OUTCOME OF EARLY RHEUMATOID ARTHRITIS

- With special reference to early institution of drug treatment

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Academic dissertation

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CONTENTS

ABBREVIATIONS ........................................................................................................ 8
LIST OF ORIGINAL PUBLICATIONS ....................................................................... 9
1. ABSTRACT .............................................................................................................. 10
2. INTRODUCTION .................................................................................................... 12
3. REVIEW OF THE LITETERATURE ........................................................................ 14
    3.1. Epidemiology and aetiology ............................................................... 14
    3.2. Diagnostic and classification criteria ................................................ 16
    3.3. Clinical course ................................................................................... 17
    3.4 Antirheumatic treatments ................................................................. 18
        3.4.1 Traditional DMARDs ................................................. 18
        3.4.2. Modern DMARDs .................................................... 19
        3.4.3 Treatment strategies ................................................... 20
        3.4.4. Combination therapy ................................................ 20
        3.4.5. Biological treatments ................................................ 21
        3.4.6. Timing and efficacy of the treatment ....................... 21
        3.4.7. DMARD therapy and remission ............................... 21
        3.4.8. Factors contributing to the effect of treatment ......... 22
        3.4.9. DMARD therapy and side effects ............................ 23
    3.5. Evaluation of radiographic progression ................................................. 23
    3.6. Predicting radiographic progression ..................................................... 24
        3.6.1. Laboratory markers ..................................................... 24
        3.6.2. Other prognostic factors ............................................. 26
            3.6.2.1. Gender ....................................................... 26
            3.6.2.2. Age and disease duration .............................. 26
            3.6.2.3. Baseline radiological changes ............... 26
            3.6.2.4. Clinical picture ......................................... 27
    3.7. Functional disability ................................................................................... 27
        3.7.1. General ......................................................................... 27
        3.7.2. Factors affecting functional capacity ............................. 27
        3.7.3. Predictors of functional outcome .................................. 28
        3.7.4. Age and functional capacity ........................................ 28
        3.7.5. Development of functional capacity ............................. 28
6.3.3. Outcome
6.4. Effect of treatment on the outcome of very early RA
   6.4.1. General
   6.4.2. Treatment and outcome
6.5. Permanent work disability in patients with early RA
6.6. Mortality among early RA patients treated actively
   according to the `sawtooth´ strategy

7. DISCUSSION
   7.1. General
   7.2. Intramuscular gold and sulphasalazine
   7.3. Effect of age on outcome
   7.4. Effect of treatment on the outcome of very early RA
   7.5. Permanent work disability in early RA patients treated
        actively with disease modifying drugs
   7.6. Mortality among early RA patients

8. SUMMARY AND CONCLUSIONS

9. ACKNOWLEDGEMENTS

10. REFERENCES

ORIGINAL PUBLICATIONS
ABBREVIATIONS

ACR  American College of Rheumatology
ARA  American Rheumatism Association
CI   Confidence interval
CRP  C-reactive protein
CVD  Cardiovascular disease
DMARD Disease modifying antirheumatic drug
EORA Early onset rheumatoid arthritis
ERA  Early rheumatoid arthritis
ESR  Erythrocyte sedimentation rate
GS   Grip strength
HAQ  Health Assessment Questionnaire
LORA Late onset rheumatoid arthritis
MCP  Metacarpophalangeal
MS   Morning stiffness
MTP  Metatarsophalangeal
NSAID Nonsteroidal anti-inflammatory drug
OR   Odds ratio
PIP, IP Proximal interphalangeal, interphalangeal
RA   Rheumatoid arthritis
RF   Rheumatoid factor
SASP Sulphasalazine
SMR  Standardised mortality ratio
VAS  Visual analogue scale
VERA Very early rheumatoid arthritis
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by the Roman numerals I-V:


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1. ABSTRACT

The main interest in the present study was to evaluate the outcome in patients with early rheumatoid arthritis (RA) treated actively according to the `sawtooth´ strategy. A total of 150 patients were prospectively followed up from the time of diagnosis onwards. The study population consists of 2 different patient populations: in the first cohort patients with duration of symptoms < 12 months were included in the study between 1986-1989 and in the second cohort patients with duration of symptoms < 24 months were recruited between 1991 and 1993.

The effect of intramuscular gold and sulphasalazine on the radiological progression was compared in the first study. Almost half of the patients discontinued the initial drug within the first year due to side effect or inefficacy. Despite favourable and parallel improvement in clinical and laboratory variables, significant and statistically equal radiological progression was observed in both groups.

In the second study the effect of age on the clinical picture and outcome of early RA was evaluated. At the time of diagnosis only the laboratory inflammation markers and Larsen scores for hands were higher among older patients; otherwise there were no differences between older (> 55 years at the time of diagnosis) and younger patients. The patients were treated equally. The tolerability and efficacy of disease-modifying antirheumatic drug (DMARD) therapy was similar in both groups. After a 3-year follow-up all clinical and laboratory variables had improved significantly and the radiological progression was parallel among both older and younger patients.

Patients with very short duration of symptoms (< 4 months) before diagnosis appear to have more active disease. The radiological progression evaluated by the Larsen score per month before the time of diagnosis and the functional status were higher among patients with very early RA (VERA). During the first 3 years the number of different DMARDs used was slightly higher among VERA patients. Despite significant improvement in all clinical variables, the erythrocyte sedimentation rate (ESR) and Ritchie index remained significantly higher among VERA group members. However, after the initiation of DMARDs, radiological progression was retarded more effectively among VERA patients and the annual progression was parallel during the first 3 years.
The effect of active treatment on permanent work disability was evaluated among 102 patients, who were working at the time of RA diagnosis. The number of patients still working after a 10-year follow-up was higher than has been previously shown in other studies. However, despite active treatment with various DMARDs work disability increased constantly among this patient group. Older age, increased functional disability, ESR and physical demands of work at the time of diagnosis were the best predictors for work disability.

In the final study the mortality among these actively treated early RA patients was analysed. The patients have been followed up between 7 and 14 years. Twenty-four out of 150 patients have died. The mortality rates evaluated either separately in both study cohorts or throughout the study population did not differ from the mortality rates of the normal Finnish population. The clinical picture at onset was more active among those patients who had already died. Diseases of the circulatory system and malignancies were the most common causes of death among these patients. Older age at onset was a significant predictor of mortality.
2. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic disease with a heterogeneous clinical picture. Its course can vary from a benign, low-activity arthritis to a rapidly progressive, destructive polyarthritis. Although arthritis is usually the predominant feature of RA, other manifestations contribute to the outcome as well. So far no good prognostic tools for individual patients exist, although in large patient cohorts some clinical and laboratory markers have been connected with poorer prognosis (Mitchell et al. 1986, Scott et al. 1987, Möttönen et al. 1998, Wolfe and Sharp 1998).

The use of antirheumatic therapies is based on various studies in which the beneficial effects of antirheumatic treatment on symptoms (Forestier 1935, Pullar et al. 1983) and radiological progression (Luukkainen et al. 1977, Abu-Shakra et al. 1998) have been observed. In Finland the treatment of RA was earlier based on the use of aurothiomalate, but later in the late 1980s and early 1990s sulphasalazine (SASP) became an important alternative to gold. The importance of initiating the disease-modifying therapy as early as possible has also been shown (Luukkainen et al. 1977, Egsmose et al. 1995). These observations have directed Finnish rheumatologists to treat all RA patients as early and as actively as possible from the time of diagnosis onwards.

The efficacy and tolerability of different DMARDs varies from one patient to another. Whether age, gender or the activity of the disease affects the outcome is not self-evident. The importance of the effect of age on the clinical picture and outcome of RA is emphasized, since the median age at onset of RA increases continuously (Kaipiainen-Seppänen and Aho 2000). Previous studies on the effect of age on the clinical picture (Deal et al. 1985, van der Heijde et al. 1991) and on the efficacy and tolerability of drugs (Pincus et al. 1992, Capell et al. 1993) have given controversial results.

Many investigators (Mäkisara and Mäkisara 1982, Yelin et al. 1987) have observed the risk of increased work disability among RA patients. The risk factors for losing working capacity have included educational level (Doeglas et al. 1995), the characteristics of work (Wolfe and Hawley 1998), poor functional capacity (Mau et al. 1996) and gender (Albers et al. 1999). Comparisons between different studies are difficult to perform, since the social insurance systems vary among countries. In Finland, several studies of work disability in RA patients have been published (Mäkisara and Mäkisara 1982, Jäntti et al. 1999, Sokka et al. 1999a), which has made it possible to compare the effect of active treatment on work disability. Although the decrease in working
ability is continuous, it has been observed to be most rapid during the early years of RA (Reisine et al. 1995).

RA is associated with increased mortality rates. Although the results in community-based studies have often been more favourable than in hospital-based studies, in most studies the standardized mortality ratios (SMR:s) have been higher compared with those found in the normal population (Mitchell et al. 1986, Pincus and Callahan 1986, Isomäki 1992). Although the beneficial effect of DMARDs on functional ability has been shown in many studies (Egsmose et al. 1995, Fries et al. 1996, Möttönen et al. 1996), the mortality rates have not decreased among RA patients during the last 4 decades (Gabriel et al. 1999a).

In the present study 150 patients with early RA have been followed up for at least 7 years. The patients have been actively treated from the time of diagnosis according to the so-called `sawtooth´ strategy (Fries 1990). The outcome of the patients with respect to initial therapy, age, timing of therapy, work disability and mortality is described.
3. REVIEW OF THE LITERATURE

3.1 Epidemiology and aetiology

The aetiology of RA is unknown, although many environmental factors have been proposed as a causative agent. The findings that RA was observed in Europe after the European incursions into the affected areas of North America (Rothschild et al. 1992) suggest that RA is a vector (microorganism or allergen) transmitted rather than a genetic disease. One feature that might point to a strong environmental component is the evidence of secular trends or disease clusters in time or space. Although some evidence of secular clusters has been found in one study from Rochester (Gabriel et al. 1999b), no evidence of such clustering was shown in another study from Norfolk, England (Silman et al. 2000). Infection, especially with viral or other microbial agents, is considered to be one of the most probable environmental triggers for the development of RA. Human parvovirus has been linked to the occurrence of inflammatory arthritis (Cohen et al. 1986). However, in studies from Finland (Nikkari et al. 1995) and from the Norfolk Arthritis Register (Harrison et al. 1998), no significant association between the aetiology of RA and parvovirus infection was observed, although in some cases parvovirus infection may precede the onset of RA.

The familial nature of RA has long been recognized, suggesting that genetic risk factors are also important in the aetiology of RA. Twin studies have shown that monozygotic twins have 3-4-fold higher risks of developing RA compared with dizygotic twins, who also have 3-4-fold higher risks of RA compared with nonrelatives (Aho et al. 1986, Silman et al. 1993). The first evidence showing the importance of genetic markers in RA was observed by Stastny, who found the association between RA and human leukocyte antigen (HLA)-DR4 (Stastny 1978). This association has since been defined to a certain region (shared epitope) within a subgroup of HLA-DR4 genes (Gregersen et al. 1987). Variation in the population prevalence of this shared epitope may partly account for the distribution of RA throughout the world. However, HLA association is likely to explain only one-third of the genetic susceptibility of RA (Deighton et al. 1989, Rigby 1992).
There is some epidemiological evidence that smoking is a risk factor for developing RA. Exposure to tobacco smoke or some factor associated with smoking may trigger the production of rheumatoid factor (RF), leading to the development of clinically manifest RA among men (Heliövaara et al. 1993). In a study from Norway (Uhlig et al. 1999) a significant association between smoking and the risk of developing RA, especially seropositive RA, was found among men. In another recent study, duration of smoking was connected with the risk of RA among over 300,000 female healthcare professionals (Karlson et al. 1999). Another possible risk factor might be coffee consumption, which was associated with RF positive RA in a recent study (Heliövaara et al. 2000). No other environmental factor predisposing for RA has so far been found.

The influence of hormonal factors has been debated due to higher incidence of RA among women, especially after menopause. Pregnancy itself appears to reduce the risk of developing RA, but 12 months after delivery the risk appears to increase (Silman et al. 1992). Brennan and colleagues reviewed 17 studies investigating the possible effect of oral contraceptives (OC) on the risk of developing RA, and in 11 studies OCs were found to have a protective effect, but in six other studies no such effect was found (Brennan et al. 1997). In their own studies based on 115 incident cases, current use of OCs appeared to prevent development of RA.

The prevalence of RA varies between 0.5% and 1.0% in most western adult populations (Gran 1987). In Finland the prevalence of seropositive RA in the population ≥ 30 years of age was 0.8% in the Mini-Finland study carried out during 1978-1980 (Aho et al. 1989). In a later study by Hakala and associates (Hakala et al. 1993a) the prevalence of RA satisfying the American Rheumatism Association (ARA) 1987 criteria was 0.8% in the community of Kuusamo in northern Finland. Most studies have shown a female-to-male excess of between 2 and 3 times (Linos et al. 1980, Symmons et al. 1994, Kaipiainen-Seppänen et al. 1996).

The annual incidence rate of RA in a population-based study from Norfolk, UK, between 1990 and 1991 was 0.36/1000 in females and 0.14/1000 in males (Symmons et al. 1994). In men the rate of incidence increased sharply with age compared with females in whom the rate of incidence remained quite stable between the ages of 45 and 75 years and then declined later on. In Finland the incidence of RA has declined during the recent decades: in the 1980s the incidence was 38-39 /100,000, but in 1995 it was only 34/100,000 (Kaipiainen-Seppänen et al. 1996, Kaipiainen-Seppänen and Aho 2000). Similar trends have been observed in the USA (Doran et al.
2002). At the same time the mean age at disease onset has increased from 52.3 years to 59.0 years (Kaipiainen-Seppänen and Aho 2000).

