Tuulikki Sokka

Extensive use of antirheumatic drugs improves long-term outcomes in patients with rheumatoid arthritis

ABSTRACT

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Rheumatoid arthritis (RA) is a chronic inflammatory disease, whose hallmark is symmetric polyarthritis. In the long-term, the majority of patients with RA experience anatomical changes in joints, joint deformities, functional declines, work disability and even increased mortality.

The purpose of the present study was to obtain information on the influence of the early, continual, and serial use of disease-modifying antirheumatic drugs (DMARDs) known as the 'sawtooth' strategy on the long-term outcomes of patients with RA.

The patient population consisted of 135 cases with recent-onset RA at Jyväskylä Central Hospital. The first group (n=58, mean age 48 years) was diagnosed in 1983-85, and the second group (n=77, mean age 52 years) in 1989-89; 73% of the patients were seropositive. The patients were prospectively followed up with regular clinical visits up to 15 years, and treated according to the 'sawtooth' strategy. Radiographs of wrists, hands and feet were taken at intervals of one to two years, and assessed according to the Larsen score (0-100). Functional disability was assessed by the Health Assessment Questionnaire (HAQ) (0-3). Employment status and deaths were documented.

The median coverage of DMARDs was 88% of the observation time. Serious drug related adverse events were exceptional. Inefficacy rather than adverse events was the leading reason for discontinuation of the drug treatment (51% vs. 28%).

Radiographic damage of 85 seropositive cohort patients progressed over the 8-year period, but developed slower than in the historical control cohort treated more sparsely with DMARDs. In eight years, the median (IQR) Larsen score increased to 12 (4, 28.5) in the study cohort compared to 25.5 (8, 43) in the control cohort (p=0.001).

The mean HAQ score reached 0.75 for group I in 13 years, and 0.55 for group II in 8.5 years. In several historical control cohorts with disease duration >5 years the mean HAQ scores exceeded 1.

During the first ten years of the disease, 44% of the patients were retired wholly or partially due to RA. Most of them lost their working capacity during the first 2 years after the onset of the disease.

Twenty-five patients died during the 1,422 person-years of observation. The mortality rate of 1.28 (95%CI 0.83-1.89) was not higher than that of the population of the county of Central Finland.

Extensive use of DMARDs and their combinations was safe. The long-term outcome of patients with early RA treated according to the 'sawtooth' strategy was better than that of the historical controls. Early, continual, and serial use of DMARDs improves the course of RA in the long-term.

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To Timo,
Taimi, Toivo, Touko, and Taisto

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CONTENTS

ABBREVIATIONS

COMBO	Combination of at least two disease-modifying antirheumatic drugs	
CRP	C-reactive protein	
CI	Confidence interval	
DAS	Disease activity score	
DMARD	Disease-modifying antirheumatic drug	
	AURA	auranofin
	AZA	azathioprine
	CB	chlorambucil
	CYA	cyclosporin-A
	CYP	cyclophosphamide
	DPA	d-penicillamine
	GST	aurothiomalate, intra muscular gold
	HCQ	hydroxychloroquine
	MTX	methotrexate
	PODO	podophyllotoxine derivatives
	SASP	sulphasalazine
ESR	Erythrocyte sedimentation rate	
FC	Functional capacity	
GH	General health	
HAQ	Health Assessment Questionnaire	
LN	Logarithm, natural	
MCP	Metacarpophalangeal	
MHAQ	Modified Health Assessment Questionnaire	
MTP	Metatarsophalangeal	
NSAID	Non-steroidal anti-inflammatory drug	
PIP, IP	Proximal interphalangeal, interphalangeal	
RA	Rheumatoid arthritis	
RF	Rheumatoid factor	
SMR	Standardized mortality ratio	
SQRT	Square root	
VAS	Visual analoque scale	

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred by their Roman numerals:

I Sokka T, Hannonen P: Utility of disease-modifying antirheumatic drugs in 'sawtooth' strategy. A prospective study of early rheumatoid arthritis patients up to 15 years. Ann Rheum Dis 1999 (accepted).

II Sokka T, Kaarela K, Möttönen T, Hannonen P: Conventional monotherapy compared to 'sawtooth' treatment strategy in the radiographic progression of rheumatoid arthritis over the first eight years. Clin Exp Rheumatol 1999 (accepted).

III Sokka T, Möttönen T, Hannonen P: DMARD use according to the 'sawtooth' strategy improves the functional outcome in rheumatoid arthritis: results of a long-term follow-up study with review of the literature. Rheumatology (manuscript).

IV Sokka T, Kautiainen H, Möttönen T, Hannonen P: Work disability in rheumatoid arthritis ten years after the diagnosis. J Rheumatol 1999 (accepted).

V Sokka T, Möttönen T, Hannonen P: Mortality in early 'sawtooth' treated rheumatoid arthritis patients during the first 8-14 years. Scand J Rheumatol 1999 (accepted).

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease, whose hallmark is symmetric polyarthritis. Its causes are unknown, prognosis is poorly predictable, and there exists no definite cure.

As recently as in the 1980s, RA was considered, even in textbooks to be a benign disease (in: McCarty 1985, Kelley 1989). Accordingly, patients with RA were treated mostly with symptom relieving drugs; so called disease-modifying antirheumatic drugs (DMARDs), which are targeted to suppress inflammation and retard the progression of the disease, were started years after the diagnosis, if ever. However, findings in the 1970s and early 1980s in Finland and in other countries revealed that the traditional treatment strategy had failed to prevent serious long-term consequences of the disease: joint deformities, functional decline, work disablity, and increased mortality (Isomäki et al. 1975, Mäkisara and Mäkisara 1982, Pincus et al. 1984). These findings encouraged Finnish rheumatologists to treat patients with RA early and actively with DMARDs in order to improve long-term outcomes of the disease (Luukkainen et al. 1978). Later, more active treatment strategies for RA were commonly recommended (Wilske and Healey 1989, Fries 1990, Pincus and Wolfe 1991).

