 10 patients (14%) fulfilled the ACR remission criteria (Pinals et al. 1981). The ACR remission rates during the early phase of the study were 27% at year 1, 24% at year 2, 43% at year 4 and 45% at year 5. The remission rate improved when effective and well-tolerated DMARD treatment was found for most of the patients during the first 3 years of the study. The remission rate at year 10 (38%) may have been overestimated, due to the low number of patients (42/86) participating in that visit. The substantially decreased number of patients with remission at the 15-year visit was associated with those whose RA flared up when their DMARD treatment was discontinued and with those whose RA was continuously active, despite of uninterrupted DMARD treatment. In addition, some of the patients transferred to primary health care or to occupational health care showed mild or moderate disease activity when participating in the 15-year examination.

In previous studies remission has seldom been used as an outcome measurement. Observational cohort studies done in Finland (Möttönen et al. 1996) were among

the first reporting ACR remissions as an outcome assessment. A multicentre, randomized study in Finland comparing the efficacy and tolerability of an initial combination of three DMARDs (MTX, SASP and HCQ) and DMARD monotherapy (SASP as the first DMARD) according to the sawtooth strategy, the FIN-RACo study (Möttönen et al. 1999), was one of the first clinical trials with ACR remission as an aim and as the main outcome measure of the study. The 11-year follow-up results of the FIN-RACo study reported that the difference in remission rates between 68 patients in the original DMARD combination treatment group (37%) and the 70 patients of the original single DMARD group (19%) was still evident and very similar to the remission rates after 2 years of RA: 37% and 18% respectively (Rantalaiho et al. 2009). The ACR remission rate (38%) at 10 years in the present study was very similar to the results of the FIN-RACo study. The low participation (42/86 patients) in that visit may however, have caused skewing of the 10-year results.

The remission according to the DAS28 remission criteria in the FIN-RACo study was equally achieved in both groups. The strict ACR remission criteria (fulfilment of all five criteria) appear to be more sensitive to differences in remission rates between different treatment groups. Some authors have proposed that strict ACR remission and also DAS remission represent more reliable true clinical remission than DAS28 remission (Mäkinen et al. 2005b, Landewe et al. 2006). This was explained at least partially by the lack of evaluation of the feet and ankle joints in the DAS28 score. In addition the high weight of the ESR in the DAS28 may have resulted in overestimation of the impact of ESR on the score, especially when the ESR is elevated, due to illnesses other than RA (Mäkinen et al. 2005b).

5.2.2   FUNCTIONAL CAPACITY

In the present cohort, the 15-year functional capacity assessed with mean HAQ remained favourable [0.52 (95% CI: 0.41–0.64)] in the entire study population. Of the 70 patients participating in the 15-year visit 26% had an HAQ score 0 and a total of 58% had HAQ scores ≤ 0.50. Eleven patients (16%) had HAQ scores ≥ 1.00 and only one of these was severely disabled (HAQ > 2). In the present study, the HAQ score was not assessed until the third year of the follow-up. This is a limitation of our data and may also have influenced patients' assessments of the HAQ later during the study. When the HAQ was assessed for the first time in the third year of the study, the high initial disease activity and joint pain in most patients had already decreased. The change in the HAQ during first years of RA and its association with DMARD treatment could not be evaluated in our patients. In the third year, the mean HAQ calculated for 78 patients with the HAQ scores available was 0.25, in the fifth year 0.43 for 83 patients and in 10 years 0.43 for 58 patients. Functional capacity from the third year onwards was analysed separately in the RF-positive

and RF-negative patients. The mean HAQ over the following 12 years was slightly lower in the RF-negative patients than in those who were RF-positive (Figure 1).
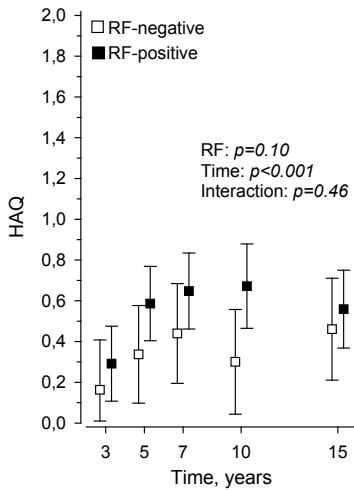

Figure 1. Functional capacity assessed with mean HAQ in RF-positive and RF-negative patients from year 3 to year 15.

The 15-year mean HAQ (0.54) in the present study was lower than in previously published follow-up studies of patients with early RA after a 9–12-year follow-up time (mean HAQ 0.64–1.1) (Drossaers-Bakker et al. 1999, Welsing et al. 2001, Lindqvist et al. 2002). The mean HAQ in the FIN-RACo study after 11 years of RA was 0.34 for patients treated initially with combination treatment and 0.38 for patients treated with DMARD monotherapy (Rantalaiho et al. 2009). Early-initiated and intensive DMARD therapy during the early phase of RA is the most probable explanation for the favourable remaining functional capacity both in the FIN-RACo study and in the present study. However, some contributing factors in measuring the HAQ should be borne in mind: patients with established RA may overestimate their functional capacity (van den Ende et al. 1995). The HAQ values were higher both in elderly individuals of the general population and in elderly patients with RA (Sokka et al. 2003b). Those patients participating in the 15-year examination were on average younger than those who died during the follow-up. In general, the patients in the present study were younger than those in the Swedish cohort reported by Lindqvist et al. (2002) with a mean age of 51 years at baseline.

5.2.3 IMPACT OF DMARD TREATMENT CONTINUITY ON LONG-TERM OUTCOME

Over the 15-year follow-up the DMARD treatment was discontinued, due to clinical remission (at least 12 months) or to symptom-free periods with minor disease activity in 20 (29%) of the 70 patients. The disease flared up in 9 patients (45%), while 11 patients (55%) remained in remission. The clinical outcome at 15 years was studied in the following patient groups according to the continuity of DMARD treatment: group A with continuous DMARD treatment (n = 50), group B with discontinued and restarted DMARD treatment (n = 9) and group C with permanently discontinued DMARD treatment (n = 11). The baseline demographics and clinical characteristics of the groups are shown in Table 19.

Table 19. Baseline demographics, clinical characteristics and radiographic findings of patients with continuous DMARDs (group A), of those with discontinued and restarted DMARDs (group B) and of those with permanently discontinued DMARDs (group C).

Variable	Group						P-value
	A (n = 50)		B (n = 9)		C (n = 11)		
Demographics							
Number of females, n (%)	46	(92)	7	(78)	6	(55)	0.007
Age (years), mean (SD)	43	(11)	46	(14)	39	(12)	0.39
Duration of disease (months), mean (SD)	8	(4)	9	(5)	6	(2)	0.16
RF present, n (%)	34	(68)	7	(78)	5	(46)	0.27
HLA-DR4, n (%)	32	(64)	7	(78)	5	(46)	0.34
Disease Activity							
ESR (mmHg), mean (SD)	30	(20)	41	(25)	28	(28)	0.34
Number of swollen joints, mean (SD)	5	(6)	6	(5)	3	(2)	0.55
Number of tender joints, mean (SD)	14	(9)	13	(9)	12	(7)	0.93
DAS28, mean (SD)	4.5	(1.1)	4.8	(1.0)	3.8	(1.0)	0.15
Radiographics							
Larsen score, median, (IQR)	2	(0,5)	3	(1,4)	0	(0,6)	0.67
Erosive disease, n (%)	26	(52)	4	(44)	5	(46)	0.87

The median (range) duration of DMARD treatment before discontinuation was 60 (20–117) months in group B and 53 (11–76) months in group C. Two thirds of the patients in group B and 82% in group C met the ACR remission criteria before the DMARD discontinuation. The mean (range) DMARD-free interval before

restarting the previously used or starting a new DMARD in group B was 50 (3–137) months. The mean (range) number of different DMARDs during the study was 6.1 (1–11) in group A, 3.4 (1–7) in group B and 1.9 (1–4) in group C. The total DMARD treatment time as a percentage of total follow-up time was 84% in group A, 66% in group B and 31% in group C.

Disease activity assessed with the mean (SD) DAS28 at the 15-year follow-up visit was higher in groups A [3.37 (1.01)] and B [3.68 (1.23)] than in group C [2.08 (1.01)], as were the median numbers of tender and swollen joints (Figure 2). In DAS28 remission, there were 15 patients (30%) in group A, 2 patients (18%) in group B and 8 patients (73%) in group C. The ACR remissions at the 15-year visit were infrequent in patients of group A [6% (95% CI: 2–16)]. None [0% (95% CI: 0–34)] of the patients in group B met the ACR remission criteria. In group C, 64% (95% CI: 31–89) of patients maintained remission.
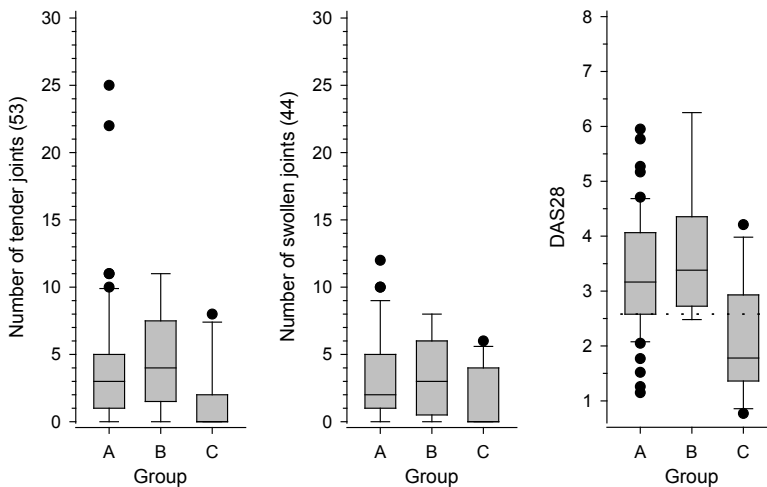
Figure 2. Median, interquartile range (IQR) and 95% confidence intervals (95% CI) of number of tender joints, number of swollen joints and DAS28 at 15 years in patients with continuous DMARDs (group A), those with discontinued and restarted DMARDs (group B) and those with permanently discontinued DMARDs (group C). Median, IQR and 95% CI are illustrated with a cross-line, box and vertical line and outliers with dots above and below range.

The average functional capacity of the patients at 15 years remained favourable with a mean HAQ of 0.52 for the entire study group. All but two of the 11 most disabled (HAQ score ≥ 1.0) patients were found among those whose active disease required continuous DMARD therapy (group A); mean (SD) HAQ of this group was 0.60 (0.49). The final mean (SD) HAQ score in group B was 0.38 (0.51) and 0.24 (0.39) in group C. The number of patients with different levels of final HAQ scores in each group is presented in Table 20.

Table 20. Distribution of HAQ scores in patients with continuous DMARD (group A), in those with discontinued and restarted DMARD (group B) and in those with permanently discontinued DMARD (group C).

| | HAQ score | | | | |
	0	0.01–0.5	0.51–1.0	1.01–1.5	> 1.5
Group A	9	16	16	7	2
Group B	3	4	0	2	0
Group C	6	3	2	0	0
All patients (%)	18 (26)	23 (33)	18 (26)	9 (13)	2 (3)

Functional capacity in RA is associated both to the disease activity and to the radiographic joint damage (Drossaers-Bakker et al. 1999, Welsing et al. 2001). Welsing et al. (2001) showed that the impact of joint damage increased in the later disease course. Differences between the treatment groups similar to those in the mean HAQ scores were found in the 15-year radiographic progression of small joints measured with mean (SD) LS: 54 (36) in group A, 25 (30) in group B and 12 (18) in group C. This could suggest that differences in final functional capacity also reflect the impact of a different level of radiographic progression at the endpoint in this patient cohort.