### 3.2 Diagnostic and classification criteria

In 1956 the ARA introduced the diagnostic criteria for RA (Ropes et al. 1956), but 2 years later these criteria were updated with minor changes (Ropes et al. 1958). These 1958 ARA criteria were the most widely used, especially in clinical trials, until new, revised criteria were published in 1988 (Arnett et al. 1988). The main difference between these ARA 1987 revised criteria for the classification of RA and older criteria was that the newer ones designated only one single disease compared with older criteria that defined RA with various degrees of certainty as classical, definite, probable and possible. According to the ARA 1958 criteria the diagnosis of classical RA required at least 7 of the 11 possible criteria (Table 1), the definite RA required 5 of the 11 criteria, probable RA at least 3 of the criteria and possible RA at least 2 of the following 6 criteria: morning stiffness (MS), tenderness or pain on motion, joint swelling, subcutaneous nodules, elevated ESR or C-reactive protein (CRP) and iritis. Another difference between these two criteria is that in ARA 1987 criteria changes in hand and finger joints are emphasized (criteria 3 and 7). In clinical trials, standardizing of patients must be based on universally accepted criteria, although among individual patients they are not always helpful due to the variation in the clinical picture of RA.
**Table 1**

Comparison of the 1958 ARA criteria and the revised ARA 1987 criteria for the classification of rheumatoid arthritis

<table>
<thead>
<tr>
<th>1958 criteria</th>
<th>1987 criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Morning stiffness</td>
<td>1. Morning stiffness of $\geq$ 1 hour</td>
</tr>
<tr>
<td>2. Pain on motion or tenderness in at least 1 joint</td>
<td>2. Arthritis in 3 or more joint areas$^2$</td>
</tr>
<tr>
<td>3. Swelling in at least 1 joint</td>
<td>3. Arthritis in a hand joint (PIP, MCP, wrist)</td>
</tr>
<tr>
<td>4. Swelling in at least 1 other joint</td>
<td>4. Symmetric swelling of 1 joint area (as defined in 2)</td>
</tr>
<tr>
<td>5. Symmetric joint swelling</td>
<td>5. Rheumatoid nodules</td>
</tr>
<tr>
<td>6. Rheumatoid nodules</td>
<td>6. Positive rheumatoid factor</td>
</tr>
<tr>
<td>7. Radiographic changes$^3$</td>
<td>7. Radiographic changes in hand and/or wrist joint$^3$</td>
</tr>
<tr>
<td>8. Positive rheumatoid factor</td>
<td></td>
</tr>
<tr>
<td>9. Poor synovial fluid mucin precipitate</td>
<td></td>
</tr>
<tr>
<td>10. Positive synovial biopsy</td>
<td></td>
</tr>
<tr>
<td>11. Positive nodule biopsy</td>
<td></td>
</tr>
</tbody>
</table>

$^1$Criteria 1-5 (1958) and criteria 1-4 (1987) must have been present for at least 6 weeks

$^2$Right or left proximal interphalangeal (PIP), metacarpophalangeal (MCP), wrist, elbow, knee, ankle and metatarsophalangeal (MTP) joints

$^3$Erosions or periarticular osteopenia present

### 3.3 Clinical course

The natural history of RA varies from self-limited, nonerosive to severe, destructive disease. The onset may be acute, subacute or insidious, which is the most common type. RA may begin as monoarthritis from one joint and then gradually spread to other joints, or as polyarthritis. One variation of acute-onset RA is palindromic rheumatism, in which variable episodes of mono- and polyarthritis lasting from hours to some days or weeks are followed by spontaneous remissions and symptom-free periods. Often palindromic RA gradually progresses to a continuously active disease (Guerne and Weisman 1992).
It has been estimated that in approximately 10% of patients the clinical course of the disease is continuously progressive (Masi 1983). However, in most patients the disease follows a relapsing-remitting or continuously active pattern, in which the remissions usually are incomplete. Whether the type of onset or pattern of disease has any prognostic value is not clear. Some evidence is available that insidious onset may mean a poor prognosis (Fleming et al. 1976). In contrast other studies (Jacoby et al. 1973, Luukkainen et al. 1983, Sherrer et al. 1986) have suggested that the type or site of onset had no prognostic value.

The presence of differences in the clinical picture and course of disease in different age-groups has long been. Female-to-male ratios among older RA patients have been almost equal compared with the 2-3:1 seen among younger patients in many studies (Terkeltaub et al. 1983, Deal et al. 1985, van der Heijde et al. 1991, van Schaardenburg et al. 1993). The acute type of disease onset has been observed more frequently among elderly patients (Terkeltaub et al. 1983, Deal et al. 1985, van der Heijde et al. 1991), although the difference has not always been significant. The site of onset has also varied according to age at onset, since younger patients tend to have only small joint involvement (46 - 56% of the patients) compared with large joint involvement (either alone or in association with arthritis of the small joints) among older patients (Deal et al. 1985, van der Heijde et al. 1991).

The clinical course of the disease includes activity different time points and the ultimate outcome. The clinical activity of the disease can be assessed using different clinical measurements (number of affected joints, laboratory parameters, symptoms and signs such as duration of MS etc.). Functional disability, which can already be apparent in the early stages of the disease, and the radiographic changes indicating permanent destruction of joints are often considered as long-term outcome measures. The final outcome of RA includes work disability, comorbidities and premature death.

### 3.4 Antirheumatic treatments

#### 3.4.1 Traditional DMARDs

The aim of antirheumatic treatment is not only to relieve the symptoms and signs of the disease, but also to prevent permanent structural damage of the joints. The first studies from 1930s
already showed that gold compounds had beneficial effects on both clinical signs and functional capacity in RA patients (Forestier 1935), and therefore gold was considered as a drug of choice in the treatment of active RA for many decades in most countries, including Finland. However, the effect to retard radiographic progression among RA patients treated with aurothiomalate was first shown in 1974 (Sigler et al. 1974). During the 1930s RA was believed to have an infectious aetiology, and this led to the introduction of SASP during the 1940s for the treatment of RA (Svartz 1941, 1948). It was not until 3 decades later, after encouraging results by McConkey et al. (1980), that SASP became an alternative to gold compounds in the treatment of RA. The effect of SASP was considered to be equal to that of aurothiomalate, but with fewer adverse effects. In 1987 it was reported (Pullar et al. 1987) that SASP appeared to slow the radiographic progression in RA. Since the 1950s, the antimalarials (hydroxychloroquine and chloroquine), and later on auranofin and D-penicillamine, have been used for RA. With less efficacy or more toxicity their role has remained less significant compared with that of aurothiomalate.

3.4.2 Modern DMARDs

During the late 1980s and early 1990s drug treatment of RA changed dramatically. Firstly azathioprine, cyclosporine, later on leflunomide, and especially methotrexate began to gain ground, and now for almost a decade methotrexate has been the most widely used DMARD in the world. In 2001 methotrexate was the most widely used DMARD in Finland among patients with rheumatic diseases (Klaukka and Kaarela, personal communication). In 1985 Williams and coworkers published a placebo-controlled study of 189 treatment-resistant RA patients who were given methotrexate for 18 weeks (Williams et al. 1985). In this study, a statistically significant difference in laboratory variables was observed, although one-third of patients had to be withdrawn due to side effects as well. When the efficacy of aurothiomalate, SASP, D-penicillamine and methotrexate were compared, Felson and associates found no difference between any of these drugs in 1990 (Felson et al. 1990). However, later studies showed that the probability of continuing DMARD therapy is highest with methotrexate (Pincus et al. 1992a, Maetzel et al. 2000), indicating that methotrexate as a single therapy might be the drug of choice in RA.
3.4.3 Treatment strategies

Previously RA was treated traditionally, using a management pyramid. The base of this pyramid was rest, physical therapy, aspirin and nonsteroidal anti-inflammatory agents (NSAIDs). DMARDs were included only if the initial treatment failed. When the number of potential DMARDs was increased, the pyramidal strategy for treating RA was also questioned. In 1990 Fries proposed the so-called `sawtooth´ strategy for the treatment of RA (Fries 1990). This strategy included 6 principles: early DMARD use, continual serial DMARD use, regular quantitative monitoring of disability to detect insidious progression, setting a disability ceiling for the individual patient, sequential change in DMARD treatment when the ceiling is reached, and deployment of analgesics and NSAIDs as adjunctive rather than first line therapy.

3.4.4 Combination therapy

However, since the effects on disease activity or on radiographic progression of RA with single DMARDs were not satisfactory, initiation of combination therapy with 2 or more DMARDs has become increasingly popular. The first study on the use of successful combination therapy with gold and chloroquine was already published in 1963 in Finland (Sievers and Hurri 1963). Since then, results on the efficacy of combination therapies have been contradictory. In some studies combination therapy has not been more effective compared with single therapy alone, such as in studies on parallel use of methotrexate and azathioprine (Willkens et al. 1992) and on parallel use of methotrexate and SASP (Haagsma et al. 1997). On the other hand, many recent studies have shown that combination therapies are superior to single therapy, as in a study with cyclosporine and methotrexate (Tugwell et al. 1995), in which cyclosporine was included in the treatment in patients who were initially methotrexate failures. In parallel treatment with SASP, methotrexate and hydroxychloroquine among patients with advanced RA (O’Dell et al.1996) and among early RA patients in the Fin-RACo study the treatment with SASP, methotrexate, hydroxychloroquine and prednisolone (Möttönen et al. 1999) was also superior compared with single therapy. In a study by Sokka et al. (1999b) various combinations were more effective compared with single therapy with respect to radiographic progression.
3.4.5 Biological treatments

New biological treatments such as antitumor necrosis factor-α (anti-TNF-α) antibodies, soluble TNF-α receptors and interleukin-1 (Il-1) receptor antagonist have now become available, and more biological treatments are being developed. Short-term results with these new agents are very promising (Moreland et al. 1997, Bresnihan et al. 1999, Maini et al. 1999). TNF-α blockers appear to be able to retard radiographic progression more effectively compared with older DMARDs (Bathon et al. 2000, Lipsky et al. 2000) and Il-1 receptor antagonists have also been shown to decrease the appearance of radiographic changes compared with placebo (Breshinan et al. 1999). However, with no long-term results available, the exact role of these new treatments remains to be seen.

3.4.6 Timing and efficacy of the treatment

Timing of the initiation of DMARD therapy is very critical. As early as in 1935 Forestier (1935) suggested that gold treatment should be initiated as early as possible to obtain the best possible result from the treatment. In 1977 it was shown (Luukkainen et al. 1977) that there was a significant difference in the radiographic progression in hands and feet of patients with disease duration of < 10 months before initiation of aurothiomalate compared with patients with disease duration between 21 and 36 months before the initiation of gold therapy. In another study (Egsmose et al. 1995) early RA patients with disease duration of < 2 years were divided into 2 groups: the first group began auranofin treatment at the entry of the study and the other group, after initial treatment with placebo, began auranofin after a delay of 8 months. After a 5-year follow-up a significant difference in clinical variables and radiographic progression was observed between these 2 groups. Not only the timing of DMARD therapy initiation but also the effectiveness of the DMARD therapy affects the radiographic and clinical outcome. Stenger et al. (1998) and Albers et al. (2001) showed that early, aggressive treatment resulted in the reduction of radiographic progression and better clinical outcome compared with conventional treatments.

3.4.7 DMARD therapy and remissions

The aim of antirheumatic treatment should not only be the retardation of radiographic progression but also the induction of remission. In 1981 the ARA defined preliminary remission criteria (Pinals et al. 1981). These criteria include: MS absent or not more than 15 min, no fatigue, no
joint pain by history, no joint tenderness, no joint or tendon sheath swelling, and no elevation of ESR. The presence of at least 5 out of these 6 criteria is required for clinical remission. The rate of spontaneous remissions is estimated to be 14% and with conventional single therapy the rate is approximately 18% (Wolfe and Hawley 1985). Most commonly, remissions appear early in the course of RA and are transient. In a Finnish study of early RA patients treated according to the `sawtooth´ strategy (Fries 1990), 27% attained remission after a 2-year treatment and after a follow-up of 5-6 years the remission rate had increased to 31% (Möttönen et al. 1996). Despite the high remission rate, 89% of the patients in remission had erosions at their last visit. In the Finnish RACo trial (Möttönen et al. 1999) the remission rate after a 2-year follow-up among patients receiving combination therapy was approximately 40%. The highest remission rate of 50% has been achieved with the combination of cyclophosphamide, azathioprine and hydroxychloroquine (Csuka et al. 1986). Unfortunately, this triple therapy caused a number of side effects such as malignancies and at least 3 deaths (10% of all patients).

3.4.8 Factors contributing to the effect of treatment

The response to various antirheumatic therapies can be evaluated according to the American College of Rheumatology (ACR) 20% improvement criteria (Felson et al. 1995). These criteria include 20% improvement in tender and swollen joint counts and 20% improvement in 3 out of 5 remaining measures: patient and physician global assessments, pain, disability and an acute-phase reactant. However, these criteria are of limited use, since they leave out the radiographic changes, which are markers of permanent joint damage. On the other hand, these criteria make it easier to compare different studies. In a large meta-analysis from 14 trials of second-line drugs in RA, factors predicting favourable response to treatment according to these criteria were evaluated (Anderson et al. 2000). In addition to longer disease duration, any prior use of DMARDs, higher disease functional class according to Steinbrocker criteria (Steinbrocker et al. 1949), low disease activity (according to patient’s global assessment) and female sex predicted lower response rates to any DMARD therapy. Although age is known to affect drug metabolism, elderly patients with RA appear to respond to DMARD therapy equally well compared with younger patients (Kean et al. 1983, Wolfe and Cathey 1991, Pincus et al. 1992a).
3.4.9 DMARD therapy and side effects

In addition to inefficacy, adverse effects may result in treatment termination. In a study by Situnayake et al. (1987), 37% of those patients who were on SASP, 41% of those on penicillamine and 57% of those on gold therapy had stopped taking their medication due to side effects. Pincus and coworkers (1992a) studied the probability of continuing DMARD therapy. They observed that the median time of continuing different DMARDs varied between 10 (auranofin) and > 60 months (methotrexate), and in 19-45% the reasons for discontinuation were toxicity.

3.5 Evaluation of radiographic progression

Radiographic progression is known to begin in the early course of the disease. It was already shown in 1977 that 71.3% of early RA patients developed erosive changes during the first 5 years of the disease (Brook and Corbett 1977) and the erosions occurred earlier in the feet than in the hands. Later studies have emphasized that the appearance of erosions is most rapid during the first 2-3 years (Möttönen 1988, van der Heijde et al. 1992, Paimela 1992a). Although the pattern of progression may vary among individual patients (Graudal et al. 1998), on the average the progression rate appears to remain stable during longer follow-ups (Jäntti et al. 2002). On the other hand, radiographic remissions have been shown to occur in 26% of RA patients in a 20-year follow-up study (Jäntti et al. 2001). Despite the presence of radiographic remissions, most patients develop erosive changes during long-term follow-up (Kaarela et al. 1993).

Evaluation of radiographs can be performed in several ways. Larsen and Sharp developed the 2 most widely used scoring methods. The Larsen score was introduced in 1974 (Larsen 1974), but it was soon modified by Larsen, Dale and Eek (Larsen et al. 1977). In this internationally established version of Larsen’s scoring method, each individual joint was graded from 0 to 5 with respect to the degree of radiographic damage. This scoring system can be applied to most joints. The joints that are often evaluated include 10 MCP joints, IP joints of both thumbs, 8 PIP joints of the fingers, 10 MTP joints (or excluding the first MTP joints due to the common occurrence of osteoarthritis in these joints), IP joints of both toes, both wrists and sometimes subtalar joints, and both wrist and the subtalar joint scores may be multiplied by 5 to obtain the maximum total
score of 260. Larsen´s scoring system was later modified later in 1995 (Larsen 1995, Scott et al. 1995) and in 1997 (Kaarela and Kautiainen 1997).