Several studies on the favourable influence of early and sustained use of DMARDs on long-term outcomes of RA have been reported. The studies by Luukkainen et al. (1977), Heikkilä and Isomäki (1994), Möttönen et al. (1996), and Abu-Shakra et al. (1998) showed that the use of DMARDs can retard the progression of radiographic joint damage in RA in the long-term. Further, better functional capacity has been associated with active DMARD therapies in several RA studies (Suarez-Almazor et al. 1994, Porter et al. 1994, Egsmose et al. 1995, Fries et al. 1996, Möttönen et al. 1996, Ward et al. 1998, Munro et al. 1998, Capell et al. 1998). So far, only Borg et al. (1991) have reported that early DMARD treatment in recent onset RA may protect against work disability. Furthermore, sustained use of intra muscular gold and methotrexate therapies has been associated with reduced mortality in patients with RA (Lehtinen and Isomäki 1991, Wolfe et al. 1998).

At Jyväskylä Central Hospital a total of 135 recent-onset patients were recruited to two early RA studies in 1983-1985 (Möttönen 1988) and 1988-1989 (Hannonen et al. 1993). These patients have since then been treated with DMARDs continually and serially, a strategy later designated by Fries as the 'sawtooth' strategy (Fries 1990). In the present study I evaluate the utility of the use of DMARDs according to the 'sawtooth' strategy in the treatment of patients with RA and study its impact on radiographic findings, functional and working capacity, and mortality.

2. REVIEW OF THE LITERATURE

2.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease which affects up to 1% of the population (Gran 1987). The first symptoms and signs of RA are tenderness, stiffness, and swelling of joints, caused by the inflammatory process in synovial tissue which consists of humoral and cellular components with inflammatory mediators, tissue destructive enzymes, and amplifying cytokines. Subsequently, the inflammatory process leads to pain, to the progressive destruction of cartilage, bone, and other adjoining tissues, as well as systemic manifestations in vital organs such as kidney, lung, and vasculature some patients (Panayi 1995). As a consequence, patients develop joint deformities, decline in functional capacity, preterm work disability, and may even die earlier than others (Pincus and Callahan 1989).

The course of RA is highly variable. The most favourable type of RA has a self-limited course, which in population based surveys accounted for most of the cases (Mikkelsen and Dodge 1969, O'Sullivan and Cathcart 1972) which met the earlier classification criteria for RA (Ropes 1959). However, patients with RA seen in clinical settings generally have a more progressive disease (Nissilä et al. 1983, Lichtenstein and Pincus 1991).

Both environmental and genetic factors have a role in the etiopathogenesis of RA. Smoking is so far the only avoidable risk factor that has been found (Heliövaara et al. 1993, Silman et al. 1996, Symmons et al. 1997). On the other hand, familial clustering of RA is not uncommon (Lawrence 1970, del Junco et al. 1984). The concordance rate for RA is higher in monozygotic twins compared to dizygotic twins - 30% vs. approximately 5% (Aho et al. 1986). More recently, however, the concordance rates in monozygotic twins have been shown to be as low as 15% (Silman et al. 1993, Järvinen et al. 1995). Genetic susceptibility to RA appears mostly to be associated with the presence of HLA-DR4 and HLA-Dw4, as initially demostrated by Stastny (1974, 1978). Over the past two decades, these findings have been confirmed in most populations (Reveille 1998). Furthermore, the detailed molecular characterization of HLA polymorphism during the 1980s gave rise to the 'shared epitope' hypothesis (Gregersen et al. 1987). It has been estimated, however, that MHC linked genes account only for one third of the genetic contribution to risk for RA (Rigby 1992, Deighton et al. 1989).

The course of RA in an individual patient can not be predicted with accuracy at the onset. Early studies indicated that positive rheumatoid factor (RF), presence of subcutaneous nodules, erosions, Raynaud's phenomenon, and extra-articular disease were associated with

poor long-term outcomes (Bywaters et al. 1961, Ragan and Farrington 1962, Reah 1963, Cats and Hazevoet 1970, Benn and Wood 1972, Jacoby et al. 1973, Gordon et al. 1973, Fleming et al. 1976, Feigenbaum 1979). More recent reports have revealed that also low social class, short formal education, poor functional status (Pincus and Callahan 1985, Pincus et al. 1987), and high clinical disease activity at the onset (Möttönen et al. 1998) contribute to poor long-term outcomes. Opinions are divided as to whether the dosage of the 'shared' epitope gene affects the course and outcomes of RA (Weyand et al. 1992, Möttönen et al. 1998).

2.2 The rationale for the use of disease-modifying antirheumatic drugs for RA

Until ten years ago, RA was in textbooks considered in the majority of patients to be a disease with a good prognosis which could be controlled by means of well-accepted conservative regimens (in: McCarty 1985, Kelley et al. 1989). Accordingly, the aim of the treatment was simply to relieve the symptoms. Non-steroidal anti-inflammatory drugs (NSAIDs) were the basis of medication. Patients were treated with these palliative drugs for many months or years in the early phases of the disease, which, in fact, may be the most important therapeutic window for disease-modifying drugs. The DMARDs were used cautiously. Toxicity rather than efficacy determined the rank order of the use of the DMARDs: the least toxic drug was prescribed first followed by those which were regarded as more toxic.