Reduction and discontinuation of DMARD treatment in RA is a controversial topic. There has been a lack of randomized, controlled studies on discontinuation of DMARDs in patients with sustained remission. Previous data of small, short-term randomized and controlled studies (Cade et al. 1976, Cats 1976, De Silva and Hazleman 1981, Ahern et al. 1984, Szanto 1986, Kremer et al. 1987) have suggested that long-term maintenance of DMARD treatment is effective in preventing flare-ups of disease in RA. One study of parental gold (Sander et al. 1999) reported that a positive disease activity-controlling effect continued in some patients for 3 years after the treatment was withdrawn. Similar long-lasting remission at best for several years after discontinuation of parental gold was evident in some of this study's patients in groups B and C.

The first randomized, double-blind, placebo-controlled 52-week follow-up study of discontinuation of DMARD therapy was undertaken in the 1990s (ten Wolde et al. 1996). This study included 285 patients on DMARD monotherapy who were in clinical remission according to the ACR criteria (I), had used DMARDs at least 2 years (II) and had stable disease for at least 1 year (III). The patients were randomly assigned to the placebo group (n = 143) or to the group continuing their ongoing DMARD therapy (n = 142). Patients with previous unsuccessful attempts to discontinue DMARDs or those using GCs were excluded from the study. At 52 weeks, the disease had flared up in 38% of the patients in the placebo group and in 22% of the patients with continued therapy. The risk of a flare-up was twice as high

for the patients receiving placebo than for those continuing DMARDs. Other risk factors for flare-up were high maintenance dose of DMARDs, presence of painless swollen joints and positive RF.

Later, 51 patients whose RA had flared up after discontinuation of DMARDs were followed up after reinstitution of the DMARDs (ten Wolde et al. 1997). Three months after resumption of the same DMARD that was used before discontinuation, only 24 of the 51 patients responded to their previous DMARD and half of these achieved the same level of disease activity as before discontinuation. Still, after 12 months the disease activity was moderate or severe in 22% of the patients and mild in 43%. Clinical remission was achieved in 35% of the patients. In our study none of the patients whose DMARDs were discontinued and restarted after a flare-up of disease (group B) achieved the ACR remission at 15 years and the mean DAS28 of these patients was higher than in the patients with continuously treated with DMARDs (group A).

Both results of ten Wolde et al. and of the present study indicate that patients whose DMARD treatment is discontinued due to remission or minimal disease activity should be followed up carefully and frequently enough to detect a flare-up. For those whose RA flares up, DMARD treatment should be restart immediately, as concluded in a recent meta-analysis on withdrawal of DMARDs in patients with RA (O'Mahony et al. 2010). In the present study, the unfavourable 15-year outcome of the patients with flare-ups after DMARD discontinuation is partially associated with long intervals between the control visits in the later course of RA. The resumption of DMARD therapy was delayed, particularly in those patients who were no longer followed up by the rheumatologists.

5.3 RADIOGRAPHIC OUTCOMES

5.3.1 RADIOGRAPHIC PROGRESSION OF THE SMALL JOINTS

The mean radiographic progression of the small joints was assessed with the mean LS of the entire study group over 15 years, including 70 patients followed up over 15 years and remaining 16 patients up to their last radiographs (Figure 3). The mean LS was 4 (95% CI 2–5) at baseline, 11 (95% CI 8–14) at year 1, 16 (95% CI 12–20) at year 2, 19 (95% CI 14–24) at year 3, 25 (95% CI 20–31) at year 5, 30 (95% CI 23–36)) at year 7, 37 (95% CI 28–46) at year 10 and 44 (95% CI 34–52) after 15 years. The average annual progression calculated over 15 years was 2.5 LU. The variation in both rate and pattern of progression between individual patients was considerable, varying from eight patients (11%) without progression at 15 years to seven patients (10%) with widespread small joint damage with LS ≥ 100. Of the one third of the patients with severe radiographic progression defined as LS ≥ 80 [a mean LS of 88 (95% CI: 80–96)] at 15 years, 70% already had radiographic changes (LS ≥ 2) at baseline and 82% showed progression (LS ≥ 8 LU) during the first 2 years.
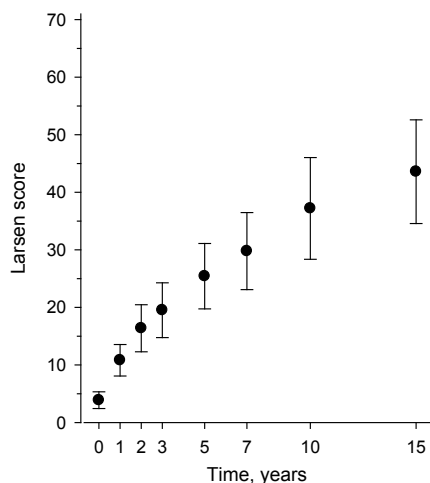
Figure 3. Radiographic progression of small joints in all 86 patients presented as mean Larsen score with 95% confidence intervals.

Comparison of radiographic progression in RA between studies is challenging, due to different methods and their various modifications used to evaluate and score radiographic joint damage. The SHS system has been widely used in randomized controlled trials, and currently many observational follow-up studies have also presented radiographic progression with SHS. In reporting long-term radiographic outcome, the final SHS or LS at endpoint or the change in the score from baseline to endpoint have been presented.

In the present study, LS with a scale from 0 to 200 was initially chosen for the method to evaluate radiographic progression in the small joints. Previous Finnish cohort studies of RA have reported radiographic outcome with LS scales of 0–200 or 0–100. The first such cohort study of patients with early RA, conducted in the Rheumatism Foundation Hospital, Heinola, where the patients were collected in 1973–1975, reported a mean LS (scale 0–200) of 4 at baseline, 56 after 8 years, 77 after 15 years and 86 after 20 years (Kaarela and Kautiainen 1997). The mean 15-year LS of the Heinola cohort was higher (77) than the mean LS (44) of the present cohort, even though the baseline LSs were equal in both these cohorts. Similar differences were evident between the Heinola cohort and a 1983–1989 collected cohort of patients with early RA from Jyväskylä Central Hospital at 8 years. The mean LS (scale 0-100) was 26 in the Heinola cohort and 12 in the Jyväskylä cohort (Sokka et al. 1999c).

The differences in the 15-year radiographic outcome between the Heinola cohort and the present study may be explained by several factors. First, all patients of the Heinola cohort were RF-positive, compared with 65% of patients being RF-positive in the present cohort. Secondly, the data suggested that radiographic progression in patients with early RA became milder during the 1980s and 1990s (Sokka et al.

2004, Finckh et al. 2006a). The third factor may be impact of the early initiation and intensity of DMARD treatment on the long-term radiographic outcome. The recently published 11-year results of the FIN-RACo study suggested that early-initiated and intensive DMARD therapy is a key factor in reducing long-term radiographic progression. The mean change in LS (scale 0-200) from baseline to 11 years was 17 in the initial combination treatment group and 27 in the initial monotherapy group (Rantalaiho et al. 2010).

Comparison of radiographic progression over the follow-up periods was performed between the Heinola cohort, with 66/103 patients collected in 1973-1975 and followed up over 20 years (Kaarela and Kautiainen 1997), the present (Helsinki cohort) with 86 patients collected in 1986-1989 and followed up over 15 years (in case of 10 deceased patients and in 6 dropouts the last available radiographs were included in the analysis) and the FIN-RACo study with 138/199 patients collected in 1993–1995 and followed up over 11 years (Korpela et al. 2004, Rantalaiho et al. 2010). The mean annual change in LS in percentage of the maximum score (200) between the time points available (in the Heinola cohort at onset, at 1, 3, 8, 15 and 20 years, in the Helsinki cohort at onset, at 1, 2, 3, 5, 7, 10 and 15 years and in the FIN-RACo study at onset, 1, 2, 5 and 11 years) was calculated, and the pattern of progression was illustrated for each of these studies (Figure 4).
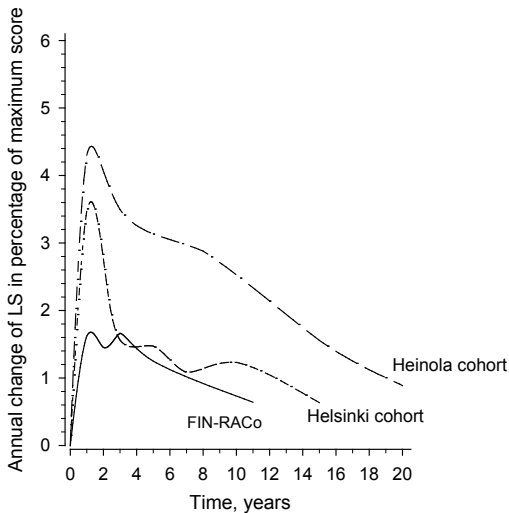
Figure 4. Mean pattern of radiographic progression in three Finnish cohorts of patients with early RA presented with mean annual progression of Larsen score as percentage of maximum score.

The mean radiographic progression was extremely rapid and sharp during the first 2–3 years of RA, both in the present cohort and in the Heinola cohort. In the FIN-RACo study, the average annual progression of all 138 patients showed a slight peak

of progression during the first 2 years of RA and decreased evidently since the fifth year. In the present cohort, the average annual radiographic progression decreased sharply from year 2 to year 3; since then the decrease was more gradual. In the Heinola cohort, the average annual progression after 3 years remained higher than in the other two study populations. In the FIN-RACo study, radiographic progression during the first 2 years was milder in patients who were treated with the initial combination therapy than in those treated with initial monotherapy (Rantalaiho et al. 2010). In this study, the mean radiographic progression over the 11-year follow-up was lower in patients who were in clinical remission at year 1 than in those being not in remission. The early radiographic progression in the present and Heinola cohorts explains the long-term radiographic outcome in these cohorts, both by the actual amount of early radiographic progression and by the predisposition to continued progression in the patients, with remarkable early radiographic progression, as presented later (Figure 7). The mean LS in the present cohort was 30 at 7 years, 37 at 10 years and 44 at 15 years and in the Heinola cohort 56 at 8 years, 77 at 15 years and 86 at 20 years, compared with 26 in the FIN-RACo study at 11 years. This finding highlights the importance of halting radiographic progression during the very first years of RA for favourable long-term radiographic outcome.

The difference in radiographic progression rates after the first 2–3 years between the Heinola cohort and the present cohort resulted most probably from the high number of RF-positive patients in the Heinola cohort and from the differing treatments and strategies in these studies. Most of the patients in the Heinola cohort were treated during the first years of RA, either with intramuscular gold or HCQ as monotherapy or with one of these DMARDs in combination with prednisolone (Jäntti et al. 2002). Some patients (10%) were followed up without any DMARD treatment. As described earlier, the treatment strategy of the present study was early-initiated, more intensive and individually tailored than therapies usually were in the 1980s. The favourable impact of early-initiated DMARD therapy on later radiographic progression was reported in a meta-analysis of shorter, 1–5-year follow-up studies (Finckh et al. 2006b).

We analysed radiographic progression separately in 57 RF-positive and in 29 RF-negative patients over 15 years. The RF-positive patients already had somewhat higher mean (SD) LS of 5 (7) at baseline than the RF-negative [3 (5)]. The change in mean LS from the baseline to each time-point in the RF-positive and RF-negative patients is presented in Figure 5. The mean (SD) change in LS from baseline to 15 years was 47 (37) in the RF-positive patients and 27 (14) in the RF-negative patients, leading to mean final LS (SD) of 52 (38) and 30 (16), respectively.