Sharp and his colleagues introduced their method initially in 1971 (Sharp et al. 1971). This method included assessments of the degree of both joint space narrowing in 27 and bony erosions in 29 different joint areas in the hands and wrists. In 1985 Sharp and co workers reproduced a simplified scheme using a combination of 17 joints to score erosions and 18 joints to score joint space narrowing (Sharp et al. 1985). Since Sharp’s original method included only evaluation of the hand and wrist joints, a modified Sharp’s method was developed by van der Heijde et al. (1989) to account for the assessment of foot joints as well.

These radiographic scoring systems are useful methods in allowing comparison of the results of different studies and giving an estimation of disease progression. However, the healing phenomena of erosive changes, which are known to occur even in the early phases of RA (Jalava and Reunanen 1982, Rau and Herborn 1996), are rarely reported in any studies. The inability to detect reparative changes limits the ability of these radiographic scoring systems to observe the actual progression of the disease.

3.6 Predicting radiographic progression

3.6.1 Laboratory markers

The development of radiographic erosions in patients with RA is accepted as a reliable and objective measure of disease outcome. Since the first radiographic changes appear early during the disease course, reliable measures for predicting these high-risk patients are needed. Of the conventional laboratory measures used, high baseline ESR and/or CRP values have been associated with poor prognosis in many studies (Fex et al. 1996, Meyer et al. 1997, Möttönen et al. 1998). Nearly all studies at present agree that the presence of RF predicts a poor prognosis. The high level of initial RF and the persistently high RF level have been shown to predict more destructive disease in one study (Paimela et al. 1995). In a recent study an association with rapid radiographic progression and the presence of perinuclear antineutrophil cytoplasmic autoantibodies (pANCA) was found, and the progression was also correlated with the level of baseline pANCA (Mustila et al. 2000). Other antibodies, e.g. antinuclear, antikeratin and
antiperinuclear, have also been analysed, but so far only antikeratin antibodies have been
associated with poor prognosis (Paimela et al. 1992b, Meyer et al. 1997). One problem with these
inflammatory markers is that they are nonspecific.

In addition to these markers measuring overall inflammation, markers reflecting either
inflammation in the synovium or changes in the metabolism of cartilage or bone as predictors of
joint destruction have been extensively investigated. The high level of serum hyaluronan, which
appears to be derived from inflamed synovium in RA patients, has been associated with increased
radiographic progression (Paimela et al. 1991). However, the predictive value of hyaluronan was
no better than that of ESR or CRP in another study from Sweden (Fex et al. 1997). In the same
study other tissue-derived molecules, e.g. cartilage oligomeric matrix protein or bone
sialoprotein, were of no value in predicting joint destruction in the hands or feet.

The degradation product of type I collagen, which accounts for about 90% of the organic matrix
of bone and is also a major matrix protein in tendons, ligaments and soft connective tissues, is
associated with disease severity in RA (Hakala et al. 1993b). Furthermore, the serum levels of
this degradation marker, carboxyterminal telopeptide (ICTP), predict radiographic progression
during the first 3 years of RA (Paimela et al. 1994). The predictive value of elevated serum ICTP
(odds ratio (OR) 3.1) is even increased in the presence of positive serum RF (OR 9.1 with both
markers elevated; Åman et al. 2000).

All the above-mentioned markers can predict the destruction of joints in patient cohorts, but not
the progression in a single patient, and therefore cannot be used in clinical practice.

The role of genetic factors in predicting the disease outcome is controversial. The presence of the
shared epitope has been shown to predict destructive disease in early arthritis patients (Emery et
al. 1992). On the other hand, in other prospective studies of early RA patients HLA-DR4, HLA-
Dw4 or the shared epitope did not significantly affect the radiographic outcome (Young et al.
markers as predictors of RA outcome does not appear to play an important role in clinical
practice.
3.6.2 Other prognostic factors

3.6.2.1 Gender

In addition to laboratory measures, other clinical and demographic variables may also be used in predicting radiographic progression. Controversy exists regarding the importance of demographic factors. Compared with males, the female gender was associated with a higher radiographic progression rate in the study by Fex et al. (1996), while in the study by Uhlig et al. (2000) gender was not a predictor of radiographic progression. The difference in these results cannot be explained by the study design since both studies were prospective 5-year follow-up investigations of early RA patients, and the patients in both studies came from geographically similar surroundings.

3.6.2.2 Age and disease duration

Previous studies suggest that age does not appear to have significant prognostic value in predicting radiographic outcome (van der Heijde et al. 1991, van Schaardenburg et al. 1993), although some tendency toward more progression among elderly patients has been previously observed (Ferraccioli et al. 1984, Kuiper et al. 2001). Patients with short histories of joint symptoms at presentation appear to have better prognosis with respect to radiographic progression than patients with longer disease duration (Brennan et al. 1996).

3.6.2.3 Baseline radiographic changes

The effect of baseline radiographic damage on progression appears to be controversial. In some studies, where the prediction of radiographic destruction has been the major issue, the baseline values have been associated with radiographic progression (Luukkainen et al. 1983a, van der Heide et al. 1995, Uhlig et al. 2000). However, in other studies no correlation between baseline damage and progression of radiographic changes has been found (Scott et al. 1987, Möttönen et al. 1998, Wolfe and Sharp 1998a).
3.6.2.4 Clinical picture

The relationship between joint symptoms and radiographic outcome is debatable. There is some evidence that the number of swollen joints (Luukkainen et al. 1983b, Brennan et al. 1996, Möttönen et al. 1998) or the number of tender joints (Wolfe and Sharp 1998 a) correlates with radiographic outcome, but on the other hand other studies have found no correlation between clinical variables and radiographic progression (Coste et al. 1996, Fex et al. 1996). In conclusion, better tools for predicting radiographic outcome are needed, especially measures suitable for application in clinical practice when treating individual patients would be useful.

3.7 Functional disability

3.7.1 General

The functional status of RA patients can be evaluated quantitatively by using different physical measures, like grip strength (GS), walking time and button test, and questionnaires regarding activities of daily living. The two most widely used RA-specific questionnaires are the Stanford Health Assessment Questionnaire (HAQ; Fries et al. 1980) and Arthritis Impact Measurement Scales (AIMS; Meenan et al. 1980). The HAQ scores vary between zero (no disability) and 3 (severe disability). The HAQ is mainly focused on the activities of daily living (dressing, eating, hygiene, walking, household management), while AIMS also includes the impact of psychological and social stresses. Steinbrocker et al. (1949) introduced the first classification of functional capacity in 1949. In this classification functional capacity is divided into 4 classes, where Class I means complete functional capacity and Class IV largely or wholly incapacitated.

3.7.2 Factors affecting functional capacity

The development of functional disability, as in radiographic progression, is most rapid during the first years after disease onset (Sherr et al. 1986, Wolfe and Cathey 1991b). Among early RA patients the most important factors affecting functional disability include joint tenderness and ESR as a marker of inflammatory activity, whereas among patients with more established disease, declining functional disability is more related to the amount of joint destruction (Guillemin et al. 1992, Van Leeuwen et al. 1994, Scott et al. 2000). However, although the
importance of joint damage increases with time, disease activity has a significant influence on functional capacity throughout the course of RA (Drossaers-Bakker et al. 1999).

3.7.3 Predictors of functional outcome

During the course of RA, many patients show improvement in measures reflecting inflammatory activity, such as MS, but functional capacity remains low. To maintain functional capacity it would seem appropriate to initiate aggressive therapy as early as possible prior to irreversible damage. In a community-based study, 29% of 381 early inflammatory polyarthritis patients were functionally disabled after a 1-year follow-up (Harrison et al. 1996). In this short-term study the strongest predictors of future disability were high baseline HAQ, large joint involvement, female sex and longer disease duration. High baseline HAQ score or poor functional class have been the strongest predictors of functional outcome in many other studies as well (Scott et al. 1987, Pincus and Callahan 1992b, Eberhardt and Fex 1995, Jansen et al. 2000).

3.7.4 Age and functional capacity

Age has also been shown to predict functional disability in long-term studies. A retrospective study showed that, although functional capacity at the final visit was equal in both older and younger RA patients, at some point older patients tended to have greater functional incapacity than younger patients (Terkeltaub et al. 1983). In other studies age at the onset of disease, either alone or in association with the female gender, has also been shown to have predictive value (Sherrer et al. 1986, Scott et al. 1987, Kuiper et al. 2001).

3.7.5 Development of functional disability

Functional disability increases constantly as was shown in the long-term prospective study by Scott et al. (1987). This study consisted of 112 RA patients, of which 26 patients at baseline were in modified Steinbrocker functional class I/II, 70 in III and 16 in IV/V. After 20 years 19 patients were in class I/II, 29 in III, 20 in IV/V, 37 had died and 7 were lost to follow-up. In a private-practice rheumatic disease clinic in the USA, 1274 patients were followed up between 1977 and 1988, and the functional capacity was evaluated using HAQ scores. A total of 50% of all patients had attained a level of score 1 (moderate disability) in 10 years, score 2 (severe functional disability) in 20 years and score 2.5 (even more severe impairment) in 35 years (Wolfe and
In a prospective follow-up study of 681 RA patients, only 10% did not develop significant disability during a follow-up of approximately 11.9 years (Sherr  et al. 1986).

3.7.6 Effect of DMARD therapy on functional capacity

The effect of treatment on functional outcome has been evaluated in both short-term and long-term studies. Aurothiomalate improved the HAQ scores 45.3% from the baseline value in a 1-year follow-up study (Wolfe et al. 1993). Methotrexate, leflunomide, SASP and infliximab have also had beneficial effects on functional outcome in short-term trials of < 2 years (Maini et al. 1999, Smolen et al. 1999).

Reduction of long-term disability is associated with long-term DMARD use, as was shown in a long-term (approximately 9 years) follow-up of 2888 RA patients in 1996 (Fries et al. 1996). A significant difference in HAQ scores was found among patients with constant use of DMARDs compared to patients with no use of DMARDs. The effect of taking DMARDs was more pronounced in more seriously ill patients. Möttönen and coworkers evaluated the effect of aggressive treatment (using the `sawtooth´ strategy) on long-term functional disability in another prospective hospital-based follow-up study of 142 early RA patients (Möttönen et al. 1996). After an average of 6.2 years, 24% of patients had ended up in Steinbrocker functional class III or IV. In a community-based study of all subjects with RA (103 patients, mean disease duration 16 years) in Kuusamo (rural area in northern Finland), only 1 patient was in functional class IV, while according to the HAQ score two-thirds of the patients had only mild or at most moderate disability (Hakala et al. 1994). The lower level of disability in this particular population was explained by early and aggressive drug therapy and a high proportion of total joint replacements. The beneficial effect of early initiation of DMARD therapy on long-term functional outcome has been shown in various studies (Egsmose et al. 1995, Munro et al. 1998).

3.8 Work disability

3.8.1 General

RA has been shown to have an enormous impact on the working capacity of RA patients. Not only the activity of the disease, but also age at the onset of RA, educational level of the patient
and the work structure have been proposed as predictors for work disability (Mäkisara and Mäkisara 1982, Yelin et al. 1987, Reisine et al. 1995, Doeglas et al. 1995). The risk of losing work capacity begins during the early years of the disease (Fex et al. 1998, Barrett et al. 2000).

3.8.2 Early studies of work capacity among RA patients

In a large retrospective, hospital based study from Finland (Mäkisara and Mäkisara 1982), 405 RA patients treated in the Rheumatism Foundation Hospital, Heinola, between 1963 and 1978 were analysed. In all, 60% of patients who had had RA for 5 years, 50% with RA for 10 years and 33% with RA for 15 years were still working. As in functional capacity, work capacity was better in those patients who had developed their disease at early age. On the other hand, those patients with heavy work and/or lower educational levels were at greater risk of losing their work capacity. In another cross-sectional study from California (Yelin et al. 1987), in which 180 RA patients were interviewed concerning the impact of RA on work capacity, parallel figures were observed: 50% of the patients had stopped working after 10 years, 60% after 15 years and 90% after 30 years. The nature of work, age and functional level were factors contributing to the loss of work capacity.

3.8.3 Predictors of work disability

The predictors of work disability have been analysed in prospective studies of both early RA patients and patients with more advanced disease. In a large study, 823 RA patients (out of 1563 enrolled in a data bank at the Wichita Arthritis Center) were interviewed in 1994 regarding employment and work history (Wolfe and Hawley 1998). The mean disease duration was 5.8 years and mean age 52.6 years. A total of 509 patients had been employed since the arthritis had begun. In all, 25% of patients with disease duration of 6.4 years and 50% with duration of 20.9 years were not able to work, due to RA. In addition to the associations with educational level, work characteristics and functional status, it was shown that current smokers, nonwhites, obese and those with 2 or more comorbid conditions were more prone to lose their work ability. In another study from the USA, 498 employed RA patients with median disease duration of more than 5 years were followed up for 5 years, and during that time 34% of patients lost their work capacity (Reisine et al. 1995). In this study the risk of work disability increased with increasing age, more severe disease (measured by the number of deformed joints or the number of joints with flare), greater complexity of work tasks, reduced working hours and wanting to be home.
3.8.4 Early RA patients and work disability in Finland

Work disability develops early in the course of disease. Due to different study settings and heterogeneous social security systems in different countries, the results are variable. Patients with early RA were treated more actively during the late 1980s and 1990s and this may explain some of the differences between older and newer studies. In a Finnish 20-year prospective, early RA follow-up study, 31% of the patients were already unable to work after the first year, and after 20 years the number had increased to 80% (Jäntti et al. 1999). The follow-up of these 103 patients with very early seropositive RA (disease duration of less than 6 months) was begun between 1973 and 1975, and the DMARDs used during the first 8 years included aurothiomalate and/or chloroquine. The physical demands of work, age and severity of the disease appeared to contribute to the ability to work (Kaarela et al. 1987). In another prospective follow-up study from Finland (Sokka et al. 1999a) 82 patients with recent-onset RA (mean disease duration 6.4 months) were followed for a mean of 10 years. After 2 and 9.9 years since diagnosis, 19% and 44%, respectively, had retired merely because of RA. These patients were recruited at least 10 years later than patients from an earlier Finnish study and were treated according to the ‘sawtooth’ strategy with more DMARDs already available, which may explain at least some of the differences between these studies.