The findings in the 1970s and 1980s revealed that the traditional approach to treatment failed to prevent joint damage, disability and mortality in most patients with persistent polyarthritis (Isomäki et al. 1975, Mäkisara and Mäkisara 1982, Pincus et al. 1984, Scott and Bacon 1985, Wolfe and Hawley 1985, Sherrer et al. 1986, Pincus and Callahan 1989). Consequently, the paradigms concerning RA were changed, and the traditional treatment strategy, the so called 'pyramidal model of treatment' was challenged by more active treatment modalities. Luukkainen et al. (1978) suggested early initiation of intra muscular gold before signs of radiographic joint damage. Fries (1990) introduced early, serial, and continual use of DMARDs, known as the 'sawtooth' strategy. Other authorities, too, advocated a more active approach (Wilske and Healey 1989, Pincus and Wolfe 1991). Active treatment strategies were expected to provide potency for better long-term outcomes for RA.

Since the causes of RA have not been established, the targets for therapies remain unknown. Thus the basis of drug treatment for RA is empirical. However, several drugs with different chemical structures have been found to suppress inflammatory activity in RA compared to

NSAIDs or placebo. These drugs are known as disease-modifying, slow-acting or second line antirheumatic drugs. The compounds include intra muscular (GST) and oral (AURA) gold, antimalarials (HCQ), sulphasalazine (SASP), methotrexate (MTX), azathioprine (AZA), D-penicillamine (DPA), cyclosporin-A (CYA), cyclophosphamide (CYP), chlorambucil (CB), and podofyllotoxine derivatives (PODO). These drugs differ from each other with respect to their disease-modifying properties and toxicity profiles as well as drug survivals (Wolfe et al. 1990, Pincus et al. 1992, Felson et al. 1992).

2.3 Process and outcome measures of RA

Several types of quantitative measures have been developed to assess the level of activity of the disease and to judge, monitor, and predict its course. These measures include demographic parameters, clinical and laboratory measures to mirror systemic or local inflammatory activity, physical measures or questionnaires to assess symptoms and signs of the disease as well as the functional status of the patient. On the other hand, valid long-term outcome measures in RA include measures reflecting the patient's functional status and the extent of joint damage by numerically scored radiographs as well as observations on the ultimate social and physical results of the disease: work disability and premature death. Tables 1 and 2 show core-sets of measures recommended by consensus meetings to assess outcome of RA in clinical trials and in longitudinal observational studies (Tugwell et al. 1993, Wolfe et al. 1999).

Table 1. Core-set of endpoint measures in RA clinical trials.

Joint pain/tenderness: 28 joints
Joint swelling: 28 joints
Acute phase reactants
Pain
Patient's global assessment of disease activity
Physician's global assessment of disease activity
Physical disability
Radiographs (for studies > 1 year)

Table 2. Core-set of domains for longitudinal observational studies.

Health status
QOL / Health status instruments
Symptoms
Physical function
Psycho-social function
Disease process
Joint tenderness / swelling
Global assessment of disease activity (by patient and by clinician)
Acute phase reactants
Damage
Imaging
Deformity
Surgery
Organ damage
Toxicity / Adverse reactions
Mortality
(Work disability)
(Costs)

2.4 DMARDs and clinical disease activity in RA

Clinical disease activity can be measured by several methods: laboratory tests (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP], haemoglobin, and platelets), counts of tender and swollen joints, physical measures and questionnaires to assess symptoms and functional status as well as patient's and physician's global assessments of the disease. Because it is impossible to measure disease activity in RA by a single variable, several indices have been developed to make the interpretation of disease activity more unambiguous. The first of these was the Landsbury systemic index (Landsbury 1956) succeeded by the Mallya/Mace index (Mallya and Mace 1981), and the Stoke index (Davies et al. 1990). The most widely used, however, is the Disease Activity Score (DAS) (van der Heijde et al. 1993, Prevoo et al. 1995), which is a statistically derived index combining tender and swollen joint counts, ESR, and by self-assessed general health.

Controlled clinical trials lasting from a few months to two years have shown that DMARDs suppress inflammatory activity in RA, and thus can be separated from placebo or NSAIDs,

which do not possess this property (Borg et al. 1988, Nuver-Zwart et al 1989, Hannonen et al. 1993, Peltomaa et al. 1995, Landewe et al. 1994, van der Heide et al. 1996, Clark et al. 1998, Suarez-Almazor et al. 1998a, 1998b, 1998c, 1998d). In addition, maintenance therapy with DMARDs is effective in preventing flare-ups of the disease when compared to placebo (ten Wolde et al. 1996). Although the course of RA is variable with single, periodical or persistant flare-ups, measures of inflammatory activity tend to decrease over time (Hawley and Wolfe 1992, Callahan et al. 1997). On the other hand, no drug has been found to control the inflammatory process completely for prolonged periods. In advanced RA, fewer than 1% of patients treated with GST or DPA experienced remissions lasting longer than 3 years (Wolfe and Hawley 1985), while in recent-onset disease it was possible to discontinue DMARD therapy in 4-6% of cases, due to remission (Wijnands et al. 1992, Suarez-Almazor et al. 1995).

Suppression of disease activity in short-term clinical trials was earlier thought to provide a reasonable surrogate marker for long-term outcomes in RA (Fleming and DeMets 1996). Activity markers, however, are reversible and thus merely reflect the process of the disease, while damage of organs is mostly irreversible (e.g. joint deformity) and is required in documenting true long-term outcomes in RA (Pincus 1988).

2.5 DMARDs and radiographic joint damage in RA

Radiographs are traditionally used to measure joint damage. Steinbrocker was the first to quantitate the extent of radiographic damage (Camp 1971). Later Larsen (1977), Sharp (1983), Genant (1983), and Kaye (1987), and their colleagues have developed more detailed scoring systems for joint destruction shown in radiographs.