The results are consistent with a study examining 10-year radiographic progression in 34 RF-positive and 16 RF-negative patients with classical or definite RA. In this study, the mean initial LS (scale 0-200) of RF-positive individuals was 24 and of RF-negative individuals 19, and the mean final LS was 39 and 27, respectively (Scott et al. 1986). Several studies have confirmed the role of RF as

a predictor of radiographic progression in early RA (Combe et al. 2001, Bukhari et al. 2002, Dixey et al. 2004). Recently, a cohort study of 61 RF-positive and 61 RF-negative patients suggested that radiographic progression of joint damage in the RF-positive patients is associated both with higher levels of disease activity in these patients and with independent effects of RF on bone damage, in particular on the erosion score of SHS (Aletaha et al. 2013). During the past 10 years, ACPAs have been shown to be predictive for radiographic joint damage (Lindqvist et al. 2005, Syversen et al. 2008, Mustila et al. 2011).
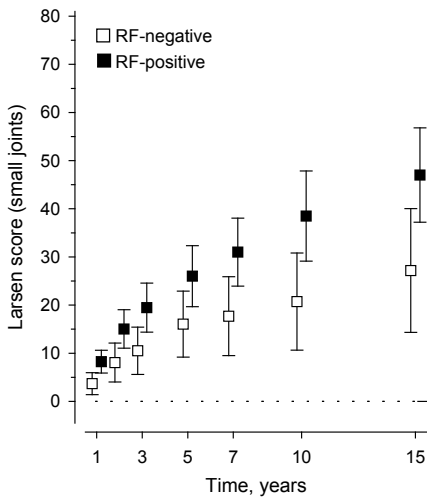
Figure 5. Radiographic progression of the small joints presented as a mean change in LS with 95% confidence intervals over 15 years in RF-positive and RF-negative patients.

5.3.2   IMPACT OF EARLY RADIOGRAPHIC REMISSION ON LATER RADIO-GRAPHIC OUTCOME

In addition to RF-positivity, elevated ACPA and high disease activity, erosive changes in radiographs at baseline are predictive of later radiographic progression (Combe et al. 2001, Bukhari et al. 2002, Guillemin et al. 2003, Dixey et al. 2004, Courvoisier et al. 2008). We evaluated the impact of early radiographic remission [ERR (halting of radiographic progression during the two first years of RA)] on 15-year radiographic outcome. ERR was defined as an increase in LS ≤ 1 LU between two sequential sets of radiographs of small joints. The 69 patients with full sets of both early (baseline, year 1 and year 2) and 15-year radiographs of the hands and feet were included in the analysis. The patients were grouped as follows: 18 patients (26%) with no radiographic progression during the first 2 years of RA (sustained ERR, group A), 20 patients (29%) who were radiographically stable either at year 1 or

year 2 (temporary ERR, group B) and 31 patients (45%) who showed progression ≥ 2 LU during both first years of RA (no radiographic remission, group C). These groups showed no significant differences in demographics, clinical disease activity and radiographic findings at baseline (Table 21).

Table 21. Baseline demographics, clinical disease activity and radiographic status of 69 patients grouped according to early radiographic remission.

| Variable | Early radiographic remission group | | | |
	Sustained n = 18	Temporary n = 20	No remission n = 31	P-value
Number of females, n (%)	17 (95)	16 (80)	25 (81)	0.41
Age (years), mean (SD)	40 (2)	45 (12)	43 (11)	0.48
Duration of disease (months), mean (SD)	8 (4)	9 (3)	7 (4)	0.23
RF present, n (%)	9 (50)	14 (70)	22 (71)	0.32
DAS28, mean (SD)	4.0 (1.0)	4.5 (1.2)	4.6 (1.2)	0.16
Larsen score, mean (SD)	2 (3)	3 (4)	5 (8)	0.22

During the 15-year follow-up, the groups differed in intensiveness of the DMARD therapy. Patients with continuous early radiographic progression (group C) were treated on average more intensively than those with temporary ERR (group B) and with sustained ERR (group A). The mean number of various DMARDs or DMARD combinations and the number of patients who were treated with MTX, oral GCs or TNF-α-inhibitors is shown in Table 22 and the total time on DMARD treatment during the 15-year period in each group is shown in Figure 6.

Table 22. Number of DMADSs or DMARD combinations, use of methotrexate and TNF-α-inhibitors in various early radiographic remission groups during 15 years.

	Early radiographic remission group		
Treatment	Sustained n = 18	Temporary n = 20	No remission n = 31
Number of DMARDs or DMARD combinations, mean (range)	4.7 (1–10)	4.6 (1–10)	7.0 (1–11)
Number of patients, n (%)			
treated with methotrexate	11 (61)	10 (50)	24 (77)
treated with TNF-α-inhibitors	0 (0)	1 (5)	4 (13)
treated with oral glucocorticoids			
during 15-year visit	3 (17)	6 (30)	13 (42)
at some phase of the study	3 (17)	5 (25)	12 (39)
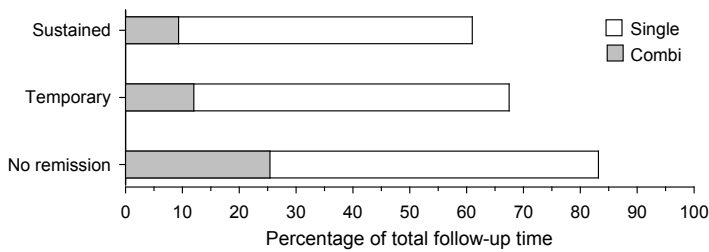
Figure 6. Time on DMARD treatment in percentages of total follow-up time in the various early radiographic remission groups. White columns illustrate the time on DMARD monotherapy (Single) and grey columns the time on combination therapy (Combi).

Even though the patients with early radiographic progression (group C) were treated more intensively than those of the other two groups, the 15-year radiographic outcome in this group was poorer than in the patients with either sustained (group A) or temporary ERR (group B). The mean LS was 67 (95% CI: 45–85) in group C, 33 (95% CI: 13–54) in group B and 14 (95% CI: 0–22) in group A, (p < 0.001) (Figure 7). The average annual increase in LS was 4.1 in group C, 2.1 in group B and 0.7 in group A. The low average increase of LS in group A was contributed by seven nonerosive patients in this group. When these seven patients were excluded from analysis, the average LS increase in group A was still low (1.4) and the linearity of the change in LS after adjusting for age, sex, RF and baseline LS, remained statistically significant (p < 0.001).
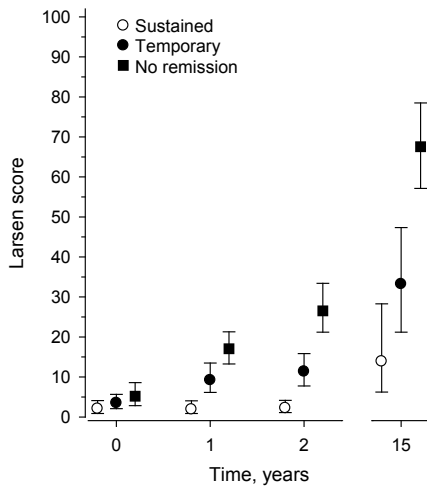
Figure 7. The 15-year radiographic outcome; mean Larsen score of the small joints with 95% confidence intervals in relation the early radiographic remission (ERR) during the first two years of RA. Patients with sustained ERR (○), temporary ERR (●) and no ERR (■).

The groups already began to separate during the early phase of RA (Figure 7), and the difference was even more prominent after 15 years. The differences among individuals' radiographic progression in long-term RA were analysed in previous studies (Graudal et al. 1998, Plant et al. 1998). Summaries of the results of these two studies following patterns of progression have been described: linear progression, rapid onset with a later plateau, slow onset with acceleration and no progression at all (Scott 2004). In clinical practice, it would be worthwhile if the patients whose radiographic joint damage will progress could be identified as soon as possible.

In the present study, the ERR group was associated with the mean change in LS from baseline to 15 years in a regression model (Table 23). Of the baseline variables, only RF positivity (but not the baseline LS) was associated with the change in LS in the present cohort. In addition to well-known risk factors of radiographic progression (e.g. positive RF or ACPA and high clinical disease activity), detection of ERR or early radiographic progression may be helpful in allocating more intensive DMARD treatments or biological agents to those patients at greatest risk for radiographic progression.

Table 23. Relationship of the early radiographic remission and main baseline demographics and clinical characteristics to the change in Larsen score from baseline to 15 years in a regression model.

Variables	Coefficient (95% CI)	P-value
Early radiographic remission		$p < 0.001$*
Sustained	Reference	
Temporary	16 (-2 to 34)	
No remission	50 (31 to 68)	
Female sex	12 (-8 to 32)	0.25
Age at RA diagnosis	-0.1 (-0.8 to 0.6)	0.75
Rheumatoid factor positivity	18 (2 to 34)	0.032
DAS28 at baseline	3.6 (-4.6 to 11.8)	0.39
Larsen score at baseline	-1 (-3 to 1)	0.22

* Test for linearity

In the 2000s, it became clear that MRI detects radiographic changes earlier and is more sensitive than plain radiographs. Early finding of bone oedema and erosions is predictive for later radiographic progression (McQueen et al. 2003, Hetland et al. 2010). MRI is, however, an expensive method and is not available without restrictions in routine rheumatologic practice. It can be used only for a restricted number of joints, usually the wrists or feet, when screening for potential erosions or bone oedema. It has been suggested that radiographic changes may progress in some patients even when they are in clinical remission (Cohen et al. 2007, Aletaha et al. 2009). Based on these arguments, it could be postulated that plain radiographs should not be ignored in assessing DMARD therapy response in early RA, and halting of radiographic progression (radiographic remission) should be one of the goals of treatment in RA.

5.3.3 LARGE JOINT DAMAGE

Large joint changes were evaluated systematically at the 15-year visit. In the final 15-year analysis, large joints with known changes at baseline were excluded: the hips of one patient with Legg-Calve´-Perthes disease and the knees of another patient with primary osteoarthritis. A total of 31/69 patients (45%) had damage in at least one large joint. The joints most often affected were the shoulders in 22 patients (32%), ankles in 16 patients (23%) and elbows in 13 patients (19%). Of the eight patients with no radiographic changes in the small joints over 15 years, only one at baseline a 19-year-old female patient had moderate joint damage in the knees at 15 years. In a previous study reporting radiographic large joint damage in RA, none

of the patients whose hands and feet were nonerosive, showed large joint damage after 12 years (Drossaers-Bakker et al. 2000).

The percentage of patients with radiographic large joint damage in the various ERR groups was 17% of patients with sustained ERR (group A), 35% of patients with temporary ERR (group B) and 68% of patients with no ERR (group C). The mean number (range) of damaged large joints was 0.4 (0–3) in group A, 0.7 (0–3) in group B and 2.0 (0–7) in group C. The mean (range) LS of large joints, which unifies both extent and severity of large joint damage, was significantly higher [6.3 (0–27)] in group C than in group B [1.9 (0–13)] and group A [0.8 (0–6)], as illustrated in Figure 8.

These findings are in line with previous studies reporting that large joint damage is associated with to small joint damage measured with the SHS method (Kuper et al. 1997, Drossaers-Bakker et al. 2000). The association between the total damage progression of the small joints and damage in the large joints was also evident in a recent study with 290 patients from a large treatment strategy study with an 8-year follow-up (Dirven et al. 2012). These findings suggest that later large joint damage should be suspected, particularly in those patients who show significant radiographic small joint damage or, as in the present study, early radiographic progression of the small joints.
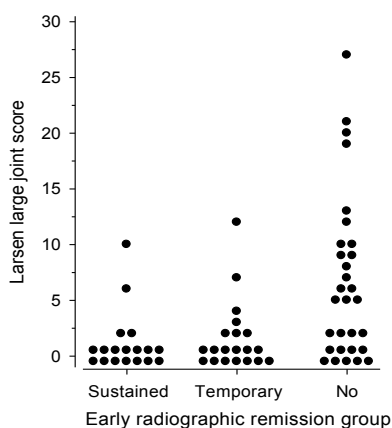
Figure 8. Larsen score of large joints in the various early radiographic remission groups.