3.8.5 Other early RA studies and work disability

The results of work disability among early RA patients in various studies are shown in Figure 1. The majority of patients in a Swedish study (Fex et al. 1998) stopped working during the first year after disease onset, in other words before referral to rheumatologist. A total of 78% of those patients who continued to work had to adjust their working conditions (reduced working hours, change in work tasks, re-education) due to RA. In a German study, the most rapid decline occurred during the first 3 years (Mau et al. 1996). The highest numbers among early RA patients (disease duration of less than 1 year at the entry of follow-up) were obtained from the Netherlands, where the risk of work disability appeared to be 4-15 times higher among RA patients than in the general population: after a 3-year follow-up 42% of patients and after 5 years 72% had already lost their work ability (Albers et al. 1999). The relative risk of work disability among females was 14.5 compared with 4.1 among men. Other baseline risk factors for work disability in these prospective early RA studies have included poor functional capacity,

![Work disability among early RA patients](image)

**Figure 1.** Work disability in various early RA studies.

### 3.9 Mortality

#### 3.9.1 General

Most studies have associated RA with shorter life expectancy (Mitchell et al. 1986, Isomäki 1992, Jacobsson et al. 1993, Pincus et al. 1994, Wolfe et al. 1994, Myllykangas-Luosujärvi et al. 1995a, Gabriel et al. 1999a, Kvalvik et al. 2000). The reduction in median life expectancy has varied from 3 to 10 years in females (Myllykangas-Luosujärvi et al. 1995a, Mitchell et al. 1986) and from 4 to 7 years in males (Vandenbroucke et al. 1984, Myllykangas-Luosujärvi et al. 1995a). During the first 5 years of RA, the mortality rates of RA patients are similar to those of the general population, but the rates increase gradually thereafter (Young and van der Heijde 1997). The SMRs, which express the numbers of observed deaths compared with the expected
numbers of deaths in the general population, have usually varied from 1.1 to 3, depending on the follow-up period and study settings. Despite all the improvement in the field of RA treatment and understanding of the pathogenesis of RA, the excess mortality associated with RA has not changed during recent decades (Gabriel et al. 1999a).

3.9.2 Mortality in population-based studies

Few population-based studies are available on mortality among RA patients. In an epidemiological study from Rochester, Minnesota, the mortality among RA patients was not increased compared with that of the total population during the follow-up period of 1950-1974 (Linos et al. 1980). In other studies increased mortality rates have been observed, although usually lower than in clinic-based studies. In a large longitudinal epidemiological study conducted among 2979 Pima Indians between 1965 and 1989, age- and sex-adjusted mortality rates were slightly higher in RA subjects than in subjects without RA (mortality ratio 1.28) (Jacobsson et al. 1993). Risk factors for increased mortality included older age, male gender and proteinuria in both RA and non-RA subjects and positive RF among RA patients. In another community-based study from Finland poor functional status, as measured by the lower extremity component of the Keitel function test (Keitel et al. 1971) was the strongest predictor of mortality (Söderlin et al. 1998).

3.9.3 Mortality in hospital-based studies

Hospital-based studies have usually shown greater mortality rates, compared with community-based studies. The differences between patient cohorts may vary considerably, depending on patient selection (age, gender), disease duration or possibly also between therapies administered to patients. In a large study by Wolfe et al. (1994), 3501 patients (mean disease duration 7.3-14.2 years) from 4 different centres were followed up between 1965 and 1990 (9-35 years of follow-up, depending on the centre). Mortality rates in this cohort were over 2-fold higher (SMR 2.26) and the rate increased with time. In another study Mitchell and colleagues observed an increase of 50% in the mortality rates in a 12-year follow-up study of 805 RA patients with mean disease duration of 10 years at study entry (Mitchell et al. 1986). Factors predicting mortality included higher age, RF, male sex, poor functional ability and increased number of affected joints. In Birmingham UK, 448 patients with RA, assembled during 1968-1974, were followed up to 1990 and by the end of follow-up 59% of the patients had died (SMR 2.7). These patients were divided
into 2 groups according to the duration of RA: those patients with disease duration of less than 5 years at entry had a significantly lower mortality rate (SMR 2.5) after an 11.4-year follow-up compared with patients with longer disease duration at entry (SMR 3.6 after 11.4 years of follow-up), and the same trend continued towards the end of the study (Symmons et al. 1998). In a recent 17-year prospective study of 187 RA patients from Norway (Riise et al. 2001), the mortality rate ratio was twice as high compared with the control age-and gender-matched population. This study may be considered as a population-based study, since all RA patients in this area of 225 000 inhabitants are referred to the only referral centre in the study area. The influence of the presence of RF on the mortality rates differs from that shown by previous studies (Mitchell et al. 1986, Wolfe et al. 1994), since in this Norwegian study RF had no predictive value.

3.9.4 Early RA patients and mortality

The mortality rates in early RA patients have been evaluated in 3 different prospective follow-up studies. In a study from Finland (Isomäki 1992), 201 early RA patients with disease duration of less than 6 months were followed up and the combined outcome index (joint count, functional outcome, radiographic destruction and CRP/ESR) was calculated at the 8-year point. None of the individual factors or positive RF could predict mortality during the following 6 years as accurately as the outcome index at the 8-year point. In another study by Reilly et al. (1990), 100 early RA patients with disease duration of less than 1 year were followed up for 25 years. The SMR in this cohort was 1.4 and the favourable prognostic factors included better functional ability and lower ESR at the entry of the follow-up and also conversion to RF-negative or fall in RF level during the follow-up. In the latest study from Finland (Sokka et al. 1999c) 135 actively treated early RA patients were followed up for 8-14 years from the time of diagnosis and, although not statistically significant, increased mortality rates were observed especially among women. Twenty-five patients died during the follow-up and RA was closely related to death in 5 cases. Age was the only significant prognostic factor for mortality.

Although excess in mortality rates among RA patients has been found in most studies, some contradictory results have been observed. In 1995, a low mortality rate (SMR 1.09; 95% confidence interval (CI) 0.76-1.52) was observed in a 20-year follow-up of early RA patients with active treatment from disease onset in a Finnish study (Isomäki et al. 1995). More recently, in 2 prospective follow-up studies of early RA patients from Sweden (Lindqvist and Eberhardt 1999) and the Netherlands (Kroot et al. 2000), no increase in mortality rates was observed.
compared with control populations. In the study from Sweden 183 RA patients entered the study between 1985 and 1989. The mean disease duration at entry was 11 months and the mean follow-up period 9.8 years. Eighteen of the patients died during the follow-up, compared with 20 expected deaths. In only 2 cases was death contributed to by RA, while in other cases the causes of death did not differ from those in the general population. In the other study from the Netherlands, 622 patients with early RA (disease duration of less than 12 months) were followed up from 1985 to 1997, with a mean follow-up of 5.8 years. Most of these patients (95%) were treated at some point during the follow-up with DMARDs. The mortality rates in this study population were also comparable with those observed in the control population. Two patients died of amyloidosis and in 2 cases the death was attributed to treatment of RA; in both these studies the only predictors of death were male sex and age at entry. However, there were differences in improvement of functional capacity between these 2 study groups: in the Swedish study the functional capacity deteriorated during the first 5 years (Eberhardt and Fex 1995), but in the Dutch study (Kroot et al. 2000) the functional capacity improved, which could be explained by the active use of DMARDs.

3.9.5 Predictors of mortality

Predictors of the causes of mortality fall into 3 categories: disease burden (disease activity, disability), use of therapies, and sociological factors. Wolfe et al. (1994) and Pincus et al. (1994) showed that high joint count, accumulated erosions (damage) and disability are predictors for all causes of mortality among RA patients. Higher mortality has also been observed among patients with extra-articular features such as serositis and cutaneous vasculitis (Erhart et al. 1989, Turesson et al. 1999). Van Schaardenburg and associates showed a significant (69%) excess mortality among RA patients and positive RF, comorbidity and age were found to have predictive values in stepwise regression analysis (van Schaardenburg et al. 1993). The results were similar when all ages were analysed together or when elderly patients were analysed separately. In another study from Norway male sex, age and RF-positive RA increased the mortality risk among elderly patients (over 60 years) with recent onset arthritis (Glennås et al. 2000). Formal education level provides a significant predictive marker for mortality (Pincus and Callahan 1986) and is often considered as a surrogate marker for overall socioeconomic status.

The influence of RA as a disease itself on excess mortality as a primary or secondary cause of death in RA patients is difficult to evaluate. In most studies data on causes of death is based on
death certificates. Unfortunately, death certificates are not always reliably filled out and RA as a contributing factor may have been underestimated. Wolfe and coworkers estimated that 21.8% of 898 deaths in their 35-year follow-up of 3501 RA patients were either caused by or contributed to by RA (Wolfe et al. 1994). Higher figures from 33% up to 50% have been observed in other studies (Benn and Wood 1972, Allebeck 1982, Reilly et al. 1990).

3.9.6 Causes of death

The increased mortality is mainly due to cardiovascular diseases (CVDs) (Mutru et al. 1985, Jacobsson et al.1993, Myllykangas-Luosujärvi et al. 1995b, Symmons et al. 1998), infections (Vandenbroucke et al. 1984, Mutru et al. 1985, Mitchell et al. 1986, Myllykangas-Luosujärvi et al. 1995a), pulmonary (Wolfe 1996) and renal diseases (Mutru et al. 1985, Myllykangas-Luosujärvi et al. 1995b). The explanation for the increased risk of CVDs among RA patients is not clear, because the prevalence of known risk factors (hypertension, diabetes mellitus, smoking) has not usually been reported. However, there is evidence that the immunological / inflammatory mechanism of RA and coronary heart disease have some similarities (Pasceri and Yeh 1999). Increased levels of inflammatory markers, e.g. CRP, could also predict future myocardial events among healthy persons (Ridker et al. 1997). Pulmonary infections and generalized sepsis are the main infections present in RA patients. It is likely that the underlying RA disease process coupled with potent immunosuppressive treatments together contribute to this increased risk. Amyloidosis has been the major contributor to the excess in renal mortality among RA patients, especially in Finland (Mutru et al. 1985, Myllykangas-Luosujärvi et al. 1995a). Mortality rates due to malignant diseases overall do not exceed those observed among the general population, but the risk of haematological malignancies appears to be increased, especially among patients with longer-duration RA (Isomäki et al. 1978, Laakso et al. 1986, Wolfe et al. 1994, Myllykangas-Luosujärvi et al. 1995c, Symmons et al. 1998) and in those with high inflammatory activity and inadequate use of DMARDs (Bäcklund et al. 1998).

3.9.7 Effect of treatment on mortality

The effect of DMARD therapy on the mortality rates has not been widely studied. Lehtinen and Isomäki (1991) published their study, in which the effect of long-term gold treatment on mortality was evaluated. During the follow-up period (beginning between 1961 and 1966 and ending in 1989) 251 out of a total 573 RA patients had died. Long-term aurothiomalate treatment
was associated with a higher survival rate. In another Finnish study the mortality rates among early RA patients compared with those of the control population were slightly increased, although lower compared with other reports of early RA patients. These patients were actively treated according to the `sawtooth´ strategy (Sokka et al. 1999c).

The role of medication as a cause of death was studied in 1666 Finnish RA patients, who died in 1989. Forty-seven of the deaths were attributed to antirheumatic medication, of which 30 were NSAIDs (mostly gastrointestinal bleeding/perforation), 11 glucocorticoids (2 perforations of the lower intestinal tract, 5 osteoporotic fractures, 3 septicaemias and 1 adrenal insufficiency after abrupt discontinuation of treatment) and only 6 DMARDs (2 cases of bone marrow depression attributed to SASP and 2 to methotrexate, 1 lymphoma induced by azathioprine and 1 hydroxychloroquine intoxication; Myllykangas-Luosujärvi et al. 1995d). Patients treated with azathioprine have been shown to have an increased risk of contracting lymphoproliferative malignancies (Silman et al. 1988). It has been suggested that treatment with immunosuppressive therapy increases the 10- year risk of malignancy (and death due to malignancies), but not mortality from other causes in RA patients (Jones et al. 1996). There is also some evidence that methotrexate, which may give rise to serum concentration of homocysteine, a risk factor for CVDs, increases mortality and cardiovascular morbidity among RA patients (Landewe et al. 2000). To avoid the rise of homocysteine, rheumatologists are nowadays giving folic acid as a concomitant drug with methotrexate therapy. On the other hand, in another study a favourable response to methotrexate treatment among patients with severe RA was associated with reduced mortality (Krause et al. 2000). In addition to DMARDs and NSAIDs, there is also some evidence that corticosteroids may result in excess in cardiovascular mortality rates (Maxwell et al. 1994). The use of corticosteroids has also been shown to be a risk factor for serious NSAID-associated gastrointestinal side effects (Fries et al. 1991). However, a strong association was found between disease activity in RA patients, but not with any specific medication, and the risk of developing lymphoma in a large study from Sweden (Bäcklund et al. 1998). In conclusion, there is some drug-related excess mortality in RA patients, and most probably the most dangerous drugs are NSAIDs. The contribution of DMARDs to higher mortality rates among RA patients is not yet clear.
4. AIM OF THE STUDY

The purpose of the present study was to evaluate the effect of active DMARD treatment on the outcome of early RA patients. The study population consists of 150 early RA patients, who have been followed from the time of diagnosis and treated actively according to the ‘sawtooth´ strategy. The specific items for this thesis were:

1. To compare the effect of intramuscular gold and SASP on radiological progression in patients with early RA.

2. To evaluate the effect of age on the outcome of early RA patients.

3. To examine the effect of treatment on the outcome of very early RA patients treated within 4 months of the onset of symptoms.

4. To study the impact of early RA on work disability in early RA patients on active therapy.

5. To evaluate the impact of RA and its treatment on the mortality rates and causes of deaths among early RA patients.
5. PATIENTS AND METHODS

5.1 Patients

The study population consists of 2 different cohorts of patients. The first cohort was collected between 1986 and 1989 and these patients were followed up either in the Second Department of Medicine, Helsinki University Central Hospital or in the Department of Rheumatology in Helsinki City Hospital. The patients were referred either from the City of Helsinki or surrounding communities with a population of approximately 1 000 000 (out of which Helsinki consists of 500 000). The second cohort was collected between 1991 and 1993 and followed up in the Department of Rheumatology in Helsinki City Hospital. All patients in both cohorts were referred from primary healthcare centres or from private outpatient clinics for diagnostic and therapeutic purposes.

The first cohort of patients consists of 87 patients. All patients had to fulfil the ARA 1958 diagnostic criteria for definite or classical RA. The age of the patients was between 18 and 65 years and the duration of symptoms ≤ 12 months at study entry. Later the study was extended and a new cohort of 63 patients, with duration of symptoms ≤ 24 months and age ≥ 18 years, was collected. The patients in the second cohort fulfilled the 1987 revised criteria of ARA. No previous treatment with DMARDs or oral corticosteroids was permitted in either cohort; only NSAIDs were allowed. The baseline demographic and clinical characteristics of the patients are shown in Table 2.

One patient from the first cohort has been lost to follow-up and he has been excluded from all except one study. The number of patients included in different studies is variable. In the first study, which compared the effect of intramuscular gold and SASP treatments, only those patients with duration of symptoms < 1 year and under 66 years of age at onset were included (n = 128). In the second study, which evaluated the effect of age on the outcome, only those patients who were referred to Helsinki City Hospital (n = 113), were included. The third study dealing with the effect of treatment on the outcome of very early RA consisted of 149 patients. In the study on work capacity only those 102 patients who were working full time at the onset of RA were included. All 150 patients are included in the last study, which evaluated the mortality among early RA patients.
Table 2. Demographic and clinical variables of the patients in 2 cohorts at study entry.