Erosions of cartillage and bone structure as well as narrowing of the joint space start to appear within the first few years of the disease (Thould and Simon 1966, Brook and Corbett 1977, Scott et al. 1985, Fuchs et al. 1989). These reports also suggest that the rate of radiographic damage is at its most rapid in the early stages of the disease. Damage, however, appears to progress at least up to 20 years after the diagnosis (Kaarela and Kautiainen 1997).

In evaluating the efficacy of DMARDs, joint damage observed in radiographs has been the gold standard, although radiographic assessment is an insensitive measure in the short-term (up to 12 months) (Pincus 1995a). Several DMARDs including MTX (Weinblatt et al. 1988, Reykdal et al. 1989, Jeurissen et al. 1991, Rau et al. 1991, Drosos et al. 1997, van Riel 1995), CYA (Forre et al. 1995, Pasero et al. 1996), SASP (van Riel et al. 1995, van der Heijde et al. 1989), GST (van Riel et al. 1995, Sigler et al. 1974), and CYP

(Cooperating Clinics 1970), have been shown to slow radiographic progression of the peripheral small joints of patients with RA in the short-term, while there is little evidence to suggest that DMARDs change the long-term radiographic outcome of RA. Luukkainen et al. (1977) found that the progression of radiological destruction was statistically significantly less marked in those patients with RA who were able to continue intra muscular gold therapy compared to those who were not. Heikkilä and Isomäki (1994) analyzed hand and foot radiographs of RA patients who had been admitted to the Rheumatism Foundation Hospital in Heinola in 1962, 1972, 1982 and 1992. They found a decline in the number of eroded joints over time, and concluded that the finding might be due to the improved therapy. In a prospective study of early RA patients, Möttönen et al. (1996) found that the rate of peripheral joint erosiveness was markedly slower in Finnish patients who had been treated actively with DMARDs than in Swedish patients treated more sparsely with DMARDs (Eberhardt et al. 1990). Furthermore, Rau and Herborn (1996) found reparative changes in joints of RA patients treated actively with DMARDs over long periods. Finally, a paper from Israel indicated that the radiographic outcome of patients never treated with DMARDs was poorer in comparison to DMARD recipients (Abu-Shakra et al. 1998).

2.6 DMARDs and functional capacity in RA

The functional capacity of the musculosceletal system can be assessed by various physical measures including e.g. grip strength, walking time, and the button test (Lee et al. 1973, Deohar et al. 1973, Clawson et al. 1971). In general, however, the functional capacity of patients with RA is assessed by self-administered questionnaires such as the Stanford Health Assessment Questionnaire (HAQ) (Fries et al. 1980) and Arthritis Impact Measurement Scales (AIMS) (Meenan et al. 1980). While the HAQ addresses domains of activities of daily living (dressing, arising, eating, walking, hygiene, reach, grip, and outside activities), the AIMS also include psychological and social domains. The most widely used assessment instruments in the clinical monitoring of RA are the HAQ and its modified version MHAQ (Pincus et al. 1983), which provide a valid, reliable, and feasible method to assess patients' functional status (Hawley and Wolfe 1992).

The questionnaire scores have been shown to correlate significantly with both disease activity and joint damage measures (Pincus et al. 1989, Hakala et al. 1993, Kaarela and Sarna 1993, van Leeuwen et al. 1994, Guillemin et al. 1994, Eberhardt and Fex 1995). In early RA, the functional capacity of a patient is mainly determined by activity of the disease, while in late disease, the joint destruction plays an increasing role (Guillemin et al. 1992). Thus, functional capacity may mirror different aspects of RA, depending on the phase of the disease.