The radiographic damage of the large joints was evaluated separately in initially RF-positive and RF-negative patients. Of the 24 RF-negative patients with full sets of radiographs, 11 (46%) showed large joint changes compared with 22 (49%) of the 45 RF-positive patients. The RF-positive patients more often had several damaged large joints than the RF-negative patients: ≥ 3 damaged large joints in 13 (28%) of the RF-positive patients and 3 (13%) of RF-negative patients. Only two (8%) of

the RF-negative patients had an LS of the large joints ≥ 10 compared with the 9 (20%) of the RF-positive patients, suggesting that the large joint damage tended to be more widespread and severe in the RF-positive patients (Figure 9).
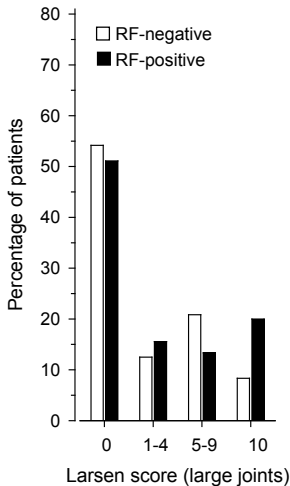

Figure 9. Large joint damage in RF-positive and RF-negative patients shown with percentages of patients having increasing amount and severity of radiographic damage evaluated with the Larsen score of the large joints.

In addition to radiographic outcome, large joint damage can be evaluated by the number of joint replacements, as discussed earlier. In a 20-year follow-up 16/83 Finnish patients (19%) with RA in the Heinola cohort needed LJR (Jäntti et al. 2002). The total number of operated joints in this cohort of 83 patients collected in 1973–1975 was 29 (15 hips, 10 knees, 2 shoulders and 2 elbows). After 25 years, the cumulative number of the LJRs in this cohort has increased to 41 performed for 23 patients, with increasing numbers of arthroplasties of the elbows after 20 years (Palm et al. 2002).

In the present study, 7 LJRs were performed for 6 (8%) of the 70 patients followed up over 15 years: for three patients unilateral hip arthroplasty and for single patients bilateral knee arthroplasty, unilateral knee arthroplasty and unilateral shoulder arthroplasty. The FIN-RACo study's 11-year follow-up results (Rantalaiho et al. 2010) reported a total of 6 knee and 6 hip joint replacements in 4/68 of patients (6%) in the initial combination treatment group and in 5/70 of patients (8%) in the initial single-DMARD treatment group. The tendency for joint replacements to decrease in patients with RA is supported by the data from TJR in Central Finland between 1986 and 2003 (Sokka et al. 2007). The age-adjusted incidence rate ratios for TJR did not increase in patients with RA, while the incidence rate ratio for TJR

of the knee increased 9.8-fold and for TJR of the hip 2-fold in other patients during the same period. Recent nationwide register data showed that the annual incidence of primary joint replacements of the hips, knees, shoulders and elbows for RA has declined from 18.5 per 10^5 inhabitants in 1995 to 11 per 10^5 in 2010 (Jämsen et al. 2013). The authors suggested that increased use of synthetic DMARDs most likely explained this trend. The above-mentioned improvement occurred before new biological agents were available. During the 2000s, introduction of TNF-α-inhibitors and later other biological agents (Singh et al. 2009) increased possibilities to retard radiographic progression in several patients with RA.

5.4   COMORBIDITY

5.4.1   OCCURRENCE OF COMORBIDITIES

Adequate data on comorbidities was available at baseline and at endpoint (at the 15-year examination or at time of death) in 80/87 patients. We focused on patients with early RA and ages of ≤ 65 years. Due to the low mean age (44 years) at baseline, only 16 patients (20%) had comorbidities at study entry. Hypertension was the most common comorbidity at baseline. After 15 years or at time of death 48 patients (60%) had one or several comorbidities; 27 (34%) of these had one, 15 (19%) two and 6 (8%) three or more comorbid conditions. Of the RF-positive patients, 62% had at least one comorbid condition at endpoint compared with 54% of the RF-negative patients; the mean number of comorbidities was 1.8 and 1.4, respectively. The most common comorbidities and the number of patients having comorbid conditions are shown in Table 24.

Table 24. Comorbidities of 80 patients with RA at time of diagnosis and after the 15-year follow-up or at time of death.

Comorbid condition	Patients with baseline comorbidity n (%)	Patients with comorbidity at endpoint n (%)
Hypertension	7 (9)	24 (30)
Ischaemic heart disease	1 (1)	7 (9)
Cerebrovascular accident	1 (1)	4 (5)
Asthma	1 (1)	4 (5)
COPD	1 (1)	2 (2)
Pulmonary fibrosis	0 (0)	0 (0)
Past tuberculosis	1 (1)	1 (1)
Diabetes	1 (1)	4 (5)
Osteoporosis	0 (0)	9 (11)
Hypothyroidism	0 (0)	4 (5)
Peptic ulcer disease	1 (1)	6 (8)
Liver disease	0 (0)	1 (1)
Renal disease	1 (1)	1 (1)
Depression	0 (0)	5 (6)
Epilepsy	0 (0)	0 (0)
Parkinsonism	0 (0)	1 (1)
Dementia	0 (0)	1 (1)
Malignancy	1 (1)	9 (11)

COPD = Chronic obstructive pulmonary disease

At the endpoint, hypertension was the most common comorbid condition in 24 (30%) of the patients. The CVDs were diagnosed in a total of 13 patients (16%): three patients (4%) had experienced myocardial infarction and four patients (5%) had ischaemic heart disease defined with the clinical exercise test. Cerebrovascular disease was diagnosed in four patients (5%). One patient had peripheral arteriosclerosis, and one patient died due to the rupture of an aortic aneurysm.

The occurrence of ischaemic heart disease and cerebrovascular events in 11 (14%) of the 80 patients was in line with two cross-sectional studies with equal mean ages and mean durations of RA: 15% in 380 Austrian patients with a mean age of 61 years and a mean of 12 years of disease duration (Radner et al. 2010) and 19% in 624 Australian patients with a mean age of 60 years and a mean of 16 years of disease duration (Briggs et al. 2009). In a study done in Netherlands (the COBRA trial) in which an initially combination of MTX and SASP with high-dose prednisolone was compared with SASP monotherapy, 17% of patients in the combination group and 19% of patients in the monotherapy group had cardiovascular events during an 11-year follow-up (van Tuyl et al. 2010). The mean age of these patients at the

time of data collection was 60 years. The 11-year results of the FIN-RACo study reported CVDs in 15% of patients treated initially with a DMARD combination and in 13% of those treated with DMARD monotherapy (Rantalaiho 2012).

In comparing the results of these studies, the differences in the study populations, study designs and definitions of comorbidities should be taken into consideration. Two of the studies were cross-sectional (Briggs et al. 2009, Radner et al. 2010), two were randomized studies of DMARD treatment strategies (van Tuyl et al. 2010, Rantalaiho 2012) and the present study was a cohort investigation following up patients with early RA and treated with early-initiated DMARD therapy. Collection of comorbidity data could be based on patients' self-reported medical history, as in the Australian study or on patients' medical records, as in the Austrian study. In the Dutch study and in the present study, comorbidity data were collected from the patients' medical records or death certificates, and additional examinations were performed to detect osteoporosis. The antirheumatic treatments and the treatment strategies of the studies varied substantially; the patients in the present cohort study were treated mainly with synthetic DMARDs or with DMARD combinations. All of the patients in the Australian study were treated with biological drugs and thus probably had more severe disease than those of the present study. The Dutch COBRA trial and the FIN-RACo study were initially randomized controlled trials comparing two treatment strategies in patients with early RA. The Austrian study did not report data on the patients' treatments.

Baseline data on CVD risk factors in the present study were not available, with the exception of known hypertension in 9% of and diabetes in 1% of the patients. At the 15-year examination, the occurrence of these two comorbid conditions increased to 30% and 5%, respectively. At the 15-year examination elevated blood glucose values were very infrequent, and actual diabetes was not diagnosed in other patients, except for four with known diabetes. The high number of patients with evident dyslipidaemia, 52% of patients having total cholesterol (TC) > 5.0 mmol/l or low-density lipoprotein (LDL) cholesterol > 3.0 mmol/l was an alarming finding. Recent studies (Peters et al. 2009, Lindhardsen et al. 2011) have indicated that RA is as equal a risk factor for CVD as diabetes, emphasizing that greater attention should be focused on both reducing disease activity in RA and on examining and reducing traditional CVD risk factors (Peters et al. 2010).

An intervention regarding smoking is essential because smoking is a risk factor both for CVD and for RA itself. In the present study, the smoking habits of 70 patients participating in the 15-year visit were evaluated retrospectively. Of these 35 (50%) never smoked, 21 (30%) stopped smoking after a mean of 19 years and 14 (20%) smoked currently (11 of these 14 patients had smoked over 30 years). Of the ex-smokers 13/21 (62%) and of the current smokers 9/14 (64%) had comorbidities after 15 years, compared with 17/35 (49%) of those patients who never smoked. The mean number of comorbidities was higher (1.9) among currently smoking patients than among ex-smokers (1.6) and nonsmokers (1.5). Of the 70 patients

examined at the 15-year visit, either coronary heart disease or a cerebrovascular event was diagnosed in 8 patients during the follow-up; 6 (75%) of these patients were either ex-smokers or current smokers. In a Swedish early RA cohort (recruited between 1985 and 1989) of 78 patients with some comorbidity condition at outset of the study 46% were nonsmokers, compared with 49% of 105 patients without comorbidities at baseline (Kapetanovic et al. 2010). In this cohort, 16% of all 183 patients had CVD at baseline, and an additional 30% developed a new CVD during a 20-year follow-up. The association of CVD and smoking could not be evaluated in this cohort, due to missing data of smoking status in 10% of the patients.

Malignancies in 9 patients (11%) and osteoporosis in 9 patients (11%) the next most commonly found comorbidities. Breast cancer was diagnosed in four women. The remaining malignancies were uterine cancer, lung cancer, prostate cancer, liver cancer and metastatic epidermoid cancer. The number of malignancies in our study (11%) was in line with the Australian patients (10%) (Briggs et al. 2009) and with the Dutch patients of the COBRA trial (8% in patients of the combination treatment group and 14% in patients of the monotherapy group) (van Tuyl et al. 2010), but higher than in the Austrian study (4%) (Radner et al. 2010). The Swedish study with a 20-year follow-up reported malignancy being present in 6% of patients before the RA was diagnosed. New malignancies were found in 18% of patients during the follow-up (Kapetanovic et al. 2010). The haematological malignancies (five lymphomas and three leukaemias) in the Swedish cohort were more common than in the Austrian study with two cases of lymphoma. None of the patients in the present study had lymphoma, probably due to the small study population and too a short follow-up period in the present study, since lymphomas are rare comorbid conditions and develop after several years of RA with high disease activity (Baecklund et al. 2006, Kaiser 2008). In the FIN-RACo study, one case each of lymphoma, of leukaemia and of multiple myeloma were diagnosed in 158 patients during 11 years (Rantalaiho 2012).