<table>
<thead>
<tr>
<th></th>
<th>I cohort</th>
<th>II cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>87</td>
<td>63</td>
</tr>
<tr>
<td>Age, years, mean (range)</td>
<td>44.9 (18-65)</td>
<td>59.4 (27-83)</td>
</tr>
<tr>
<td>Duration of symptoms, months, median (range)</td>
<td>8 (2-12)</td>
<td>6 (2-24)</td>
</tr>
<tr>
<td>Gender, female, number (%)</td>
<td>69 (79%)</td>
<td>46 (73%)</td>
</tr>
<tr>
<td>Seropositive, number (%)</td>
<td>57 (65%)</td>
<td>55 (87%)</td>
</tr>
<tr>
<td>Erosive, number (%)</td>
<td>29 (33%)</td>
<td>46 (73%)</td>
</tr>
<tr>
<td>ESR, mm/h, mean (SD)</td>
<td>34 (25)</td>
<td>49 (31)</td>
</tr>
<tr>
<td>CRP, mg/l, mean (SD)</td>
<td>23 (29)</td>
<td>31 (34)</td>
</tr>
</tbody>
</table>

ESR = erythrocyte sedimentation rate, CRP = C-reactive protein

All patients were referred from primary health care centres or private outpatient clinics. The duration of symptoms before the first medical encounter and the time needed by a primary physician to refer the patient to a rheumatologist were recorded. The treatments (intra-articular corticosteroid injections, NSAIDs and antibiotic treatments) given to the patients prior to referral were recorded.

The patients entered the study at the time of diagnosis, when antirheumatic therapy was also initiated to all except 2 patients. Seventy-three patients received SASP as an initial drug, 73 received intramuscular gold (= aurothiomalate) and 2 hydroxychloroquine. Of those 2, who refused any medication at entry, one (female, seropositive and erosive disease at the onset) has not received any DMARDs during the 9 years of follow-up and the other patient (male, seropositive and nonerosive at the time of diagnosis, but later erosive disease) initiated SASP treatment after 40 months of follow-up. The reason for changing DMARD therapy included inefficacy, toxicity or remission. The nature of toxicity was recorded. If the initial medication had to be withdrawn either because of side-effects or inefficacy, other DMARDs individually tailored were used either as a single therapy or in combination. These other DMARDs included methotrexate, azathioprine, oral gold (= auranofin), D-penicillamine, cyclosporine, podophyllotoxine, and later also leflunomide and anti-TNF-α blocking agents. Low-dose oral corticosteroids (usually 5-7.5 mg prednisone daily) were used in 40% of patients during the
follow-up, either permanently or temporarily when clinically indicated. Most of the patients were also using NSAIDs, either regularly or as necessary.

5.2 Methods

5.2.1 Clinical evaluation

At entry in the study, the following demographic data were collected: possible family history of rheumatic diseases, comorbidities, educational level, type and physical demands of occupation and working capacity. The duration of symptoms before the diagnosis and type and site of onset of arthritis were also documented. A complete physical and rheumatological examination was conducted. Thereafter, patients were examined prospectively every 3 months during the first year, every 4 months during the second year, every 4-6 months during the third year and once or twice per year thereafter. The following data were collected at every visit: the number of tender (53 joints) and swollen joints (44 joints), Ritchie articular index (Ritchie et al. 1968), pain assessed by the visual analogue scale of pain (VAS; Scott and Huskisson 1976), duration of MS in minutes and GS of both hands by using a sphygmomanometer. Functional capacity was evaluated by using the HAQ (Fries et al. 1980). Changes in antirheumatic medications were also reported at every visit. The number of surgical operations performed for RA and the remissions, defined according to 1981 ARA preliminary remission criteria (Pinals et al. 1981) and changes in working capacity were recorded annually. The presence of extra-articular manifestations was recorded cumulatively.

5.2.2 Laboratory examination

Laboratory investigations were performed simultaneously with the clinical examination and these included ESR (Westergren’s method), CRP (quantitative immunoprecipitation), haemoglobin (=Hb), white blood cell count and platelet count, and also tests for liver and kidney function, according to safety guidelines. RF was determined either with the Waaler-Rose test (titres 1:64 or more were regarded as positive) or with nephelometry (values over 50 IU/ml were regarded as positive). In most patients RF was measured with both tests at entry in the study.
5.2.3 Radiological methods

Radiographs of hands, wrists and feet were examined at entry and after 1, 2, 3, 5, 7 and 10 years of follow-up. Radiographs of other joints were also examined when clinically indicated. The radiographs were evaluated according to the method of Larsen et al. (1977). The radiographs of the first cohort have been analysed up to 10 years, but the radiographs of the second cohort only up to 3 years. Joints included in the evaluation were: I-V MCP of both hands, I-V PIP of both hands, both wrists, I-V MTP joints of both feet and the IP joints of both toes. Each joint was graded from 0 to 5, using reference radiographs to reflect the degree of damage. Normal joints were assigned a Larsen score of 0, and joints with soft tissue swelling, periarticular osteoporosis or joint space narrowing were assigned a Larsen score of 1. The scores from wrists were multiplied by 5, resulting in a scale of total Larsen score from 0 to 210. The radiographs were blindly read by the same observer without knowledge of the clinical data.

However, the modified rules proposed by Scott et al. (1995) for the Larsen’s scoring system were followed. In this modification a score of 1 for periarticular osteoporosis/joint swelling was used only if these were major features (III).

5.2.4 Work disability

A total of 102 patients were working full time at study entry. At entry the following data on work-related characteristics were collected: occupation, educational level (the duration of education < 9 years, 9-12 years or > 12 years) and physical demands of the work (light-moderate-heavy). During follow-up the changes in occupation and the possible time and cause of retirement were recorded. Data concerning the working capacity of these patients were collected until October 2000.

5.2.5 Causes of death

In late October 2000, every patient file was checked to analyse the mortality and each patient was traced, whether still on continuous follow-up or not. The cause and time of death were identified from death certificates and, if available, from patient files. Mortality was expressed as SMR and the population estimates were obtained from the Official Statistics of Finland. The data concerning mortality were collected until October 2000.
5.3 Statistical methods

Survo C84 (I), BMDP (II-V), SPSS 10 (IV-V), Egret 2.0.31 (IV-V) and Stata 7.0 (IV-V) statistical programs were used to perform the statistical analyses. The Student’s t-test (I, III), Mann-Whitney rank sum test (I-IV) or Fisher-Freeman-Halton exact test (IV) were applied for comparisons of continuous variables between different patients groups, and chi-square test (I-V) for categorical variables. Paired t-tests (I), or Wilcoxon signed rank test (II-III) were used for comparisons within the groups. The changes between the two treatment groups (I) were compared by using the multivariate analysis of variance of repeated measures (ANOVA).

A life table curve was calculated for patients with permanent work disability, and differences in the life table curves with respect to educational level were analysed using the log rank test. The life table method excludes patients, who retired due to age, died or were lost to follow-up. The confidence intervals (CIs) were estimated according to the method by Kalbfleish and Prentice (1980). To determine the possible baseline factors predicting permanent work disability, univariate and stepwise logistic regression analyses were applied. Stepwise logistic regression analysis with forward selection was used to determine the optimal set of explanatory variables of the permanent work disability.

The Kaplan-Meier method was used to calculate the probability of survival. The ratio between the observed and expected numbers of deaths (SMR) was calculated with 95 % CI, assuming a Poisson distribution. The expected number of deaths was calculated on the basis of person-years of observation within 5 years of the study period, multiplied by the calendar year and age-specific death rates for Finnish men and women. The prognostic factors predicting the duration of survival time were analysed using univariate and multivariate proportional hazard regression models with robust variance estimate, referred to as Cox’s regression models.
6. RESULTS

6.1 General

Among the study population the median (range) time between the initial joint symptoms and the first medical contact was 2 (0-21) months. The median (range) time between the first medical encounter and referral to the rheumatologist was 1(0-23) month. In all, 72% of the patients were referred from primary health care centres, 11% from private rheumatologists and the rest from other specialists. The clinical picture (ESR, CRP, number of tender joints, Larsen score or HAQ) was similar irrespective to, whether patients were referred from primary care units or from specialists. Of the patients, 81% had been treated with NSAIDs, 10% received intra-articular corticosteroid injections and 7% were given antibiotics for joint symptoms before the diagnosis of RA was confirmed.

The median (range) time from the onset of symptoms to entry in the study was 7 (2-24) months. After initiating DMARD therapy a clear improvement in clinical variables was observed. The median CRP values attained normal limits and the median number of swollen joints remained very low (Table 3). Functional capacity improved in many patients, and after 7 years most of the patients had no or only slight difficulties in their daily activities. However, although clinical variables and functional capacity improved, significant radiological progression was observed despite DMARD therapy. After 3 years of follow-up only 11% of the patients had no erosive changes in their hands or feet compared with 50% at the time of diagnosis. Clinical data on the patients during follow-up is presented in Table 3.
Table 3. Clinical data (median, range) of 150 patients entering the study is presented up to 7 years. The number of DMARDs indicates the cumulative number of different therapies (single or combination).

<table>
<thead>
<tr>
<th></th>
<th>Study entry (n=150)</th>
<th>1 year (n=150)</th>
<th>2 years (n=149)</th>
<th>3 years (n=142)</th>
<th>5 years (n=122)</th>
<th>7 years (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of tender joints (0-53)</td>
<td>14 (0-40)</td>
<td>6 (0-49)</td>
<td>4 (0-48)</td>
<td>3 (0-44)</td>
<td>4 (0-53)</td>
<td>4 (0-48)</td>
</tr>
<tr>
<td>Number of swollen joints (0-44)</td>
<td>5 (0-32)</td>
<td>1 (0-24)</td>
<td>0 (0-26)</td>
<td>0 (0-26)</td>
<td>1 (0-23)</td>
<td>1 (0-23)</td>
</tr>
<tr>
<td>ESR mm/h</td>
<td>34 (4-130)</td>
<td>15 (1-115)</td>
<td>15 (2-117)</td>
<td>15 (2-125)</td>
<td>17 (1-101)</td>
<td>16 (1-85)</td>
</tr>
<tr>
<td>CRP mg/l</td>
<td>17 (0-136)</td>
<td>2 (0-109)</td>
<td>6 (0-118)</td>
<td>5 (0-90)</td>
<td>5 (0-126)</td>
<td>5 (0-166)</td>
</tr>
<tr>
<td>HAQ (0-3)</td>
<td>0.45 (0-2.4)</td>
<td>-</td>
<td>-</td>
<td>0 (0-3)</td>
<td>0.1 (0-2.8)</td>
<td>0.1 (0-3)</td>
</tr>
<tr>
<td>Number of DMARDs</td>
<td>0</td>
<td>1 (0-5)</td>
<td>2 (0-7)</td>
<td>2 (0-9)</td>
<td>3 (1-10)</td>
<td>3 (1-15)</td>
</tr>
</tbody>
</table>

The initial DMARD was changed due to inefficacy in 39% (57 patients) and adverse effects in 34% (50 patients). Twenty-two patients (15%) stopped their initial DMARD therapy due to remission. By the end of the first year of follow-up the median number of DMARDs used was 1 per one patient and up to the end of the second year the respective number was 2. The mean (SD) time during which the initial DMARD was continued was 1.5 (1.6) years. Treatment of the patients during the first 7 years is shown in Table 4.
Table 4. Treatment with DMARDs of patients with early rheumatoid arthritis during the first 7 years.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>At study entry (N=150)</th>
<th>1 year (N=150)</th>
<th>2 years (N=149)</th>
<th>3 years (N=143)</th>
<th>5 years (N=128)</th>
<th>7 years (N=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gold sodium thiomalate</td>
<td>73 (49)</td>
<td>51 (34)</td>
<td>45 (30)</td>
<td>39 (27)</td>
<td>24 (19)</td>
<td>20 (16)</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>73 (49)</td>
<td>59 (39)</td>
<td>61 (41)</td>
<td>48 (34)</td>
<td>31 (24)</td>
<td>30 (24)</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>2 (1)</td>
<td>9 (6)</td>
<td>10 (7)</td>
<td>15 (11)</td>
<td>9 (7)</td>
<td>13 (10)</td>
</tr>
<tr>
<td>D-penicillamine</td>
<td>0 (0)</td>
<td>5 (3)</td>
<td>4 (3)</td>
<td>2 (1)</td>
<td>6 (5)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Auranofin</td>
<td>0 (0)</td>
<td>8 (5)</td>
<td>7 (5)</td>
<td>7 (5)</td>
<td>5 (4)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0 (0)</td>
<td>5 (3)</td>
<td>13 (9)</td>
<td>22 (15)</td>
<td>32 (25)</td>
<td>34 (27)</td>
</tr>
<tr>
<td>Podophyllotoxine</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (1)</td>
<td>3 (2)</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0 (0)</td>
<td>3 (2)</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Biologicals</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Strategy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No drugs</td>
<td>2 (1)</td>
<td>19 (13)</td>
<td>19 (13)</td>
<td>28 (20)</td>
<td>34 (27)</td>
<td>32 (26)</td>
</tr>
<tr>
<td>Single therapy</td>
<td>148 (99)</td>
<td>121 (81)</td>
<td>114 (77)</td>
<td>91 (64)</td>
<td>78 (61)</td>
<td>75 (60)</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>0 (0)</td>
<td>10 (7)</td>
<td>16 (11)</td>
<td>24 (17)</td>
<td>16 (13)</td>
<td>18 (14)</td>
</tr>
</tbody>
</table>

6.2 Comparison of the effect of intramuscular gold and sulphasalazine on radiographic outcome (I)

6.2.1 General

This was an open, uncontrolled study. At the time of diagnosis an equal number of patients (73 patients) were started on intramuscular gold and SASP as the first DMARD. Since the age distribution between these 2 treatment groups was slightly different and to avoid the effect of age on side effects, only patients under 66 years of age at onset were included in this study. The follow-up time was 1 year. Seventy patients were started on intramuscular gold and 58 patients
with SASP. At the start, the age and sex distribution was equal in both groups and no difference was observed in clinical variables. Only disease duration at the time of diagnosis was longer in patients starting intramuscular gold (7.7 months vs 5.8 months, p < 0.001). After 1 year 42 patients were still continuing intramuscular gold and 30 SASP. The reasons for discontinuing gold therapy were inefficacy in 7 patients (10%) and adverse effects in 20 patients (29%). In the SASP group, 12 patients (21%) withdrew due to lack of response and 14 patients (24%) for side effects. None of the side effects in either group were life-threatening. The numbers of patients discontinuing the treatment in the 2 groups did not differ statistically significantly.