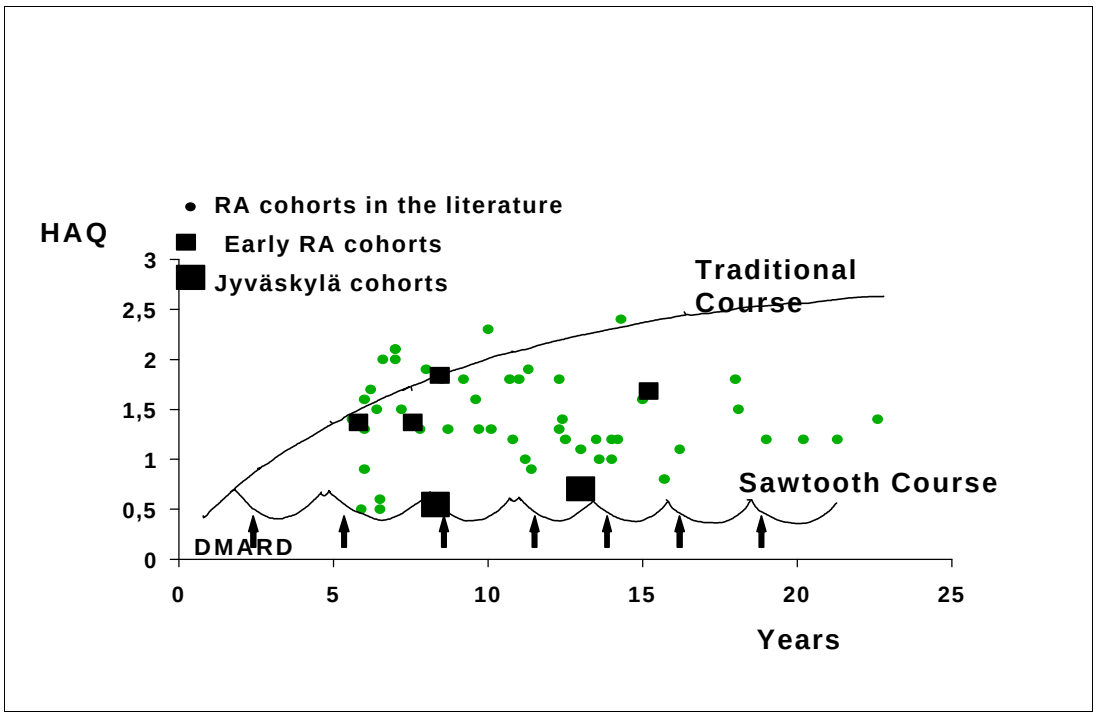

Figure 1. 'The sawtooth strategy' as illustrated by Fries (1990). The progressive deterioration of functional capacity demonstrates the natural or traditional course of RA. When DMARDs are used early, continually, and serially, the course of functional capacity is expected to show a sawtooth shape, and even after 10-20 years may remain on the same level as at the onset.
The mean or median HAQ scores of 50 cohorts as well as the mean HAQ scores of the present study (group 1 and group 2) are shown in the figure. The numbering of cohorts is explained in original publication no III.

In controlled clinical trials several DMARDs have shown a short-term improvement in functional capacity as measured by the HAQ (Wolfe et al. 1993, Ferraz et al. 1994, Tugwell et al. 1995, Mladenovic et al. 1995, Stein et al. 1997, Boers et al. 1997, Borne et al. 1998, Zeidler et al. 1998, Smolen et al. 1999). On the other hand, in long-term follow-up studies severe functional decline has been found over time (Hawley and Wolfe 1992). Figure 1, originally sketched by Fries (1990), summarizes the HAQ of 50 cohorts of patients who have suffered from RA for longer than five years as well as the mean HAQ scores of the cohorts presented in the present study.

Several beneficial results of the use of DMARDs on the relatively long-term outcome of RA have been reported. Increased use of DMARDs was associated with better long-term HAQ values in patients in the ARAMIS database (Fries et al. 1996). Improved or at least stable functional capacity was also seen in RA patients who tolerated sustained therapy with GST,

SASP or DPA in Scottish studies (Porter et al. 1994, Capell et al. 1998). Further, lower progression of functional disability in patients who had continuing care from rheumatologists in comparison to those who had only intermittent care (Ward et al. 1998) may also have been influenced by the more intensive use of DMARDs by these patients. Egsmose et al. (1995) demonstrated that RA patients who had been treated early with DMARDs had statistically significantly better five-year HAQ scores than another group with delayed DMARD initiation. In the study by Möttönen et al. (1996) the six-year mean HAQ score was only 0.64 in the patients had been treated with DMARDs from diagnosis onwards according to the 'sawtooth' strategy. A beneficial effect of early initiation with DMARDs may also have been a reason for the good functional outcome of 128 Canadian RA patients (Suarez-Almazor et al. 1994). Finally, Munro et al. (1998) reported that early therapy with GST offered a long-lasting (at least for five years) better functional capacity compared to delayed initiation with GST.

2.7 DMARDs and working capacity in RA

An important criterion for morbidity in chronic diseases like RA is work disability. The stage of work disability can be measured e.g. as number of days absent from work, or limitations in ability to be gainfully employed. Mostly, as in the present context, the concept of permanent work disability is defined as stopping paid work prior to the normal retirement age of 65 years, due at least in part to RA.

In 1982, Mäkisara and Mäkisara (1982) reported that 50 per cent of patients with RA were incapable to paid work ten years after contracting the disease. In spite of wide social and economical variations between western countries, the observation appears to concern most of them (Yelin et al. 1980, Pincus et al. 1984). Moreover, some recent reports demonstrate the development of considerable work disability already during the first few years of RA (Kaarela et al. 1987, Borg et al. 1991, Doeglas et al. 1995, Mau et al. 1996, Fex et al. 1998).

Table 3 summarizes the results of studies with regard to working capacity in RA, and indicates considerable work disability in patients from two to 30 years of onset. Older age, longer disease duration, lower educational level, physically heavier work, and low functional capacity were reported to predict or be associated with work disability (Table 3).

Little is known about the impact of drug treatments on the development of work disability. Borg et al. (1991), however, reported that early treatment with DMARDs in recent onset RA appeared to protect against work disability.

Table 3. Comparison of studies regarding working capacity in rheumatoid arthritis.
Explanations: No of pts: the number of patients gainfully employed at the onset of RA. Disease duration: Mean disease duration at the study time point. Able to work: Three figures represent: percentage of patients able to work as reported in the article/ recalculated figure indicating the percentage of patients able to work out of those who were under the age of 65 at the final evaluation / recalculated figure indicating the percentage of patients gainfully employed at the study end from those gainfully employed at the onset of RA.