Several studies did not report osteoporosis as a comorbidity condition of RA, but regarded it as secondary to RA. However, osteoporosis could cause remarkable illness in patients with RA, resulting in fractures of the vertebrae and or peripheral bones (Vis et al. 2011). In examining the bone mineral density with DEXA of the hips and the lumbar spine, osteoporosis was verified in 9 patients (11%) in the present study. Osteoporosis verified similarly with DEXA was evident in 11% of the Dutch patients treated initially with the combination treatment and in 14% of those treated with DMARD monotherapy (van Tuyl et al. 2010). In the Australian study (Briggs et al. 2009), occurrence of osteoporosis (31%) was reported by the patient's history, which may have led to overestimation of the prevalence. However, since all patients in the Australian study were treated with biological agents, these patients evidently had more severe disease than those in the present cohort and thus had greater probability of developing osteoporosis.

Of other comorbidities 6 patients (8%) had gastroduodenal ulceration verified with gastroscopy, and one patient experienced a liver transplant operation for a nonautoimmune hepatopathy. Hypothyroidism in 5 (6%) of the patients, type 2 diabetes and asthma both in 4 (5%) of the patients, were the next most common somatic comorbid conditions. Of the psychiatric diseases, 5 (6%) of the patients experienced depression during the follow-up, and of the neurological diseases parkisonism and dementia were present in a single patient. The results of the other studies representing these comorbidities in established RA are presented in Table 25.

Table 25. Occurrence of comorbidities other than cardiovascular disease and malignancy in the present study, two other follow-up studies and two cross-sectional studies.

	Present study 2013 n = 80	van Tuyl et al. 2010 n = 152	Radner et al. 2010 n = 380	Briggs et al. 2009 n = 624	Kapetanovic et al. 2010 n = 171
Type of study[1]	F	F	CS	CS	F
Mean age (years)					
at baseline	44	50/49*	-	-	51
at endpoint	60	61/60*	61	57	-
Mean duration of					
RA at endpoint (years)	15	11	12	16	20
Comorbid condition, percentage of all patients					
Hypertension	30	24/11*	-	41	-
Dyslipidaemia	52	8/17*	-	26	-
Diabetes	5	9/1*	8	10	1/7**
Osteoporosis	11	11/14*	-	31	-
Asthma/COPD	7	-	6	9	4/7**
Hypothyroidism	5	-	-	6	-
Peptic ulcer	8	7/4*	3	-	3/10**
Liver disease	1	-	3	3	-
Kidney disease	1	-	0	2	-
Depression	6	-	-	19	4/7**

[1]Type of study: F = follow-up, CS = cross-sectional

* results in patients with combination treatment/monotherapy treatment

** occurrence of comorbidity at baseline/additional comorbidity during the study

The number of patients having dyslipidaemia was higher in the present cohort than in the other two studies reporting dyslipidaemia, probably due to differences in the definition of dyslipidaemia. In the present study, the dyslipidaemia was confirmed by measuring the lipid values. In the other two studies, the data on dyslipidaemia were either collected from medical records (van Tuyl et al. 2010) or self-reporting of the patients (Briggs et al. 2009). However, the high occurrence of dyslipidaemia in the present study emphasized the importance of examining and treating all known risk factors for CVDs in patients with RA.

In the present study, the possible amyloidosis was examined by an abdominal subcutaneous fat aspiration (ASFA), which was positive in 12 (17%) of the 70 patients examined at 15 years. None of these patients had renal or other manifestations of clinical amyloidosis. Other studies have reported prevalences of 16–29% for subclinical amyloidosis detected with ASFA (Gomez-Casanovas et al. 2001, Wakhlu et al. 2003, Wiland et al. 2004, Younes et al. 2009). In further evaluations of three of these studies, 26–34% of patients with amyloidosis deposits in ASFA had clinical amyloidosis, most commonly renal involvement (Gomez-Casanovas et al. 2001, Wakhlu et al. 2003, Wiland et al. 2004). A Finnish register study reported a marked decline in the incidence of renal replacement therapy for RA-related amyloidosis. The number of patients admitted to renal replacement therapy was halved from the late 1990s to the 2000s (Immonen et al. 2011).

5.4.2 COMORBIDITY, DISEASE ACTIVITY AND FUNCTIONAL CAPACITY

The total comorbidity in the present study was assessed with the Charlson comorbidity index with ageing taken into account (CCI_a). The weights of various comorbid conditions and the number of patients with these conditions in this patient cohort at baseline and at endpoint are presented in Table 26.

Table 26. Comorbid conditions of Charlson comorbidity index (CCI) with their weights and the number of patients with these comorbidities at baseline (at time of diagnosis) and at endpoint (after 15 years or at time of death).

Comorbid condition	Weight	Patients at baseline	Patients at endpoint
Coronary artery disease	1	1	7
Congestive heart disease	1	0	3
Peripheral vascular disease	1	1	2
Cerebrovascular disease	1	0	4
Dementia	1	0	1
Chronic pulmonary disease*	1	2	6
Rheumatoid disease	1	0	0
Peptic ulcer	1	1	6
Mild liver disease	1	0	0
Diabetes mellitus, no complications	1	0	4
Diabetes mellitus with complications	2	0	0
Hemiplegia or paraplegia	2	0	0
Renal disease	2	1	1
Solid tumour, nonmetastatic	2	1	8
Leukaemia	2	0	0
Lymphoma	2	0	0
Moderate or severe liver disease	3	0	1
Metastatic solid tumour	6	0	1
AIDS	6	0	0

* Chronic pulmonary disease includes asthma and chronic obstructive pulmonary disease (COPD)

The comorbidity load of each patient at baseline was assessed by calculating age-weighted CCI_a, adding to the index one extra point for each decade of age above 50 years. The patients were grouped as follows: CCI_a 0, CCI_a 1-2 and CCI_a ≥3 to study the relationship of baseline comorbidity to disease activity during the first year of RA (DAS28 AUC_{0-12}), to long-term disease activity (DAS28 at endpoint) and to functional capacity (HAQ at endpoint). For deceased patients, the DAS28 and HAQ of their last visits were used as endpoint values. One patient who died during the first year of the study was excluded from the final analysis, due to insufficient data. The baseline data of the various CCI_a groups are presented in Table 27.

Table 27. Baseline characteristics and clinical variables in various baseline comorbidity groups.

	CCI_a 0 n = 46	CCI_a 1-2 n = 23	CCI_a ≥3 n = 10	P-value
Baseline demographics				
Female, n (%)	40 (87)	16 (70)	7 (70)	0.12
Age (years), mean (SD)	28 (5)	45 (10)	55 (7)	< 0.001
Only basic education, n (%)	9 (20)	11 (48)	7 (70)	< 0.001
Duration of disease, (months), mean (SD)	8 (4)	8 (3)	7 (3)	0.97
Rheumatoid factor present, n (%)	23 (50)	21 (91)	10 (100)	< 0.001
Clinical variables				
DAS28, mean (SD)	4.3 (1.2)	4.7 (0.9)	5.0 (1.3)	0.087
Larsen score, mean (SD)	3.3 (7.3)	4.9 (7.3)	7.5 (7.1)	0.055

The antirheumatic treatments of the groups did not differ, expect for the use of MTX during the follow-up period. The mean number of different DMARDs or DMARD combinations was 6.3 in group CCI_a 0, 5.3 in group CCI_a 1-2 and 6.3 in group CCI_a ≥3 and the percentage of patients treated with biological agents was 6%, 4% and 10%, respectively. The DMARD treatment time as a percentage of the patient's total follow-up time was calculated for each patient. The median (IQR) portion of treatment time on DMARD therapy during the follow-up was 78% (54–97%) in CCI_a 0, 88% (55–100%) in CCI_a 1-2 and 76% (66–91%) in CCI_a ≥3 and on methotrexate 23% (0– 48%), 11% (0–53%) and 2% (0–45%), respectively.

The disease activity assessed with the mean DAS28 during the first year of RA (DAS28 AUC_{1-12}) was higher in patients with comorbidity (groups CCI_a 1-2 and CCI_a ≥3) than in those with no baseline comorbidity (group CCI_a 0), as presented in Figure 7. Similar differences between the groups in disease activity were evident at 15 years or at time of death. The final functional capacity (HAQ at endpoint) showed a similar trend, even though the variation in HAQ at endpoint within the groups CCI_a 1-2 and CCI_a ≥3 was more extensive than the group CCI_a 0 and more substantial than the variation in DAS28 endpoint in these groups (Figure 10). The HAQ values increased along with growing age in the general population (Sokka et al. 2003b). The low mean age of the patients explains at least partly the low HAQ level of the present cohort.
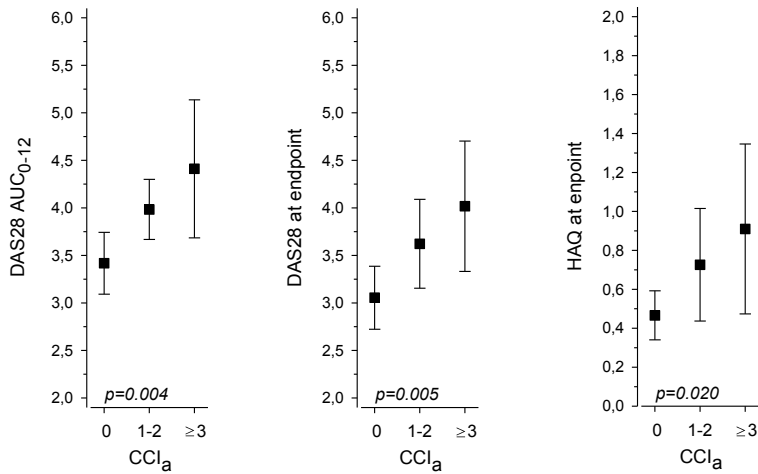
Figure 10. Disease activity during the first 12 months of RA (DAS28 AUC0_{0-12}) and at the 15-year visit or at last visit prior to death (DAS28 at endpoint) and final functional capacity (HAQ at endpoint) in relation to baseline total comorbidity load assessed with age-weighted Charlson comorbidity index (CCI$_a$).

The finding that the patients' baseline comorbidity was associated with disease activity, both in the early phase of RA and after 15 years or at the time of death, was surprising. Similar differences were found between the CCI$_a$ groups in final functional capacity. Some limitations of this study could be considered as confounding factors with respect to the above-mentioned relationships. The choice of age-weighted CCI to represent total comorbidity at baseline resulted in differences in both baseline age and educational level among the CCI$_a$ groups (Table 27). Several studies have indicated that younger patients with RA have better prognosis than older patients (Katchamart et al. 2010, Verstappen and Symmons 2011). Both high age and low educational level of the patients in group CCI$_a$ ≥3 could have contributed to their lifestyle and thus to later comorbidity and functional capacity. Other possible confounding factors include cigarette smoking and alcohol consumption. Both former and current cigarette smoking have been associated with more active and severe disease in early RA (Manfredsdottir et al. 2006). Data on patients' smoking habits were available until the 15-year visit, and there are thus no data of smoking in those patients who died before the 15-year examination. A further limitation includes missing data on the patients' alcohol consumption. Of the RA-related factors, RF and ACPA are known to be predictive for more active and severe disease in early RA (Manfredsdottir et al. 2006, Scott 2000, Verstappen and Symmons 2011). In this study, more patients in groups CCI$_a$ 1-2 and CCI$_a$ ≥3 were RF-positive than in group CCI$_a$ 0. The association between positive RF and comorbidity could have reflected an impact on early disease severity.