6.2.2 Effect of the initial treatment

The effect of treatment was evaluated only in those patients continuing the initial treatment for at least 1 year. The improvement in all clinical variables except in GS (Table 5) was statistically significant and equal in both groups and the only difference was that the effect of SASP on ESR, pain and Ritchie index appeared earlier. Despite the therapy with intramuscular gold or SASP, however, significant radiological progression was observed. At entry the mean (SD) Larsen score was 5.5 (5.8) in the intramuscular gold group and 8.9 (9.2) in the SASP group (difference not statistically significant). After 1 year the Larsen score was 11.7 (9.0) in the intramuscular gold group and 14.5 (13.2) in the SASP group. Although the change was greater in patients receiving intramuscular gold, the difference was not statistically significant. In 9 out of 30 patients (30%) who continued SASP treatment throughout the study period, and in 8 out of 48 patients (19%) who continued intramuscular gold treatment, no radiological progression was observed. However, no significant difference in the baseline values (ESR, CRP, Ritchie index, number of swollen joints, VAS, GS, MS) was observed between those patients with radiographic progression and those patients with no progression, except for the Ritchie index in the gold group (11.5 in those with progression compared with 7.5 in those with no progression, p = 0.04).
Table 5. Clinical variables (mean, SD) in intramuscular gold (GOLD) and sulphasalazine (SASP) groups are presented at entry (0) and after 1 year (1) of follow-up. Statistical significance is calculated within each group.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ESR mm/h</th>
<th>CRP mg/l</th>
<th>Ritchie index</th>
<th>GS kp/cm²</th>
<th>MS min</th>
<th>Pain cm</th>
<th>Larsen score</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD (0)</td>
<td>35 (25)</td>
<td>26 (28)</td>
<td>11 (7)</td>
<td>0.5 (0.2)</td>
<td>113 (100)</td>
<td>3.1 (2.4)</td>
<td>4.8 (5.3)</td>
</tr>
<tr>
<td>GOLD (1)</td>
<td>19 (17)</td>
<td>13 (14)</td>
<td>5 (5)</td>
<td>0.6 (0.3)</td>
<td>29 (66)</td>
<td>1.3 (2.1)</td>
<td>11.7 (9.0)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td>0.0005</td>
<td>&lt; 0.0001</td>
<td>0.9973</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>SASP (0)</td>
<td>40 (25)</td>
<td>30 (27)</td>
<td>10 (5)</td>
<td>0.5 (0.3)</td>
<td>108 (87)</td>
<td>4.7 (2.5)</td>
<td>8.7 (8.2)</td>
</tr>
<tr>
<td>SASP (1)</td>
<td>19 (21)</td>
<td>13 (7)</td>
<td>3 (4)</td>
<td>0.7 (0.3)</td>
<td>21 (34)</td>
<td>1.5 (1.7)</td>
<td>14.5 (13.2)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td>0.0008</td>
<td>&lt; 0.0001</td>
<td>1.0</td>
<td>&lt; 0.0001</td>
<td>0.0001</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

GS = Grip strength, MS = Morning stiffness, Pain = Visual analogue scale

In conclusion, both drugs were effective in reducing the clinical activity of the disease. No difference in the efficacy or tolerability between intramuscular gold and SASP were observed. However, there was significant radiographic progression in both treatment groups.

6.3 Effect of age on the 3-year outcome of RA (II)

6.3.1 General

The effect of age on the clinical picture at the onset, on the efficacy and tolerability of DMARD therapy and on the 3-year outcome was evaluated. A total of patients (referred to Helsinki City Hospital) were included in this study. The patients were divided into 2 groups according to the age at onset of RA: patients under 55.3 years at the onset of the follow-up were considered as early onset RA (EORA) patients (55 patients) and patients over 55.3 years as late onset RA (LORA) patients (58 patients). The cutoff point was chosen to be 55.3 years in order to keep the sizes of groups equal. The patients were treated similarly. Table 6 summarizes the baseline characteristics of the patients.
Table 6. Characteristics of the patients and clinical picture of RA at onset.

<table>
<thead>
<tr>
<th></th>
<th>EORA (n=55)</th>
<th>LORA (n=58)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female: male</td>
<td>42:12</td>
<td>41:17</td>
<td>0.6387</td>
</tr>
<tr>
<td>Age, median (range), yr.</td>
<td>46.4 (18.1-55.1)</td>
<td>62.1 (55.4-82.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Disease duration, median (range), months</td>
<td>8 (2-24)</td>
<td>6 (2-24)</td>
<td>0.02</td>
</tr>
<tr>
<td>RF-positive, %</td>
<td>78</td>
<td>85</td>
<td>0.5361</td>
</tr>
<tr>
<td>Erosive, %</td>
<td>69</td>
<td>66</td>
<td>0.8438</td>
</tr>
<tr>
<td>Type of onset:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Acute / subacute / insidious, %</td>
<td>13 / 64 / 24</td>
<td>31 / 48 / 21</td>
<td>0.06</td>
</tr>
<tr>
<td>First involved joint (%)</td>
<td>MTP (27)</td>
<td>MCP/wrist (33)</td>
<td>0.3678</td>
</tr>
</tbody>
</table>

Acute = within 1-7 days, subacute = within 1-4 weeks, insidious = within months

The first involved joint among EORA patients was the MTP in 27% and the MCP or wrists in 24%. On the other hand, the MCP or wrist joints were involved as the first joints in 33%, but the MTP joints only in 12% among LORA patients. At the time of diagnosis CRP (p = 0.02), ESR (p = 0.0002) and the Larsen score for hands (p = 0.02) were higher among LORA patients compared with EORA patients, but otherwise no significant difference between the groups was observed. The ESR and Larsen score for hands correlated with age, but none of the other variables showed any correlation with age.

6.3.2 Treatment

Of EORA patients 42% received intramuscular gold, 55% SASP and 3% hydroxychloroquine as the initial medication. In the LORA group 67% received SASP and 33% intramuscular gold. Most of the patients in both groups (87% of EORA and 81% of LORA patients) discontinued the initial DMARD during the 3-year follow-up due to side effects, remissions (6 patients in the EORA and 9 in the LORA group) or drug inefficacy. The number of patients experiencing adverse events was similar in the EORA (38%) and LORA (34%) groups and the difference in distribution of various adverse reactions was not statistically significant between the groups. A significantly higher proportion of LORA patients was under long-term corticosteroid treatment (42% vs 18%). Ten orthopaedic operations (synovectomies, arthrodeses or arthroplasties) were performed in both groups.
6.3.3 Outcome

All the clinical variables (ESR, CRP, Ritchie index, the number of swollen joints) in both groups showed significant improvement during the 3-year follow-up (Table 7). Only ESR was significantly higher among older patients at the end of the follow-up ($p = 0.02$). Unlike at the time of diagnosis, no correlation between age and any clinical variables was observed at the final visit. The number of patients in remission was evaluated annually and the highest remission rate was observed at the 3-year visit (32% of LORA and 38% of EORA patients). However, the differences in remission rates between the groups at any time did not attain statistical significance. During the study period more patients in the LORA group tended to have extra-articular manifestations (62% vs 28%) ($p = 0.0007$) and this was mainly due to the higher frequency of Sjögren’s syndrome (43% vs 11%, $p = 0.008$) and neuropathy (11% vs 0%, $p = 0.04$).

Despite favourable clinical response, the radiological changes progressed significantly in both groups. The progression rates were equal in both groups, whether total Larsen scores or Larsen scores for the hands or feet were evaluated separately. The only difference concerning radiological status was observed at entry in the Larsen score for hands.
Table 7. Clinical variables of 55 early onset RA (EORA) and 58 late onset (LORA) patients at entry (= 0 years) and after the 3-year follow-up (= 3 years). The numbers are presented as mean (SD). Comparisons are made between the initial and final values within the group.

<table>
<thead>
<tr>
<th></th>
<th>ESR</th>
<th>CRP</th>
<th>Ritchie</th>
<th>SJC</th>
<th>Tot. Larsen</th>
<th>Larsen-h</th>
<th>Larsen-f</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORA 0 years</td>
<td>34 (23)</td>
<td>20 (24)</td>
<td>10.6 (5.5)</td>
<td>6.3 (5.6)</td>
<td>8.5 (14.0)</td>
<td>4.2 (10.2)</td>
<td>4.1 (5.3)</td>
</tr>
<tr>
<td>EORA 3 years</td>
<td>19 (14)</td>
<td>8 (10)</td>
<td>4.5 (4.6)</td>
<td>2.4 (4.5)</td>
<td>29.4 (26.9)</td>
<td>17.7 (21.0)</td>
<td>12.0 (8.8)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td>0.0011</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LORA 0 years</td>
<td>52 (31)</td>
<td>37 (39)</td>
<td>12.1 (7.3)</td>
<td>6.9 (4.5)</td>
<td>10.9 (11.4)</td>
<td>7.5 (10.3)</td>
<td>3.7 (3.8)</td>
</tr>
<tr>
<td>LORA 3 years</td>
<td>29 (24)</td>
<td>14 (19)</td>
<td>5.7 (5.7)</td>
<td>3.5 (5.1)</td>
<td>29.9 (22.3)</td>
<td>20.7 (17.3)</td>
<td>10.9 (10.5)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>0.0003</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

SJC = the number of swollen joints, tot. Larsen = total Larsen score, Larsen-h = Larsen score for hands, Larsen-f = Larsen score for feet.

Three patients in the LORA group died during the 3-year follow-up, but none of the deaths was related to RA or treatment of RA. In conclusion, the disease onset was more active among elderly patients. However, clinical course, the radiological progression and the effect and tolerability of DMARD therapy were equal in both groups.

6.4 Effect of treatment on the outcome of very early RA (III)

6.4.1 General

In this study the 149 early RA patients were divided into 2 groups according to the duration of symptoms at study entry: 27 patients with very early RA (VERA) had symptoms less than 4 months at the time of diagnosis and 122 patients with early RA (ERA) more than 4 months. No difference between these 2 groups in baseline characteristics with respect to gender, age or the number of patients with erosive changes or RF at the time of diagnosis was observed. The clinical picture was more active at onset in the VERA group: the onset was acute (59%) or subacute (41%) in VERA patients compared with acute (12%), subacute (62%) or insidious (26%) in ERA patients (p < 0.001). The number of patients with large joint involvement (either alone or in association with arthritis of the small joints) was significantly higher among VERA patients (p =
0.009) compared with the patients with ERA. All clinical variables showed more activity in the VERA group and the difference was statistically significant in CRP (p = 0.0014), Ritchie index (< 0.001) and the number of swollen joints (p = 0.001). The activity of the disease was most probably the reason why VERA patients had significantly shorter duration of symptoms (mean, SD) before their first medical contact [1.3 (0.6) months vs 3.8 (3.8) months, p < 0.001]. The time (mean, SD) used by the first physicians to treat their patients before referring to specialists was also shorter in the VERA group compared with the ERA group [1.0 (0.6) month vs 2.9 (3.5) months, p=0.0041]. The radiological progression evaluated by the Larsen score per month of symptoms (mean, SD) before the initiation of DMARD therapy was also higher among VERA patients, indicating more active disease [2.5 (3.2) vs 0.9 (1.2), p = 0.0044].

6.4.2 Treatment and outcome

Intramuscular gold or SASP were the initial DMARDs in all VERA and in 97% of ERA patients. There were no significant differences in distribution of the initial DMARDs in these 2 groups. Two patients in the ERA group received hydroxychloroquine and 2 refused DMARD treatment at study entry. The cumulative number of DMARDs used in VERA patients was higher, although the difference was statistically significant only at the 2-year point (p = 0.046). The use of oral corticosteroids in VERA patients was significantly higher, also indicating more active disease: 70% of VERA patients were on either long-term or intermittent therapy compared with only 38% of ERA patients (p = 0.0047). Despite more active treatment in the VERA patients, CRP and Ritchie index remained significantly higher throughout the study period and the number of swollen joints was significantly higher at the 3-year point compared with ERA patients. The changes in all variables within each group were significant except for the number of swollen joints in ERA patients (Table 8). The initial functional capacity was significantly worse in VERA patients assessed with the HAQ score (p < 0.001). Improvement was observed only in the HAQ scores of ERA patients during the follow-up.
Table 8. Changes in 6 variables in 27 very early RA (VERA) patients and 122 early RA (ERA) patients at entry (= 0 years) and the end (=3 years) of the study. The numbers are presented as mean (SD).

<table>
<thead>
<tr>
<th></th>
<th>ESR mm/h</th>
<th>CRP mg/l</th>
<th>Ritchie index</th>
<th>SJC</th>
<th>Larsen score</th>
<th>HAQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERA 0 years</td>
<td>38 (27)</td>
<td>22 (27)</td>
<td>9.9 (6.0)</td>
<td>4.0 (4.5)</td>
<td>7.9 (11.4)</td>
<td>0.39 (0.39)</td>
</tr>
<tr>
<td>ERA 3 years</td>
<td>19 (14)</td>
<td>9 (13)</td>
<td>3.8 (4.2)</td>
<td>2.2 (4.2)</td>
<td>24.9 (23)</td>
<td>0.22 (0.34)</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>VERA 0 years</td>
<td>49 (32)</td>
<td>48 (41)</td>
<td>14 .4(6.3)</td>
<td>8.1 (5.2)</td>
<td>7.1 (8.4)</td>
<td>0.74 (0.62)</td>
</tr>
<tr>
<td>VERA 3 years</td>
<td>30 (30)</td>
<td>19 (18)</td>
<td>6.8 (6.6)</td>
<td>5.1 (5.5)</td>
<td>29.5 (26.8)</td>
<td>0.62 (0.82)</td>
</tr>
<tr>
<td>P-value</td>
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<td>0.0019</td>
<td>0.0005</td>
<td>0.0673</td>
<td>&lt; 0.0001</td>
<td>0.5079</td>
</tr>
</tbody>
</table>

SJC = Number of swollen joints. The comparisons are made within each group.

The annual radiographic progression (calculated as an annual progression of Larsen score per month) did not differ between these 2 groups after the initiation of DMARD therapy, although the Larsen score per month before the time of diagnosis was higher in VERA patients (p = 0.0044) (Figure 2.).

Figure 2. Radiographic progression in 2 patient groups as presented by the change in the Larsen score per month (mean) before initiation of DMARD therapy and annually thereafter.

The number of patients in remission evaluated annually was not statistically different between these 2 groups, although the higher proportion of ERA patients was in remission at every point.
Equal numbers of patients were operated on for to RA during the follow-up (19% of VERA and 15% of ERA patients). Two VERA patients and 3 ERA patients died during the follow-up, but none of the deaths were related to RA.

In conclusion, patients with very early RA tended to have more active disease at entry and during the follow-up, and their functional capacity remained worse compared with patients with early RA. However, active and early initiation of DMARD therapy appeared to retard radiographic progression in these patients and the radiological outcome was parallel to that of patients with less active disease.