First author	Country	Setting	No of pts	Disease duration	Able to work (%)	Variables predicting work disability(-) work ability(+), no association (±)
Yelin	USA 1980	Cross sectional	180	10	40	*Univariate analysis, Discriminant analysis* (-) disease severity, longer disease duration, married people (+) better premorbid earnings, white collar occupations, self-employement (±) medical or surgical therapies, physical demands of work
Mäkisara	Finland 1982	Cross sectional	144 131 130	5 10 15	60 / 60 / 60 50 / 53 / 50 33 / 38 / 31	*Univariate analysis* (-) older age, lower functional capacity (+) physically light work, better education, vocational training
Pincus	USA 1984	Longitudinal 9 yrs follow up	48 27	11 20	40 / 40 15 / 15	
Yelin	USA 1987	Longitudinal 4 yrs follow up	306; all under 65yr at the final visit	10 15 30	50 / 50 / 50 40 / 40 / 40 10 / 10 / 10	*Logistic regression analysis* (-) lower functional level, older age, disease activity (=painful joints) service work, physically heavy work (+) work adjustments (±) disease severity
Reisine	USA 1989	Cross sectional Only women	122	NR	57 / ?/ 57	*Logistic regression analysis* (-) higher HAQ score, lower work autonomy, physically demanding job, older age, more severe disease

Callahan	USA 1992	Cross sectional	175	10.7	28 / 28 / 21		*Univariate analysis, Logistic regression* (-) older age, longer disease duration, non-professional occupation, current disease activity, x-ray scores, functional disability, comorbid conditions (+) better education (±) serology, HLA-DR4
Allaire	USA 1995	Cross sectional mail survey	469	7	78 / 78 / 78		*Univariate analysis, Logistic regression* (-) older age, shorter education, longer duation of RA, more pain worse functional status, blue collar job, heavier work, less support from co-workers, greater commuting dificulty lower income when last working
Doeglas	NL 1995	Cross sectional	119	1,8	NR / 45		*Univariate analysis, Logistic regression* (-) older age in women, lower educational level, higher disease activity, higher HAQ score, more medicines and surgical treatments
Kaarela	Finland 1987	Early RA prospective	103	7.7	36 / ≥36 / 36		At study end. *Univariate analysis* (-) severity of disease including Larsen index and joint count
Borg	Sweden 1991	Early RA prospective	83	2	NR / 63	*Cox regression analysis* (-) blue collar work, older age higher HAQ score	
Mau	Germany 1996	Early RA prospective	73	7	47 / 51 / 47	*RECPAM analysis* (-) older age with severe disease (+) age<50yr with milder disease and light work	

Fex	Sweden 1998	Early RA prospective	86	8	Working full time NR / 40 / 31 Working full+part time 63 / 66 / 51	At the start of the prospective study when already 36/86 patients were disable to work predicting work status at 4yr. *Logistic regression analysis* (-) older age, lower educational level, higher HAQ score	*Univariate analysis* (-) lower educational level, higher HAQ score, higher number of active joints, more joint pain, more physical workload At study end. (-) higher HAQ score (±) age, radiological score

NR=not reported, RECPAM=RECursive Partition and AMalgation

2.8 DMARDs and mortality in RA

Nearly 50 years ago Cobb et al. (1953) showed that the mortality of RA patients was approximately 30% higher than that in the general population. Since then, reduced life expectancy has been reported in all studies on mortality in RA (Table 4) with the exception of a population based study (Linos et al. 1980), and two recent studies with early RA patients (Lindqvist and Eberhardt 1999, Kroot et al. 1998). Table 4 summarizes the studies on mortality in RA, and shows that compared to the general population, the standardized mortality ratio (SMR) is increased up to 3-fold. On the other hand, loss of life expectancy up to 15 years has been observed (Table 4).

In RA, the distribution of causes of death is similar to that of the general population. Cardiovascular comorbidity, succeeded by infections and renal diseases, however, appear to explain excess mortality in patients with RA (Mutru et al. 1985, Wolfe et al. 1994, Myllykangas-Luosujärvi et al. 1995b, Symmons et al. 1998). Several lines of evidence have connected inflammation with the atherosclerosis process in general, and with acute intravascular thrombosis, especially (Liuzzo et al. 1994, Thompson et al. 1995, Ridker et al. 1997). These findings have lead to the interpretation that RA may act as a risk factor for cardiovascular diseases.

The earliest reports indicated that severe disease with extra-articular manifestations was a risk factor for early mortality in RA (Gordon et al. 1973, Sharp et al. 1964). Pincus et al. (1984) found that decline in functional capacity, and also lower socioeconomic status measured by formal educational level predicted premature death in RA, as is also the case in other chronic diseases (Pincus and Callahan 1985).

The increased mortality ratio of patients with RA has been discussed in more detail since the 1980s (Pincus and Callahan 1986, Pinals 1987). Several authorities have suggested that awareness of the excess mortality of patients with RA should be incorporated in the management of the disease (Symmons 1988, Pincus and Callahan 1993). Recently, mortality has been recommended for inclusion in the core set of domains for longitudinal observational studies in rheumatic disorders (Table 2, Wolfe et al. 1999).

Most DMARDs may have side effects. A fear of serious and even fatal side was one of the reasons for sparse use of DMARDs in the past. Myllykangas-Luosujärvi et al. (1995a) studied documents on 1,666 Finnish patients with RA who died in 1989, and found that DMARDs contributed in only 0.0036% of the deaths .

The first report to suggest that the use of DMARDs reduces mortality was that by Lehtinen and Isomäki (1991). They found that sustained GST therapy was associated with longer survival. On the basis of a large database, Wolfe et al. (1998) found that patients who took MTX as a single DMARD

showed a 50% reduction in mortality hazard, and those on MTX regardless of concomitant treatment had a reduction of 39%.