The impact of early disease activity relative to later disease activity was shown previously (Aletaha et al. 2007). The importance of early-initiated, effective DMARD

therapy on the later outcome in RA, including the probability of achieving remission was proposed by several authorities (Quinn and Emery 2003, Furst 2004, Cush 2007, van Nies et al. 2014). The treatment response to the first DMARD is an important predictor for later treatment response and outcome in RA (Verstappen et al. 2005, Farragher et al. 2010). In the present study, the first DMARD was initiated at the time of RA diagnosis, but was changed in several (67%) patients, due to adverse effects or inadequate response during the first year. MTX was used less frequently in patients who were older and had comorbidities at baseline. Retrospectively, it could be asked whether the early treatment of older patients with comorbidity should have been more intensive. This is crucial, since the prognosis in RA is poorer in elderly patients with early RA and the baseline comorbidity is probably associated with the disease activity. Could earlier and further use of MTX have changed the disease course in these patients? The current recommendations of EULAR for the management of RA (Smolen et al. 2014) specify that this have been possible and advisable. In the late 1980s, MTX became newly available in rheumatology and its use as a DMARD in treating patients with RA was adapted more widely in the 1990s. At the beginning its use was suboptimal (with lower initiation doses and lower weekly doses than are currently recommended), due to safety reasons, particularly in treating elderly patients who had other illnesses.

5.5 WORK DISABILITY

At the outset of the study, all 86 patients were ≤ 65 years of age and still working or available for the labour force. Data on patients' retirements: date of retirement, type of pension (work disability pension, individual early pension, old-age pension) and the main cause for retirement were registered at each study visit. Of the 10 patients who died during the follow-up, all retired before their demise. Of the six patients who did not participate in the 15-year examination, three had retired during their follow-up, and employment or retirement of the remaining three patients was verified by telephone at 15 years. In all 56/86 patients retired during the follow-up. Forty-two patients (49%) retired due to work disability; of these 38 (90%) were on a full-time pension and 4 (10%) on a part-time pension. The main reason for the retirement was RA in 34/38 (89%) of the patients receiving a work disability pension. The cumulative RA-related retirement was 7% after the first year, 11% after 2 years, 19% after 5 years, 33% after 10 years and 39% after 15 years. Eight (9%) of the patients were retired due to other illnesses, mainly due to CVDs. Fourteen patients (16%) had received an old-age pension, 28 patients (33%) were working full time and two patients (2%) were unemployed. The patients employed were younger, better educated and more often RF-negative than those who retired (Table 28).

Table 28. Baseline characteristics, disease activity and radiographic joint damage of the employed and retired patients.

	Patients retired due to RA n = 34	Patients retired for other reasons n = 22	Patients working n = 30
Female, n (%)	28 (82)	15 (68)	25 (83)
Age (years), mean	46 (9)	57 (6)	34 (9)*
Only basic education (%)	12 (35)	13 (59)	5 (17)*
Heavy physical work, n (%)	17 (50)	7 (32)	17 (57)
Living alone, n (%)	3 (8)	3 (14)	9 (30)
Duration of disease, months, median (IQR)	8 (4,12)	8 (6,11)	8 (5,10)
RF present, n (%)	24 (71)	19 (86)	14 (47)*
DAS28, mean (SD)	5.0 (1.1)	4.5 (1.2)	4.1 (1.0)*
Larsen score, mean (SD)	5.7 (7.9)	5.7 (6.5)	2.6 (3.7)

* $p < 0.010$

The Kaplan-Meier estimated cumulative permanent work disability due to RA (95% CI) during the 15-year follow-up was after the first year 7% (3–16), after 2 years 14% (8–24), after 5 years 21% (13–32), after 10 years 37% (27–49) and after 15 years 47% (36–60) (Figure 11). The estimated age- and sex-adjusted 15-year cumulative retirement rate (95% CI) for the RF-negative patients [37% (22–58)] was lower than for the RF-positive patients [53% (39–69)]. The estimated age-adjusted cumulative retirement rate (95% CI) was 48% (35–62) for women and 44% (22–74) for men.
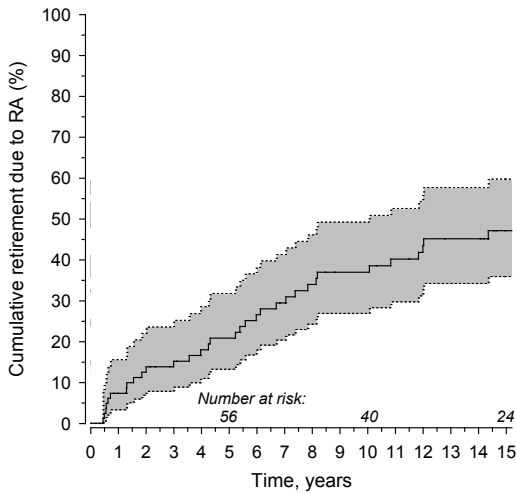
Figure 11. Cumulative work disability of 86 patients with rheumatoid arthritis (RA) during the 15-year follow-up. The age- and sex-adjusted retirement based on a Kaplan-Meier estimate with 95% confidence intervals.

The number of patients (39%) retired due to RA in the present study was lower than in the previous Finnish and Scandinavian studies evaluating retirement due to RA (44–67%) after 10-15 years of RA (Mäkisara and Mäkisara 1982, Sokka et al. 1999b, Ødegård et al. 2005, Eberhardt et al. 2007). In a cohort of 107 RF-positive patients from the Rheumatism Foundation Hospital, Heinola, 43% were work-disabled after 8 years and 80% after 20 years of RA (Kaarela et al. 1987, Jäntti et al. 1999). In two British studies, the rates of work disability varied from 39% to 49% after a mean or median 10 years of disease duration (Barrett et al. 2000, Nikiphorou et al. 2012). The latter British study estimated the probability of work cessation separately in patients with ages of < 45 years and in 45–60-year-old patients and in two patient cohorts recruited in 1985–1991 and in 1992–2001. The probability of retiring due to RA was highest in patients of older age (45–60 years) who were recruited before 1992. Comparison between the studies is complicated due to differences in study populations, study designs and follow-up periods, as appears in Table 29. In addition, definitions of work disability vary among countries and also over different periods.

Table 29. Study populations, recruitment periods, baseline demographics and retirement rates of Finnish, Scandinavian and British studies evaluating work disability in patients with RA over 10–15 years.

Study	Number of patients, Recruitment period	Mean age, years	Disease duration, mean, years	Percentage of females	RF-positive patients	Percentage of retired at 10/15 years
Longitudinal studies						
Kaarela et al. 1987	83/103 1973–75	45	< 0.5	68%	100%	43%*
Sokka et al. 1999b	82 1983–85 1988–89	40	0.5	66%	76%	38%/ -
Present Study 2013	86 1986–89	44	0.7	79%	65%	33%/39%
Eberhardt et al. 2007	148 1985–89	49	0.9	64%	75%	- /44%
Barret et al. 2000	160 1989–92	48 (F) 52 (M)	onset of RA	66%	-	39%/ -
Cross-sectional studies						
Mäkisara et al. 1982	131 130 1963–78	39 36	10 15	75% 75%	55% 60%	50% 67%
Ødegård et al. 2005	526	51	11	77%	49%	44%**
Nikiphorou et al. 2012	647	≤ 60	0.5	61%	74%	39%/ -

* rate of retirement after 8 years of RA

** 44% of patients were retired between >10–15 years since the diagnosis

The rate of permanent work disability decreased in patient cohorts collected in the 1980s compared with previous studies (Table 29). This may have resulted from the development of antirheumatic treatments and treatment strategies in RA. The number of available antirheumatic agents was limited in the 1960s and in the early 1970s, compared with DMARD selection, which was used in later decades of the 20th century. In the cross-sectional study by Mäkisara and Mäkisara (1982) > 80% of the patients received intramuscular gold and > 70% HCQ at some phase of their disease, but the exact data of the initiation or length of the treatment were not available. The patients in the Heinola cohort were treated during the first 8 years mostly with intramuscular gold and HCQ. The importance of early initiation of intramuscular gold therapy was shown in the late 1970s (Luukkainen et al. 1977). This idea was followed later in cohort studies initiated in the 1980s as part of the sawtooth strategy. The patients collected in the Jyväskylä area in 1983–1985 were

treated according to the sawtooth strategy (intramuscular gold as the first DMARD) and the patients collected in 1988–1989 were initially treated either with SASP or with placebo (Sokka et al. 1999b). In the present study, either intramuscular gold, HCQ or SASP was initiated for all patients immediately after the diagnosis and continuous DMARD therapy was used according to the sawtooth strategy. In the 2000s, the FIN-RACo study's 5-year results (Puolakka et al. 2004) supported the superiority of early-initiated and intensive DMARD therapy. Among patients treated initially with combination treatment, fewer (20%) were permanently work-disabled than among those receiving initial DMARD monotherapy (29%). In comparing the Finnish studies from different decades, it should be borne in mind that the grounds for work disability pensions have been changed. In the 1980s, commonly granted individual early pensions were withdrawn, and in year 2004, reformed legislation considered vocational rehabilitation prior to work disability pension.

In addition the disease itself, several work-related factors such as occupation, physical requirements, psychosocial demands and work circumstances influence patients' possibilities to continue or stop working (de Croon et al. 2004). Other factors associated with RA-related work disability in several studies include age, low level of education, long disease duration, high disease activity, further radiographic progression and, in particular functional disability (HAQ) (Verstappen et al. 2004, de Croon et al. 2004).

In the present study, HAQ was registered from the third year of the follow-up. Both the disease activity and radiographic progression are associated with functional capacity (Drossaers-Bakker et al. 1999, Welsing et al. 2001). The relationship of early disease activity and early radiographic progression with later RA-related permanent retirement was evaluated over 15 years. During the first year of RA, clinical disease activity (28 joint counts) and acute phase reactants were evaluated every 3 months. DAS28 scores were calculated retrospectively with three parameters at baseline and at every 3 months to form the DAS28-area-under the curve (DAS28 AUC) during the first 12 months, which represented the early disease activity of each individual. To evaluate early radiographic progression, the radiographs of hands and feet examined at baseline and at 12 months were scored with the LS. An increase of ≥ 2 LUs between these two sequential sets of radiographs was defined as representing early radiographic progression. Patients with ≤ 1 LU increase during the first year were considered to be in early radiographic remission (ERR).

The impact of early disease activity on permanent RA-related retirement was studied in 84/86 patients with complete clinical data to calculate the DAS28 AUC in the following groups: in patients with low disease activity (DAS28 AUC ≤ 3.2) and in those with moderate or high disease activity (DAS28 AUC > 3.2) during the first 12 months. Only 9/33 (27%) of the patients with DAS28 AUC ≤ 3.2 were retired during the 15-year follow-up, compared with 34/53 (64%) of those with DAS28 AUC > 3.2. None of the patients with low disease activity were retired during the first 3 years, compared with 25% of those with moderate or high disease activity (12%

during the first year of RA). The Kaplan-Meier estimated cumulative RA-related retirement rate (95% CI) of patients with moderate or high disease activity was 28% (17–43%) after 5 years, 55% (41–71%) after 10 years and 64% (50–79%) after 15 years, and of those patients with low disease activity 3% (1–22%), 10% (3–29%) and 22% (10–43%), respectively (Figure 12). The age- and sex-adjusted hazard ratio [HR (95% CI)] for premature RA-related retirement of patients with moderate or high early disease activity was 3.08 (1.30–7.28) (p = 0.010). The impact of early disease activity was even more clear in those 10 patients who showed high disease activity (DAS28 AUC > 5.1) during the first 12 months. All of these were retired during 10 years, 40% during the first year of RA, 60% during the first 2 years and 70% during 5 years.
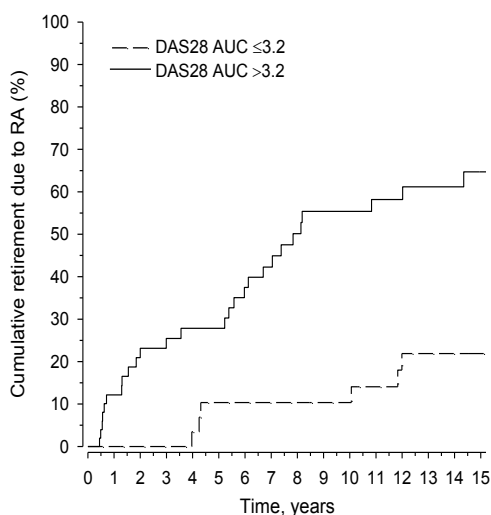
Figure 12. Kaplan-Meier estimated cumulative RA-related retirement of 84 patients in relation to early disease activity [DAS28 area-under-the curve (DAS28 AUC) during the first 12 months] over the 15-year follow-up.