6.5 Permanent work disability in patients with early RA (IV)

A total of 102 patients (68% of the entire study population) were working full time at the time of diagnosis. The mean (SD) age was 44.2 (10.7) years; 81% of the patients were female, 72% were RF-positive and 55% had erosive changes at onset. The mean (SD) HAQ score was 0.35 (0.38) and the mean (SD) Larsen score 6.3 (10.7). Of the patients, 31% had less than 9 years of education, 31% between 9 and 12 years and 39% more than 12 years. In 51% the physical demands of the work were considered to be light, in 37% moderate and only in 12% heavy.

The rate of work disability increased during the follow-up despite active treatment of RA. Permanent work disability due to RA among those patients working full time at the time of diagnosis was 6%, 16%, 24%, 32% and 36% at 1, 3, 5, 7, and 10 years after diagnosis, respectively. The initial disease activity (ESR, Ritchie index, the number of swollen joints) and HAQ scores were significantly higher in those patients ending in permanent work disability compared with those patients still working at the end of follow-up. The age (mean, SD) at the time of diagnosis of those patients still working at the end of the follow-up (42, 11) was significantly lower compared with those patients who had retired due to RA (50, 8) (p < 0.001). The educational level of those patients still working at the end of follow-up tended to be higher. The physical demands of work among those patients who remained at work throughout the follow-up period were considered to be significantly less demanding compared with the physical demands of work among those patients permanently retired due to RA (p = 0.009).
The significant predictors of work disability in univariate regression analysis were age (p < 0.001), educational level (p = 0.028), physical demands of work (p = 0.002), ESR (p = 0.007), Ritchie index (p = 0.02) and HAQ (p < 0.001). On the other hand, in stepwise logistic regression analysis the significant predictors of permanent work disability included age, ESR and HAQ. In conclusion, despite active treatment with various DMARDs, work disability increased constantly. Older age, increased functional disability, ESR and physical demands of work at onset were the best predictors for work disability.

6.6 Mortality among early RA patients treated actively according to the `sawtooth´ strategy (V)

The baseline data of all 150 patients were included in the study. The patients were followed up until November 1, 2000. The baseline data of the patient, who was lost to follow-up after 2 years is included in the study, but since it is not known whether or not the patient is still alive, he is excluded from further analysis.

The patients of the first cohort were followed up between 10 and 14 years and of the second cohort between 7 and 9 years. In addition to clinical data on these patients, comorbidities, extra-articular features and DMARD therapy were collected in the study. The time and cause of death were obtained from death certificates and from patient files, if available.

Seven patients from the first cohort and 17 from the second cohort died during follow-up. At the baseline ESR, the number of swollen joints, total Larsen score and HAQ scores were significantly higher among those patients who died during follow-up. In univariate analysis age at onset (p < 0.001), male gender (p = 0.026) and the baseline clinical variables ESR (p < 0.001), the number of swollen joints (p = 0.004) and poor functional capacity (p < 0.001) predicted poor prognosis. However, in multivariate analysis only age at onset (p < 0.001) and male gender (p = 0.0043) showed prognostic significance.

During the first year there was significant improvement in all clinical variables in both groups except the number of tender joints in those patients who died. A total of 64 patients (43%) had extra-articular features at onset or during follow-up. The most common features were sicca
syndrome in 37 patients, rheumatoid nodules in 22 patients, neuropathy in 7 patients and vasculitis in 6 patients. There was a statistically significant difference in the presence of extra-articular features among those patients who died (75%) compared with those still alive (36%) (p < 0.001).

A total of 72 patients (48%) had one or more comorbidities at entry of the study. These included hypertension (10%), degenerative joint disease or other musculoskeletal disease (9%), ischaemic heart disease (6%), diabetes (3%), asthma (3%) and psychiatric disorder (3%). Three patients had a history of tuberculosis and 3 a history of malignancy. However, no difference in the presence of co-morbidities between those patients who died and those still alive was observed.

All the patients were treated actively according to the ‘sawtooth’ strategy. SASP was the initial treatment in 71% of those patients who died and intramuscular gold among the rest of these patients. In those patients still alive intramuscular gold was the initial drug in 52%, SASP in 45%, hydroxychloroquine in 2% and 2 patients did not start any medication. Although the patients were included in the study during different time periods and the treatment strategies were improving, the number of various DMARDs did not differ significantly during the first 5 years of follow-up between the 2 patient cohorts collected at different time periods. The use of various DMARDs, either as single therapy or in combination, did not differ significantly between the groups during the first 3 years.

The SMR of the entire study population with 95% CI was 1.33 (0.85-1.98), showing that the mortality rate among these RA patients showed no statistically significant increase compared with the normal population. When analysed separately the SMR with 95% CI was 0.93 (0.37-1.92) in the first cohort and 1.62 (0.95-2.60) in the second cohort. Although the SMR in the second cohort appeared significantly higher, no statistical difference between the two cohorts (age-and-sex adjusted hazard ratio 2.09 with 95% CI 0.57-7.60) was observed. Most of the patients from the second cohort who died during follow-up were over 65 years of age at onset of the study.

In 8 patients (33% of all dead patients) the cause of death was malignancy, but none of these patients had previous history of malignant disease or any other predisposing factor. Six patients died of myocardial infarction: 3 of these had diabetes and 2 patients had a history of coronary heart disease. Other causes of death included infection (3 patients), ruptured aortic aneurysm (2
patients, one with previous history of operated aortic aneurysm), 2 cases of lung disease and 1 patient with universal arteriosclerosis. One patient developed amyloidosis after 5 years of follow-up and died soon after with a diagnosis of RA.

In conclusion, the mortality rate among this study population showed no statistically significant differences compared with the normal Finnish population. The clinical picture at onset was more active among those patients, who died during follow-up. Older age at onset was a significant predictor of mortality. Diseases of the circulatory system and malignancies were the most common causes of death among these patients.
7. DISCUSSION

7.1 General

This prospective study consists of 2 patient cohorts of early, at entry DMARD-naive RA patients treated actively according to the `sawtooth´ strategy from the time of diagnosis onwards and then followed up prospectively and continuously thereafter. During the 1980s changes in attitudes towards earlier and more active treatment of RA encouraged rheumatologists in Finland to treat all RA patients with DMARDs already at the early stages of the disease. This study was conducted to evaluate the effect of early initiated active treatment on the outcome in RA patients. All consecutive patients with early RA despite clinical disease activity were included in this study. Although this is a hospital-based study, it includes a representative cohort of early RA patients, since rheumatologists treat almost every patient with early RA in Finland.

7.2 Intramuscular gold and sulphasalazine

During the 1980s and early 1990s intramuscular gold and SASP were the 2 most widely used DMARDs in Finland. Although their effect on clinical variables had been evaluated and compared with each other in many studies (Pullar et al. 1983, Situnayake et al. 1987), no previous studies had been performed to compare their effect on radiographic progression. To unify the patient population, patients older than 65 years of age at the onset were excluded from the analysis. In addition, to avoid the bias caused by small differences in duration of symptoms in the 2 patient cohorts, only those patients with a duration of symptoms of 12 months or less were included in the analysis.

The number of patients discontinuing treatment due to adverse effects was similar to those seen in previous studies (Pullar et al. 1983, Williams et al. 1988), but due to variable follow-up times the results are not always comparable. Inefficacy as a cause of discontinuation was more common in our study compared with previous studies (Pullar et al. 1983, Williams et al. 1988), although equal or even higher numbers have also been observed previously (Bax and Amos 1985, Situnanyake et al. 1987) for SASP as well.
Although the clinical response was good, radiographic progression was significant during follow-up in both groups. Parallel radiographic progression has also been observed in another study from Finland among patients treated with SASP (Hannonen et al. 1993), but less progression has also been observed in patients treated with SASP (Australian multicentre clinical trial group. 1992) or with intramuscular gold (Luukkainen et al. 1977, Möttönen 1988). Comparison between different studies can be difficult, due to differing patient selection or radiographic scoring methods. In some patients (9 receiving SASP and 8 receiving gold during follow-up) there was no radiographic progression, but unfortunately none of the baseline values was able to predict the beneficial outcome. Thus, radiographs should always be included, when the effects of various therapies on the outcome of RA are evaluated. Our study shows that intramuscular gold and SASP were both ineffective as a single therapy for retarding the radiological progression of RA in most patients with early RA.

7.3 The effect of age on outcome

Older age at onset of RA has previously been considered to be either a good (Ehrlich et al. 1970, Deal et al. 1985) or a poor (Ferraccioli et al. 1984, van der Heijde et al. 1991, Kuiper et al. 2000) prognostic factor. In follow-up studies, such as ours, the number of patients with RF has been equal in both older and younger patients (van der Heijde et al. 1991, Bologna et al. 1996), although in cross-sectional studies the number of RF-negative patients has often been increased among older patients (Terkeltaub et al. 1983, Deal et al. 1986). An acute type of onset has been observed more often among older patients in previous studies (Deal et al. 1986, van der Heijde et al. 1991), resembling that seen in the present study. However, earlier findings that older patients with early RA present more often with large joint disease either alone or in combination with small joints (Deal et al. 1986, van der Heijde et al. 1991) was not confirmed in the present study.

Older patients (over 55 years of age at the onset) had more active disease (higher ESR, CRP, Larsen score for hands) at onset compared with younger patients in the present study. Parallel findings have been observed in other studies as well (Deal et al. 1986, van der Heijde et al. 1991, van Schaardenburg et al. 1993). The disease activity score, a composite score of Ritchie index, ESR, the number of swollen joints and general health (van der Heijde et al. 1990), has also been increased among older patients at onset as compared with younger patients (van der Heijde et al. 1991, Kuiper et al. 2000). The Larsen score for hands was higher among older patients in the
In the present study both groups responded equally to active DMARD therapy and by the end of the 3-year follow-up, no significant differences in clinical or radiographic (both total Larsen score and separate Larsen scores for hands and feet) variables were observed between the groups. Neither did the number of patients in remission at various time points differ between groups at any point. The use of DMARDs was parallel in both groups, but oral corticosteroids were more often used among older patients, which may affect the slightly better response to treatment among older patients. Functional ability, which was evaluated using the HAQ score, was also equal in both groups at the end of the follow-up.

In a Dutch study the effect on clinical and radiographic outcome was equal in both groups, but after 2 years of treatment there was still a difference in disease activity between 2 groups (van der Heijde et al. 1991). The functional capacity in the Dutch study was equal at entry and also at the final visit, which is in accordance with the present study. The results from the study by Deal and coworkers are controversial, since most of the outcome measures (functional capacity, total joint score, MS) were better among older patients, while the number of patients with no active joints was also significantly higher among older patients (Deal et al. 1986). In their study, the disease duration was also significantly longer (4.4 vs 5.4 years) among younger patients, which may explain some of the differences. In addition, there was a tendency towards increased use of DMARDs among younger patients, but on the other hand the use of oral steroids was more common among older patients, although these differences were not statistically significant.

Due to alterations in pharmacokinetics and pharmacodynamics associated with aging, the number and severity of side effects is often expected to be higher among older patients. However, the number of patients discontinuing treatment in the present study due to side effects (and inefficacy) was equal in both groups, and no difference in distribution of various side effects was observed. This finding is in accordance with previous studies, in which no significant effect of age on the tolerability and efficacy of methotrexate (Wolfe and Cathey 1991, Bologna et al. 1996), intramuscular gold (Kean et al. 1983) or various drugs (Dahl et al. 1990, Pincus et al. 1992a, Capell et al. 1993) was observed, although some tendency towards increased number of withdrawals due to side effects was seen (Pincus et al. 1992a).
The clinical picture of early RA in elderly patients is more active and slightly different compared with those with disease onset at ≤ 55 years of age, but the 3-year prognosis is equal in both patient groups. The tolerability and efficacy of DMARD therapy applied according to the `sawtooth´ strategy does not differ according to the age of a patient. However, despite the treatment, significant radiographic progression was observed, although the clinical response was fairly good.

7.4 Effect of treatment on the outcome of very early RA

In the present study the clinical picture at onset was more active among those patients with duration of symptoms less than 4 months before the diagnosis, and also functional capacity was also worse compared with those patients with duration of symptoms between 4 and 24 months at time of diagnosis. Patients with milder symptoms tended to wait longer before contacting the physician, but patients were also treated at the primary care units longer before consulting the specialists compared with patients with more active symptoms. In addition to significantly higher CRP, Ritchie index, number of swollen joints and HAQ score, involvement of the large joints (either alone or in association with small joints) was also more common among patients with shorter duration of symptoms. The Larsen scores were equal at the time of diagnosis in both groups, but when analysed with respect to the duration of symptoms before diagnosis, the Larsen score per month was significantly higher in patients with shorter duration of symptoms.

Both patient groups were treated equally with DMARDs according to the `sawtooth´ strategy, and the number of DMARDs during follow-up (except at the 2-year point) did not differ significantly. However, the number of patients with oral corticosteroid treatment (either permanent or intermittent therapy) was higher in patients with shorter duration of disease. The response, evaluated by the change in ESR, CRP, Ritchie index and the number of swollen joints, was equal in both groups and the difference in clinical activity between these 2 patient groups remained constant throughout the study. However, the effect on functional capacity was significant only in patients with longer duration of symptoms. Functional capacity in early RA has been observed to correlate more with disease activity than with radiographic outcome in previous studies (Guillemin et al.1992, Drossaers - Bakker et al. 1999). In the present study, patients with very early RA had more active disease at the end of follow-up, although DMARD therapy had a significant effect on the signs and symptoms, and the higher disease activity may contribute to
worsening of functional outcome. The follow-up period is probably too short to evaluate the effect of radiographic progression on functional outcome.

Although the radiographic progression per month before entry into the study was more rapid in patients with very early RA, after initiation of DMARD therapy the progression rate among these very early RA patients was retarded more effectively, and no significant difference in progression rate measured annually up to 3 years was observed between these 2 patient groups. This is in accordance with results from studies by Egsmose et al. (1995), in which the effect of DMARDs on radiographic progression was better in those patients receiving therapy earlier, compared with other patients whose DMARD therapy was initiated with a mean delay of 8 months.

The number of patients in remission at various time points was parallel in both groups, although there was a trend towards more remissions in those patients with longer disease duration. The remission rates are not often evaluated, but recent data from the Finn-RACo trial has shown that the remission rate with respect to the duration of symptoms is dependent on the aggressiveness of treatment (Möttönen et al. 2002). In the Finn-RACo study the remission rates at the 2-year point in the combination group were equal in both patients with disease duration of less than 4 months before the initiation of treatment and in patients with longer disease duration (4-24 months). However, in patients with single therapy (beginning with SASP) as the initial treatment, the remission rate was significantly higher in those patients with disease duration of less than 4 months compared with patients with longer duration of the disease at the time of diagnosis.