Table 4. Mortality in rheumatoid arthritis

Inclusion, place	1. author, publ.yr	Follow-up, years	N	SMR	(results)
1930-60, Boston, USA	Monson, 1976	12-42	1035	185	
1948-51, Edinburgh, UK	Duthie, 1964	9	307	214	
1950-74 Rochester/ Minnesota, USA	*Linos, 1980*	*1-25*	*521*	*116*	
1954-57, Leiden, NL	Vandenbroucke, 1984	25	209		(7 yrs loss of life exp.)
1954-66 Ontario, Canada	Uddin, 1970	4-10	475	129	
***1957-63 Bath, UK	Jacoby, 1973	8-14	100		(causes)
	Rasker, 1981	18			(5-15 yrs loss of life exp.)
	Reilly, 1990	25		140	
1959-68 Heinola, FIN	Isomäki, 1975	3	1000	177	
	Koota, 1977	5		164	
	Mutru, 1985	10		173	
1964-66 Droitwich, UK	Scott, 1983	5-10	112		(causes)
	Scott, 1987	20			(causes)
1964-78 Birmingham, UK	Prior, 1984	3-18	489	300	
	Symmons, 1986	18			(prognostic factors)
	Symmons, 1998	21.5	448	240 (M) 300 (F)	
1965-67 Stockholm, Swe	*Allebeck, 1981*	*11*	*239*	*192 (M)* *118 (F)*	
	Allebeck, 1985	*13*			*(causes)*
1965-89 Arizona, USA	*Jacobsen, 1973*	*2-25*	*172*	*128*	
1965-90 Stanford, USA	Wolfe, 1994	-25	886	308	
1966 Cambridge, UK	Lewis, 1980 11		311	113	
***1966-71 Middlesex,UK	Fleming, 1976	4.5	102		(prognostic factors)
	Corbett, 1993	15			(causes)
1966-74 Saskatoon, Can	Mitchell, 1986	12	805	151	
	Wolfe, 1994	-35	905	224	
1971 Stockholm, Swe	Allebeck, 1982	6	1165	250	
1973 Tennessee, USA	Pincus, 1984	9	75		(causes)
	Pincus, 1987				(prognostic factors)
	Pincus, 1994	15		160	
1973-79 Wichita, USA	Wolfe, 1994	-15	1405	198	
1976-79 London, UK	Erhardt, 1989 7-10		107		(causes)
1978 Santa Clara, USA	*Leigh, 1991*	*10*	*330*		*(prognostic factors)*
	Wolfe, 1994	*10*		*218*	
1984-85 Glasgow, UK	Capell, 1998	12	200		(causes)
***1985-89 Lund, Swe	Lindqvist, 1999	10	183	87	
***1987- Nijmegen, NL	Kroot, ACR-98	-10	622	100	
1989-91 Kuusamo, FIN	Söderlin, 1998	5	103		(prognostic factors)
Finland	Myllykangas-L, 1995		1666		(15-20% loss of life exp since the onset of RA)

Clinical series
Community series

* **early RA

3. AIM OF THE STUDY

The purpose of the present study was to obtain information on the influence of the extensive use of DMARDs on the long-term outcomes of patients with RA. The study was based on 135 patients with recent onset RA who have been treated with DMARDs continually and serially after diagnosis, according to the 'sawtooth' strategy. The specific aims of the present study were:

1. To examine the utility of DMARDs in the 'sawtooth' strategy in the long-term (I).

2. To compare the radiographic progression of patients with early seropositive RA who have been treated according to the 'sawtooth' strategy or more sparsely with DMARDs over eight years (II).

3. To examine the long-term functional outcome of patients with early RA who have been treated either according to the 'sawtooth' strategy, and to compare it with that of historical control cohorts (III).

4. To examine the development of work disability in patients with early RA who have been treated according to the 'sawtooth' strategy over ten years (IV).

5. To examine the 8-14 year mortality of patients with early RA who have been treated according to the 'sawtooth' strategy (V).

4. PATIENTS AND METHODS

4.1 The patients

Jyväskylä Central Hospital is the only rheumatological center in the Central Finland county, which has a population of 260,000. All new RA cases are referred to the center for diagnostic and therapeutic purposes.

In the 1980s, 135 early RA patients were recruited to two prospective RA studies at Jyväskylä Central Hospital. The first group consisted of 58 (group I) and the second of 77 (group II) early RA cases collected during 1983-85 and 1988-89, respectively. The first group was assembled to study early erosiveness in recent onset RA (Möttönen 1988), and the second to investigate the efficacy and tolerability of SASP in early RA (Hannonen et al. 1993). Subsequently all the patients were enrolled in a prospective follow-up study to evaluate the utility of continual and serial use of DMARDs or combinations (COMBOs) of these, later designated as the 'sawtooth' strategy by Fries (1990). The patients were examined every three months during the first two years and at least annually thereafter up to 15 years or until death. Arthritis was judged seropositive if RF was positive at any time during the observation period. The baseline demographics and clinical variables of the patients are shown in Table 5.

Table 5. Demographic and clinical characteristics (mean, SD) of the 135 early RA patients at the baseline (*seropositivity during the follow up).

	Group I	Group 2
N	58	77
Age, years	48.0 (16.0)	52.0 (15.2)
Duration of symptoms, months	8.1 (6.0)	5.1 (3.7)
Gender, female, # (%)	41 (73%)	49 (65%)
*Seropositive, # (%)	46 (79%)	53 (70%)
ESR	39.8 (25.3)	38.0 (20.2)

ESR=erythrocyte sedimentation rate

One patient was lost to the follow-up at one year and was thus excluded from the studies on the utility of the 'sawtooth' strategy and on the long-term functional outcome (I, III). However, he was still alive in November 1998 and was included in the study on mortality (V).

One person was initially included in the group II but was excluded because she was later diagnosed to suffer from reactive arthritis. Thus, although group II initially consisted of 78 patients, 77 cases were included in the analyses.

The historical control cohort had been collected during 1973-1975 at the Rheumatism Foundation Hospital in Heinola. Initially, 121 patients with recent-onset (less than 6 months) RA were included. A total of eight patients died, seven were lost to the follow-up, and three remained seronegative. Thus, the Heinola Follow-up Survey (Kaarela 1985) consists of the 103 patients with seropositive RA who were seen by Dr. Kalevi Kaarela at their 8-year check-up, and who were also the historical control cohort of the present study (II).