Several previous studies have shown that high joint counts (both tender and swollen joints) and more severe disease are associated with work disability, but the value of these as predictors of work disability has been inconsistent (de Croon et al. 2004, Verstappen et al. 2004). In the FIN-RACo study, poor treatment response according to ACR criteria was predictive of premature work disability during the first 5 years of RA. Of the 35 patients with less than the ACR20 treatment response at 6 months 19 (54%) became work disabled during 5 years, while 6 (21%) of the 29 patients with ACR20 treatment response and 15(23%) of the 66 patients with ACR50 treatment response 15 (23%) were retired during 5 years. None of the 29 patients who had achieved clinical remission at 6 months were retired at 5 years (Puolakka et al. 2005). Of the 23 patients in the present study who fulfilled the ACR remission criteria at 12 months, only one (4%) was retired before 5 years, 4 (17%) at 10 years and 5 (22%) at 15 years. These results are consistent with the FIN-RACo

study; patients who achieved early clinical remission preserved their work capacity longer than patients with persistently active disease.
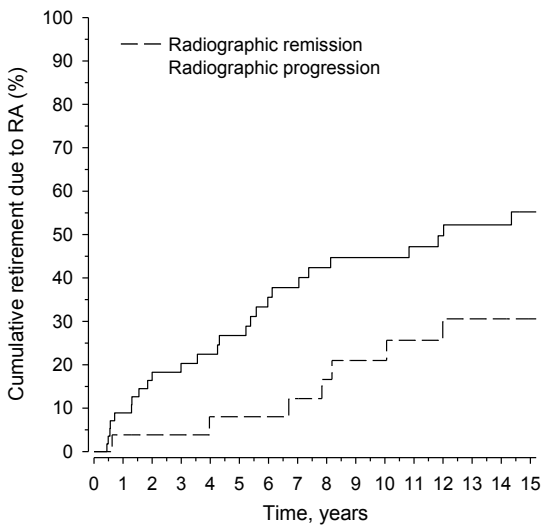
Figure 13. Kaplan-Meier estimated cumulative RA-related retirement over 15 years in 28 patients with early radiographic remission and in 58 patients with early radiographic progression.

The relationship of early radiographic progression or ERR with cumulative RA-related retirement over 15 years was evaluated with the Kaplan-Meier method. The estimated cumulative retirement rate of the 28 patients with ERR (increase in LS $\leq$ 1 LU during the first 12 months of RA) was 12% at year 5, 28% at year 10 and 33% at year 15, compared with the 58 patients with early radiographic progression (increase in LS $\geq$ 2 LUs during the first year), whose rates were 25%, 43% and 54%, respectively. The influence of radiographic progression was not as clear as the impact of early disease activity (Figure 13). The HR (95% CI) for RA-related retirement of patients with early radiographic progression was 2.31 (0.99-5.35) (p = 0.050).

The radiographic progression in RA was associated with loss of work ability in previous longitudinal studies (Jäntti et al. 1999, Sokka et al. 1999b, Young et al. 2002). Few studies have evaluated baseline or early radiographic progression in relation to later work disability. In the present study, the impact of early radiographic progression on permanent retirement was evident at 5 years in patients whose LS had increased by $\geq$ 2 LUs during the first 12 months. The retirement rate of these patients was twice as much as those patients whose radiographic progression was halted during the first year of RA. The difference between the two groups remained over 15 years. This finding, together with the previously shown impact of early disease activity on permanent RA-related work disability, emphasize the importance of DMARD treatment targeting clinical remission and halting radiographic progression in patients with RA as early as possible.

GENERAL DISCUSSION

The outcome in RA has improved during recent decades due to advances in antirheumatic therapy (Sokka and Mäkinen 2009, Verstappen and Symmons 2011) and to probable changes in the natural history of the disease (Dixey et al. 2004, Sokka et al. 2004). The increased number of synthetic DMARDs available and development of biological DMARDs together with changes in treatment strategies have modified the clinical course of RA to less serious and less destructive (Thompson et al. 2011). Along with this evolution, remission has become a realistic goal of treatment in RA and one of the main clinical outcomes. This is wide digression from the previous targets, which focused on suppression of disease activity. One of the most remarkable steps on the way towards favourable outcome in RA was understanding of the importance of early initiation of DMARD therapy (Luukkainen et al. 1977, Fries 1990, Demoruelle and Deane 2012).

The early initiation of DMARD therapy was essential to the treatment strategy of the present study, which aimed to find an effective and well-tolerated DMARD therapy for each individual patient according to the saw-tooth strategy. The initial purpose of this cohort study was to prospectively examine the course of the disease and radiographic progression in early RA and to identify possible prognostic factors for these outcomes (Paimela et al. 1991, 1992a, 1992b). The follow-up was extended up to 15 years, with special focus on the permanent consequences of RA: radiographic damage, functional disability and work disability. These outcomes were studied in relation to DMARD therapy. The impact of early disease activity and early radiographic progression on the final outcomes was also evaluated. In addition, data on comorbidities were collected and the impact of these on the disease activity and final functional capacity was determined.

The population of this study was small; however, 70 (80%) of all the 87 patients were examined at 15 years. One female patient in the initial cohort was removed from the 15-year analysis, due to a revised diagnosis. The last available radiographs of the deceased patients and of those who were lost to follow-up were used in the analysis of the radiographic outcome. Occurrence of the baseline and the final comorbid conditions could be studied both in the patients examined at 15 years and in the 10 deceased patients, whose data were collected from death certificates and the medical records. Data on permanent work disability pensions were available for the entire study population. The strengths of this study are in the detail baseline data with precise documentation of the antirheumatic treatments over the 15-year follow-up, which enabled calculation of the total time on DMARD therapy during the follow-up period for every patient.

Most of the 70 patients who participated in the 15-year visit needed continuous DMARD therapy over 15 years. In 50 patients (71%) DMARDs were discontinued only for adverse events, other illnesses or pregnancies. The mean treatment time on DMARDs as percentage of the mean follow-up time for these 50 patients was 84% and mean (range) number of DMARDs or DMARD combinations 6.1 (1–11). DMARD therapy was discontinued due to remission or symptom-free period with minimal disease activity in 20 patients (29%); 9 (45%) of these experienced a flare-up of the disease and 11 (55%) remained in remission. The average time on DMARD therapy as percentages of mean follow-up time was 66% and 31% and the mean number of DMARDs 3.4 and 1.9 in these two groups of patients, respectively.

Final disease activity assessed with the mean number of tender joints and swollen joints and with DAS28 was highest in those patients whose DMARD therapy had to be restarted, due flare-ups after discontinuation of DMARDs. At 15 years, none of these patients met the ACR remission criteria, compared with 6% of patients with continuous DMARD therapy and 64% of those who were followed up without any antirheumatic therapy after favourable discontinuation of DMARDs.

These findings are consistent with the results of the randomized, double-blinded and placebo-controlled studies performed by ten Wolde et al. in the 1990s. The disease flared up in 38% of the 143 RA patients whose DMARD therapy was discontinued when the patients were in modified ACR remission and had stable disease for at least 1 year, compared with 22% of the 142 RA patients whose DMARD therapy was continued (ten Wolde et al. 1996). Of the 51 patients with a flare-up after discontinuation of DMARDs 22% showed moderate or severe disease activity and 43% mild disease activity after 12 months of resumption of the DMARDs. Only 35% achieved clinical remission during 12 months, even though the DMARD therapy was instituted immediately after the flare-up manifested itself (ten Wolde et al. 1997). In the present study, the resumption of DMARD therapy was delayed particularly in patients who were no longer followed up by the rheumatologists.

A meta-analysis of previous smaller randomized and controlled trials concluded that remaining on DMARD therapy substantially reduced flare-ups of the disease in RA. Patients in whom DMARDs are withdrawn are three times more likely to experience a flare-up than those in whom DMARDs are continued (O'Mahony et al. 2010). The studies examining DMARD combination therapy versus DMARD monotherapy have shown that the benefits of intensive initial combination therapy are maintained after tapering off the DMARD combinations with a step-down regimen (Landewe et al. 2002, Marchesoni et al. 2003, Rantalaiho et al. 2010). In the BeSt study, 23% of patients achieved drug-free remission; in 46% of these patients the DMARD therapy had to be restarted for increasing disease activity during a 5-year follow-up period (Klarenbeek et al. 2011b). These studies suggest that drug-free remission is achievable in a minority of RA patients. Nearly half of patients whose DMARD therapy is withdrawn in sustained remission, will need later resumption of the DMARD therapy, due to

a flare-up of RA, according to the data gathered in the studies presented above.

The functional capacity, as measured by mean HAQ, of all 70 patients examined at 15 years was 0.52, which is lower than in other long-term studies (0.64–1.10) with 9-12-year follow-up periods (Drossaers-Bakker et al. 1999, Welsing et al. 2001, Lindqvist et al. 2002). The mean HAQ was poorest in patients with continuous DMARD therapy (0.60). Data on the baseline HAQ of the patients was not available, which is a weakness of this study and may have influenced the patients' later assessments of HAQ registered from the third year of the follow-up. Previous studies have shown that average HAQ scores are higher in patients with established RA, even though the patients have achieved clinical remission (Aletaha et al. 2006) and that elderly individuals in the general population have higher HAQ scores than younger individuals (Sokka et al. 2003b). The patients of the present cohort were ≤ 65 years of age (mean 44 years) at the outset of the study, and the deceased patients whose 15-year HAQ scores were not available were on average older (mean 58 years) at baseline. Both of these factors may have impact on the mean final HAQ score in this study.

Radiographic joint damage both in the small joints and large joints at 15 years was assessed with the LS. Radiographs of the small joints were examined during the first 3 years annually and later at year 5, 7, 10 and 15, and of the large joints at 15 years. The mean LS of the small joints increased gradually during the follow-up period. The average annual radiographic progression for the entire study group was 2.5 LUs. The progression was most evident during the first 3 years with an average of 5.0 LUs annually. The progression later decreased to 3.0 LUs annually during the next 2 years, to 2.5 LUs annually from year 5 to year 10 and finally to 1.4 LUs annually between years 10 and 15.

The rate and pattern of radiographic progression varied considerably among the individual patients. This cohort population was not large enough to formulate different patterns of radiographic progression throughout the follow-up period as presented in some studies (Graudal et al. 1998, Plant et al. 1998). Instead, early radiographic remission (ERR) defined as an increase in LS ≤ 1 LU between two sequential sets of radiographs was studied and its impact on the 15-year radiographic outcome was evaluated. The 69 patients with full sets of radiographs at baseline, at year 1, year 2 and at endpoint were analysed in the following groups: 18 patients (26%) with sustained ERR, 20 patients (29%) who were radiographically stable either at year 1 or year 2 (temporary ERR) and 31 patients (45%) with progression ≥ 2 LUs both during the first and second year of RA (no radiographic remission). There were no significant differences between the groups in baseline demographics, clinical characteristics or radiographic findings (Table 21). The DMARD therapy was most intensive in those patients who showed early radiographic progression (Table 22, Figure 6). The 15-year radiographic progression of the small joints was most extensive (mean LS 67) in patients who did not achieve ERR. The patients with sustained ERR had the most favourable radiographic outcome at 15 years (mean LS

14). The mean LS of patients with temporary ERR was 33. The differences between the groups remained statistically significant, even if the seven nonerosive patients in the sustained ERR group were excluded from the analysis.