Patients with more active early RA seek medical aid earlier than those patients with milder symptoms. The earlier that DMARD therapy is initiated, the better is the effect of treatment on radiographic outcome. Therefore, diagnostic delays in patients with milder symptoms should be shortened for better radiographic outcome. However, the DMARD therapy applied according to the`sawtooth´ strategy is not able to suppress the symptoms and improve functional capacity in patients with more active disease, and initiation of more aggressive treatment (combination therapy at onset or even new biological treatments) should thus be considered in such patients.
7.5 Permanent work disability in early RA patients treated actively with disease modifying drugs

A total of 102 patients were still working at the time of RA diagnosis in the present study. Permanent work disability increased constantly during the follow-up despite active treatment. By the end of the first year, 6% of those patients working full time at the onset of the disease had quitted their jobs due to RA. The figure increased up to 24% after 5 years of follow-up and up to 36% after 10 years of follow-up.

It is often difficult to compare different studies on work disability due to differing socioeconomic and social insurance systems in various countries. In Finland several studies concerning work disability in RA have been published, one of the earliest Mäkisara and Mäkisara (1982). In this study patients with longer duration of RA were at greater risk of being unable to work due to RA; 40% of patients were unable to work after 5 years of RA and 50% after 10 years. These patients were treated during the 1970s in the Rheumatism Foundation Hospital in Heinola and the treatment policy differed from the present `sawtooth´ strategy. Nissilä et al. (1983) published the first data concerning the prognosis of early RA patients treated actively within 6 months from the onset of symptoms in Heinola. After 3 years of follow-up 32% of the patients were already permanently retired due to RA (Nissilä et al. 1983), after 8 years 43% (Kaarela et al. 1987) and after 20 years 80% (Jäntti et al. 1999). These patients were treated actively, but because fewer DMARDs were available during that time, the treatment strategy differed from that used in the present study. Another difference compared with the present study was the educational level of the patients, since in the present study 70% of the patients had more than 9 years of education compared with only 15% in the early RA study from Heinola. In the study from Jyväskylä, Finland (Sokka et al. 1999a) the patients were treated according to the `sawtooth´ strategy and thus, in a similar way, compared with present study. In this study from Jyväskylä, the percentage of patients unable to work after 10 years of follow-up was 44%. However, the results from the present study were better than those from Jyväskylä, which cannot be explained by the effectiveness of treatment. One possible explanation for this difference may be the fact that Jyväskylä is a mid-sized town with rural surroundings and 72% of the patients engaged in either physically moderate or heavy work compared with the present study, where 51% of the patients engaged in physically light work. In most other studies from other parts of the world, work disability has been observed between 22% and 72% after 5 years (Wolfe and Hawley 1998,
Albers et al. 1999) and between 32% and 50% after 10 years (Yelin et al. 1987, Wolfe and Hawley 1998).

In the present study baseline functional disability as measured with HAQ scores and disease activity were higher in those patients losing their work capacity during follow-up compared with those patients still continuing to work. In univariate regression analysis age, ESR, Ritchie index, educational level, physical demands of work and HAQ score were associated with permanent work disability. Higher age at onset of disease has been a poor prognostic factor in many previous studies such as disease activity measured with ESR or joint count (Doeglas et al. 1995, Mau et al. 1996, Fex et al. 1998, Wolfe and Hawley 1998). The presence of RF at the onset of disease did not correlate with the future work capacity in the present study, which contrasts with studies by Wolfe and Hawley (1998). The higher level of education has been observed to be a favourable prognostic factor in many studies including the present (Doeglas et al. 1995, Fex et al. 1998, Wolfe and Hawley 1998). Physically light work was associated with future working capacity in the present study, as in some previous studies, although contrasting observations have also been published (Yelin et al. 1987, Reisine et al. 1995, Sokka et al. 1999a).

In conclusion, the working capacity is currently maintained in early RA patients better than earlier and this is at least partly due to more effective treatments. However, it is not only the effectiveness of the treatment, but also the nature of the work that affects the possibility of continuing work during the early years of RA. Future attention should be focused not only on more effective treatments, but also on work-related factors such as physical demands of work.

**7.6 Mortality among early RA patients**

The mortality among these 2 patient cohorts was analysed both together and separately, since the follow-up time was different and the inclusion criteria including disease duration and age at onset differed significantly. Age at onset was significantly higher, the presence of extra-articular features at onset or during follow-up was more common and the clinical picture at onset of RA was also more active among those patients who subsequently died, compared with those still alive at the end of follow-up. The presence of comorbidities did not affect mortality rates, nor did the presence of RF or erosive changes at onset of the study. Compared with the first cohort, the mortality rates were higher in the second cohort and this may be due to the criteria included at
onset, since all RA patients older than 65 years at the onset were excluded from the first cohort. However, mortality rates in neither of the study cohorts were significantly different from those shown by the normal population in Finland.

Most previous studies have shown increased mortality rates among RA patients. The SMR has usually varied between 1.1 and 3.0. In community-based studies mortality rates have usually been lower compared with those in hospital-based studies, but the length of follow-up and patient selection also contribute to the results. The highest mortality rate has been observed in the study by Prior et al. (1984), in which RA patients referred to a specialist clinic were followed up for a mean of 11.2 years. The SMR for the entire group was 3.0, but when the patients were divided into 2 groups according to duration of the disease at the time of referral to hospital, a significantly higher SMR of 3.6 was observed in those patients who had had a longer duration of RA (> 5 years), when they were seen for the first time in hospital compared with earlier presenters. In 2 recently published studies from Norway (Kvalvik et al. 2000, Riise et al. 2001), the mortality rates (SMR 1.49 and 2.0) were higher compared with those seen in the present study. However, in these Norwegian studies the patients were not early RA patients and the treatment of the patients was not analysed. In the present study all patients were seen by a rheumatologist within 2 years following the onset of symptoms, and in 99% of the patients DMARD therapy was initiated at the time of diagnosis. Early and active treatment of RA may explain lower mortality rates seen in the present study.

One of the lowest mortality rates was observed in a community-based study by Linos et al. (1980), in which all RA patients were traced between 1950 and 1974 in Rochester, Minnesota, and the mortality rates among these RA patients were calculated. An SMR of 1.16 among these RA patients was not significantly different from that seen in the entire population from the same area. In 2 recent studies, no increase in mortality rates was observed among early RA patients. In a study from Sweden (Lindqvist and Eberhardt 1999) 183 early RA patients with symptoms less than 2 years were followed up for 8-13 years and in this study an SMR with 95% CI was 0.87 (0.53-1.36). Older age and male gender were risk factors for death in this Swedish study, a finding in accordance with the present study. The same predictors were observed in another study from the Netherlands (Kroot et al. 2000), where 622 early RA patients were followed up for 10 years (mean follow-up period 5.8 years). The mean ages at onset in these 2 studies and the present study were equal. The disease activity (Ritchie index and number of active joints) also
very much resembled that seen in these 3 studies. The main difference in the Dutch and the present and Swedish studies was the follow-up time.

The predictors of increased mortality have been examined in many previous studies. Older age, male gender, poorer functional capacity, lower educational level and higher ESR level have all been connected with increased mortality (Leigh and Fries 1991, Isomäki 1992, Corbett et al. 1993, Pincus et al. 1994, Wolfe et al. 1994, Söderlin et al. 1998), and the presence of extra-articular features may also predict premature mortality (Erhardt et al. 1989, Wolfe et al. 1994, Turesson et al. 1999). The use of corticosteroids has been connected with poorer outcome (Fries and Leigh 1991, Wolfe et al. 1994), which can also be explained by the patient selection, since corticosteroids are usually given to patients with more severe disease. However, there is at least one study by Mitchell et al. (1986), in which the use of prednisone did not appear to affect survival. In the present study age, male gender, increased clinical activity, and the presence of extra-articular features were more common in those patients, who had died thus far, a situation resembling that seen in previous studies.

In many studies on RA, CVDs have been the main cause of increased mortality rates (Jacobsson et al. 1993, Wolfe et al. 1994, Symmons et al. 1998, Turesson et al. 1999). Unfortunately the risk factors for CVDs have not usually been analysed when the causes of death among RA patients have been studied. Some excess mortality due to CVDs may have been caused by the use of corticosteroids (Maxwell et al. 1994). There is also some evidence that methotrexate increases mortality and cardiovascular comorbidity in patients with RA, since methotrexate may increase serum concentrations of homocysteine (Landewe et al. 2000). However, the use of methotrexate cannot explain the increased mortality rates seen in older studies, in which methotrexate was not used for RA.

Higher proportions of infections as causes of death among RA patients compared with the normal population have also been shown in many studies (Allebeck 1982, Vandenbroucke et al. 1984, Mitchell et al. 1986, Myllykangas-Luosujärvi et al. 1995a, Symmons et al. 1998). The increased risk of infections may be due to RA itself with changes in immune response or DMARD treatment, especially cytotoxic drugs.

The risk of haematopoetic malignancies has been shown to be increased among RA patients (Isomäki et al. 1982), but the exposure to immunosuppressive therapy may also increase the risk
of malignancy (Jones et al. 1996). The mortality risk due to malignancies of haematopoetic origin has been increased in some studies (Laakso et al. 1986, Wolfe et al. 1994, Symmons et al. 1998), but not in all (Allebeck 1982). The mortality rate due to lymphoma appears to increase with disease duration (Symmons et al. 1998) and also with disease activity (Bäcklund et al. 1998).

In Finland the causes of death among RA patients have been otherwise similar to those observed in other countries, but renal diseases (due especially to amyloidosis) as causes of death are a predominant feature only in Finland (Koota et al. 1977, Mutru et al. 1985, Laakso 1986, Myllykangas-Luosujärvi et al. 1995a). None of the patients in the present study or in another Finnish study (Sokka et al. 1999c) died of amyloidosis, and this finding is in accordance with the observation from Heinola (Laiho et al. 1999) that the risk of developing amyloidosis is decreasing in Finland as a consequence of more aggressive treatments, to decreasing activity of RA or to both.

Malignancies were the second major cause of death in the present study, but only one was of haematopoetic origin. The study population was too small to make any conclusions on the overall causes of deaths, but it raises a question of, whether effective treatment, especially among elderly patients, increases the risk of malignancies, although the disease activity itself is suppressed.

The effect of DMARD therapy on mortality has not been widely studied. Lehtinen and Isomäki observed in their study in 1991 that long-term intramuscular gold therapy had a beneficial effect on mortality rates among RA patients during a 20-year follow-up. Krause et al. (2000) studied the effect of methotrexate on mortality rates in patients with severe disease. They showed that patients with good response to methotrexate had only a slightly increased mortality rate compared with the general population, but those patients who did not respond to methotrexate had an over 4-fold increased mortality. A recent study on a large population of RA patients showed that the treatment of active RA with methotrexate is associated with a substantial decrease in the mortality, especially in the risk of cardiovascular mortality (Choi et al. 2002).

Sokka et al. (1999c) also evaluated the effect of active treatment on mortality among early RA patients earlier in a Finnish study. During an 8-14-year follow-up, only slightly increased mortality was observed among 135 early RA patients treated according to the `sawtooth´ strategy. Despite the extensive use of DMARDs, none of the deaths were related to DMARD therapy. In the Swedish study (Lindqvist and Eberhardt 1999) only 62% of patients were on DMARD therapy and 16% on oral corticosteroids at some time during the follow-up, but in the Dutch
study by Kroot et al. (2000) 95% of the patients were on DMARD therapy and 34% on oral corticosteroids at some time.

In the present study 99% of the patients were on DMARD therapy during follow-up lasting for an unspecified time. The mortality rates among these early RA patients resembled those of the normal population, although there remained a proportion of patients who died prematurely. At onset the clinical picture appears to be more active among older patients, while those patients who died in the present study were older than those patients still alive. Since older patients tend to tolerate DMARD therapy as well as younger patients, more attention should be focused especially on the treatment of elderly early RA patients with active disease.
8. SUMMARY AND CONCLUSIONS

In the present study the effect of active, early antirheumatic drug therapy was assessed on the outcome of recent onset RA. A total of 150 early RA patients from 2 different cohorts were included in this prospective study. The efficacy, especially with respect to radiographic progression, of intramuscular gold and SASP as initial treatment was compared (I). The effect of age (II) and the timing of the initiation of antirheumatic treatment (III) were investigated. The development of work disability in those patients working at entry in the study was examined (IV) and finally the mortality rate and causes of death among these actively treated patients were evaluated (V).

All patients except 4 received either intramuscular gold or SASP as their initial treatment. The clinical improvement shown during the first year was equal in both groups, but the proportion of patients discontinuing was 40% in the intramuscular gold group and 48% in the SASP group. Adverse reactions were more common in the intramuscular gold group and inefficacy in the SASP group as a cause for discontinuing the initial treatment. Despite the drug therapy used, radiographic progression was significant and equal in both groups. This study shows that older antirheumatic drugs, such as intramuscular gold and SASP, are not effective enough in preventing permanent joint damage, and these results support the present strategy of treating early RA with more aggressive therapies such as methotrexate or combination therapies.

At the beginning of the study, the initial disease activity was higher among those patients who were older than 55 years at the onset of disease, and also in those patients who were diagnosed within 4 months from the onset of symptoms. Older patients responded equally well to DMARD therapy and also tolerated DMARD therapy in a way similar to that shown by younger patients. When DMARD therapy was initiated very early, the clinical picture improved as it did in patients with longer duration of symptoms, although the disease activity remained higher and the functional capacity lower among those patients with shorter duration of symptoms at the time of diagnosis. However, although radiographic progression had been more rapid before entry in the study of very early RA patients, initiation of DMARD therapy was able to retard the rate of radiographic progression. Older patients showed more radiographic changes in the hands at the time of diagnosis than younger patients, but the radiographic progression in both hands and feet was similar in both groups. In conclusion, older patients with early RA should be treated at least
as actively as younger patients and active treatment should be initiated as early as possible to prevent permanent joint damage among early RA patients.

Two-thirds of the patients were working at the beginning of follow-up and none of the patients had retired due to RA. After one year 6% of these patients were permanently unable to work. The rate of work disability increased constantly and after 10 years 36% had finished their working careers. In addition to initial disease activity and impaired functional capacity, work-related factors such as lower educational level and physically demanding work were also associated with work disability. Age, ESR and initial HAQ score predicted permanent work disability. In conclusion, the rate of permanent work disability was lower than in previous studies from Finland, which may be partly explained by initiation of early active antirheumatic drug policy in this study.

In the present study the mortality rates shown among patients with recent onset RA were examined. The increased disease activity at onset and the presence of extra-articular features appear to associate with increased mortality. Most of the patients who died were over 65 years of age at onset of the disease and as previously shown, the disease activity appears to be higher among older patients. The number of DMARDs used did not differ between those patients who died during follow-up and those patients still alive. CVDs and malignancies were the main causes of death in this study cohort. The high proportion of malignancies is not in accordance with previous studies. Age at onset and male gender were the only significant predictors of mortality in this study. However, in the present study the mortality occurring among early RA patients treated actively since onset of the disease was not increased compared with that observed in the normal population.
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