The importance of the ERR was emphasized by the finding, that radiographic damage in the large joints assessed with LS accumulated in patients who showed radiographic progression of the small joints during both year 1 and year 2 (Figure 8). The association between radiographic progression in small joints assessed with SHS and large joint damage assessed with LS was reported in two previous RA cohort studies with follow-up periods of 6 years (Kuper et al. 1997) and of 12 years (Drossaers-Bakker et al. 2000). In the study by Drossaers-Bakker et al., 54% of the 105 female patients had large joint damage at endpoint, but none of the patients with nonerosive radiographs of the hand and feet showed radiographic damage in the large joints. In the present study, only one young female patient without erosions in the small joints had moderate damage in the knees at 15 years. Recently, a significant association between radiographic progression in the small joints and damage in the large joints was reported in 8-year results of the BeSt study (Dirven et al. 2012). Based on these studies, evidence for radiographic progression in the small joints should also be taken as a warning sign for possible later large joint damage.

Novel imaging techniques, such as MRI detect both inflammatory and erosive changes more sensitively and earlier than plain radiographs (Haavardsholm et al. 2008). However, MRI is not available without restrictions in daily clinical practice and can be performed only in a limited number of joints and patients with RA. Due to its several benefits, ultrasound (US) is currently used widely in rheumatological clinical practice. It is a sensitive tool for detecting both inflammation and erosions of the joints, especially when performed by a skilful clinician or radiologist (Brown 2009). Performing US is, however, time-consuming and screening of all potentially involved joints is not always possible. As a result, plain radiographs of the hands and feet should not be ignored in the routine care of early RA. Conventional radiographs are still useful tools for identifying patients who show radiographic progression and who should be treated more intensively (Colebatch et al. 2013).

Due to the inclusion criteria of the present study, the mean age of the patients at baseline was quite low (44 years), which accounts for the relatively small number (20%) of patients with comorbidities at baseline. In the Swedish early RA cohort recruited almost at the same time period, the mean age of the patients was 52 years, and 43% of these had at least one comorbid condition at baseline. After 20 years, 82% of the Swedish RA patients had comorbidities (Kapetanovic et al. 2010). In the present study, 60% of the patients had at least one comorbid condition at the 15-year examination, the most common comorbidities being hypertension (30%), CVDs (14%), malignancies (11%) and osteoporosis (11%). The occurrence of these comorbidities was quite similar that in to other studies with follow-up periods approximately as long (11–16 years) and mean age of the patients (60–61 years) (Briggs et al. 2009, Radner et al. 2010, van Tuyl et al. 2010).

In the present study, the relationship of baseline comorbidity to disease activity during the first year of RA and at the 15-year examination was the most striking finding regarding comorbidities. The total burden of comorbidities at baseline for each patient was evaluated with a validated and weighted score of 19 comorbid conditions (Table 26), which significantly influence the relative 1-year mortality risk, the CCI (Charlson et al. 1987). In this study we used a modification of the CCI (CCI_a), which takes into account the impact of ageing on mortality by adding one extra point for each decade of age above 50 years (Charlson et al. 1994). When the relationship of baseline comorbidity to the disease activity (DAS28) was studied in the following groups: CCI_a 0, CCI_a 1-2 and CCI_a ≥3, the DAS28 was higher in patients with more comorbidity (group CCI_a ≥3) not only during the first year of RA, but also after 15 years. In addition similar trend was evident in the final functional capacity measured with HAQ (Figure 10).

RF is predictive for more severe disease in early RA (Scott 2000, Verstappen and Symmons 2011), thus higher number of RF-positive patients in groups CCI_a 1-2 (91%) and CCI_a ≥3 (100%) than in group CCI_a 0 (50%) most probably influenced the results of this study. Another possible confounding factor is the lower educational level of the patients in group CCI_a ≥3, which may have interfered with the patients' smoking habits, alcohol consumption and other lifestyle factors. These factors are known to influence both the risk of CVDs and of certain malignancies. This study, unfortunately, lacks data on cigarette smoking and alcohol consumption at baseline. The antirheumatic treatments were very similar in all three groups, with exception of use of MTX, which was less commonly used in patients with comorbidities and older age at baseline. This finding, together with the higher final disease activity and tendency to lower functional capacity in group CCI_a ≥3 than in the other two groups, indicates that elderly patients with comorbidities should have been treated as intensively or perhaps more intensively than the younger and otherwise healthy individuals.

To determine the impact of RA on work ability, we initially included in this study only patients of working age (18–65 years). All of the 86 patients were in paid labour, studying or available for the labour market at the outset of the study. During the 15-year examination, 38 (44%) of these patients were on a full-time pension and 4 (5%) received part-time pension, due to work disability. RA was the main reason for retirement in 34/38 (89%) of the patients receiving full-time work disability pension. Eight (9%) patients were retired, due to other illnesses (most commonly CVDs). Of the remaining patients 14 (16%) received an old-age pension, 28 (33%) were working full time and two patients (2%) were unemployed. The Kaplan-Meier estimated cumulative RA-related permanent work disability over 15 years was 7% at year 1, 14% at year 2, 21% at year 5, 37% at year 10 and 47% at year 15. The estimated age- and sex-adjusted 15-year cumulative retirement rate was higher in the RF-positive patients (53%) than in the RF-negative patients (37%). No significant difference was found in the estimated age-adjusted cumulative

retirement rate between women (48%) and men (44%). Comparison between various studies involves several confounding factors, such as differences in study populations, study designs and antirheumatic treatments. In addition, definitions of work disability, employment insurances and social security systems differ widely in various countries. All of these factors may have influenced the differences in results of the previous studies and of this study (Table 29).

In the present study, the early disease activity assessed with the DAS28 during the first 12 months (DAS28 AUC) clearly impacted on the estimated cumulative RA-related retirement. The estimated cumulative retirement rate of patients with low early disease activity (DAS28 AUC ≤ 3.2) was 3% after 5 years, 10% after 10 years and 22% after 15 years, compared with 28%, 55% and 64% of patients with moderate or high disease activity (DAS28 AUC > 3.2), respectively. None of the patients with DAS28 AUC ≤ 3.2 became work-disabled during the first 3 years of RA, while 40% of the 10 patients with high disease activity (DAS28 AUC > 5.1) retired during the first year, 60% during 2 years and 70% during 3 years. A similar but less substantial, trend was found in estimated cumulative RA-related retirement between the patients with ERR (increase of LS ≤ 1 LU during first year of RA) and those with early radiographic progression (increase of LS ≥ 2 LUs). Both suppressing of early disease activity and halting of early radiographic progression are crucial in aiming to a more favourable long-term outcome, including maintaining of work capacity in RA.

In this study, the favourable 15-year outcome (less severe radiographic outcome, good functional capacity and longer maintained work capacity) was in the majority of patients achieved with conventional synthetic DMARDs. Only three patients were on TNF-α inhibitor therapy at the endpoint and two other patients earlier used TNF-α inhibitor for a short period. The factors explaining the favourable long-term outcome include (1) early initiation of DMARD therapy, (2) finding effective and well-tolerated DMARDs for each individual patient, (3) tight intervals of control visits during the first 3 years of RA (3) and (4) achieving and maintaining clinical remission. Use of MTX was not yet established when this study was planned and initiated, but it was used increasingly later during the study. During the first years of the study, several combinations of the synthetic DMARDs available were used in the patients with continuous disease activity or with evidence of radiographic progression. Intra-articular GC injections and low-dose oral GCs were administered in patients showing high levels of disease activity. Later, the decision to continue DMARD treatment in patients with detectable disease activity, radiographic progression or in those with previous difficulties in controlling the disease activity, was of benefit both to the patients in this study and to the long-term outcome of the entire cohort. These practices of treatment are very much in line with today's main treatment principles and instructions presented in the Finnish Current Care Guidelines (Hakala et al. 2009) and in the EULAR recommendations for management of RA (Smolen et al. 2014).

The Finnish idea of the impact of early-initiated and effective synthetic DMARD therapy on later outcome in RA was recently confirmed by the 5-year results of the NEO-RACo trial (Rantalaiho et al. 2014). In this study, the original FIN-RACo combination (MTX, SASP, HCQ) with low-dose prednisolone was compared with the FIN-RACo combination with additional infliximab treatment (NEO-RACo) during first 6 months of RA (Leirisalo-Repo et al. 2013). The proportions of the patients in ACR remission at 5 years were equal in both patient groups: in the patients treated with the original FIN-RACo combination (61%) and in those treated with the NEO-RACo protocol (60%). The radiographic 5-year outcome assessed with the SHS score was minimal in both patient groups with a mean total SHS of 5.3 and 4.3, respectively. The NEO-RACo study raises the question of relevance of biological DMARDs in early RA and the need for further studies on the safety and benefits in relation to monetary costs of these treatments as first-line treatments. Probably, a more reasonable and cost-effective strategy would be to prescribe biological DMARDs to those patients with the most active disease or with poor prognostic factors.

A key issue in treating patients with early RA has constantly been how to identify those patients with poor prognosis who need intensified DMARD therapy. RF, ACPA, high initial disease activity and erosive disease at baseline are commonly admitted markers of poor outcome. The results of the present study suggest that early radiographic progression during the first years of RA should be considered as additional warning signs for later radiographic progression and decline of work capacity. Conventional radiographs are still a proper method for assessing early radiographic progression and evaluating prognosis of the patients. In this study, early radiographic progression of the small joints was predictive for later damage in the large joints, increasing the value of systematic evaluation of early radiographic progression in the small joints. Regarding the results of this study and other studies done in Finland, especially the FIN-RACo and the NEO-RACo trials it can be postulated that synthetic DMARDs and conventional radiographs are still essential tools for rheumatologists in treating early RA.

CONCLUSIONS

1. In this cohort of early RA patients, most of the patients needed continuous treatment with synthetic DMARDs, either as monotherapy or as combination therapy during the 15-year follow-up period. If the DMARDs are discontinued due to longstanding remission, the patients should be followed up carefully, because the disease flares up on average in 40-50% of these patients. If any disease activity occurs, the DMARD therapy should be immediately reintroduced.

2. Achievement of early radiographic remission (ERR) is essential for a favourable long-term radiographic outcome. In addition radiographic progression in the small joints, joint damage in the large joints accumulates in the patients, who did not achieve ERR. Conventional radiographs are still a proper method for detecting early radiographic progression and they are easily available in clinical practice.

3. Elderly RA patients with baseline comorbidity had higher disease activity during the first year of RA and after 15 years or at time of death. The use of MTX was less frequent in these patients than in younger, otherwise healthy patients. DMARD treatment of older patients with comorbidities should be, if possible, as intensive as the treatment of younger patients without any comorbidity. As a whole, comorbidity in this cohort was similar to that in previous studies, with hypertension, CVDs, osteoporosis and malignancies being the most common comorbid conditions after 15 years.

4. Work disability due to RA increased gradually during the 15-year follow-up to 39% after 15 years. The cumulative work disability over 15 years was lower in patients with low early disease activity (DAS28 AUC ≤ 3.2) during the first 12 months than in those with moderate or high disease activity. The patients with ERR (increase of LS ≤ 1 LU during the first year) maintained their work capacity better than those who showed early radiographic progression. These findings emphasize the importance of targeting to clinical remission and halting of radiographic progression in the early phase of the disease for the long-term outcome in RA.

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