At the baseline, all the patients met the American Rheumatism Association (ARA) 1958 criteria (Ropes et al. 1958) for definite or classical RA, as well as the American College of Rheumatology 1987 criteria (Arnett et al. 1988) for RA at some period.

4.2 Treatment with DMARDs

For group I patients GST was initiated at the diagnosis, while SASP or placebo was initially administered in group II patients. According to the written protocol, in case of inefficacy or toxicity, GST was started as the second DMARD in group II patients but otherwise the rank order choice of DMARDs was at the treating clinician´s discretion.

The median maintenance daily doses of DMARDs were 300 mg for HCQ, 2,000 mg for SASP, 450 mg for DPA, 150 mg for AZA, 200 mg for CYA, 6 mg for AURA, 300 mg for PODO, 4 mg for CB, and 150 mg for CYP. The respective median doses for GST and MTX were 50 mg monthly and 10 mg weekly. With the exception of the 1,000 mg daily dose for SASP, the same median doses were also used in COMBOs.

The use of DMARDs and systemic glucocorticoids was documented at every visit until the last visit in January 1999 or until death (25 cases). The interval from the initiation to the discontinuation of a DMARD or a COMBO was defined as a DMARD period. All DMARD periods were included in the analysis regardless of whether a patient had more than one DMARD period on a particular DMARD. All new starts of individual DMARDs or COMBOs as well as the proportion of the time the patients were on DMARDs out of the total follow-up time were calculated.

The reasons for discontinuations of DMARD periods were categorized as 1) inefficacy: a) insufficient suppression of clinical disease activity or b) loss of the beneficial effect after the primary response as assessed by the attending physician, 2) remission (Pinals et al. 1981), 3) toxicity: a) cytopenias, b)

proteinuria, c) clinically meaningful increase in serum creatinine concentration, d) clinically meaningful increase in blood pressure, e) elevation in serum transaminase activities, f) gastrointestinal adverse effects, g) dermal and mucocutaneous adverse effects, h) adverse effects in the respiratory tract, i) accelerated growth of rheumatoid nodules, and j) miscellaneous symptoms without objective findings, and 4) other reasons: a) pregnancy, b) comorbidities, c) drug costs, d) other, often the unexplained unwillingness of the patient to continue on the chosen DMARD or COMBO.

For the Heinola cohort patients, DMARD treatment with gold sodium thiomalate (GST), chloroquine (CHQ) or d-penicillamine (DPA) was started at the time of the initial hospitalization in 93 cases, and in a total of 102/103 cases during the first year. In the case of toxicity of GST and/or DPA, patients were obliged to continue with CHQ or without DMARDs (Kaarela 1985).

Point prevalences of the patients on individual DMARDs or their combinations were calculated for the Heinola cohort patients at 0, 1, 3 and 8 years, and for the Jyväskylä cohort patients yearly up to 8 years after diagnosis. The use of systemic glucocorticoids was also documented. (II)

4.3 Assessment of radiographic damage

Radiographs of hands and feet were taken at the time of diagnosis, and intervals of one to two years thereafter. In the historical cohort the radiographs were taken one, three and eight years after diagnosis.

The Larsen score (Larsen et al. 1977, Larsen 1995) was used to grade the structural damage in the small joints of the hands and feet. The radiographs were compared to the reference films to assess each joint with a scale of 0-5 reflecting the extent of the damage. Normal joints and joints with only swelling of soft tissues or osteoporosis were assigned Larsen grade 0, and joints with pre-erosive changes or manifest joint space narrowing were assigned Larsen grade 1. Erosive joints were scored from 2-5 according to the reference films. In cases of reconstructive surgery, preoperative radiographs were assessed.

The scale of the Larsen score depends on the number of joints that are included in the analysis. Larsen score 0-100 consists of the assessment of wrists, metacarpophalangeal (MCP) I-V and metatarsophalangeal (MTP) II-V joints, while Larsen score 0-210 also includes the proximal interphalangeal (PIP) joints of hands, MTP I, and interphalangeal joints (IP) of the big toes. In Larsen score 0-210, the scores for the wrists are multiplied by 5. Larsen score 0-100 was used in publication II, while Larsen score 0-210 was applied in publications III and IV.

All the radiographs of the cohort patients were assessed by Dr. Tuulikki Sokka. The radiographs for publication II were assessed by Dr. Kalevi Kaarela.

4.4 Assessment of functional capacity and related factors

In January 1997, the 111 surviving cohort patients were examined with special emphasis on the patients' functional outcome and the related factors. The examination included assessments of the number of tender and swollen joints, a blood test for ESR, radiographs of hands and feet, as well as patients' self-assessed pain, general health (GH) and functional status.

The patients' functional capacity was assessed by the HAQ scored from 0 to 3 (Fries 1980). Current disease activity was measured by the 28-joint based DAS [= 0.56 * SQRT(tender joint count) + 0.28 * SQRT(swollen joint count) + 0.70 * LN(ESR) + 0.014 * GH], ranging from 0 to 10 (Prevoo et al.1995). Pain and GH were self-assessed according to the 100 mm horizontal visual analogue scales (VAS; 0 indicating no pain or excellent general health, and 100 indicating the most severe pain or the poorest imaginable GH) (Fries et al. 1980).

A Medline computer search was performed to identify reports which contained the HAQ scores of cohorts of patients with RA who had suffered from the disease longer than for five years. Our results were compared with these historical data.

4.5 Assessment of work disability

A total of 82 out of the 135 cohort patients were gainfully employed at the onset of RA. The patients' data were analyzed until January 1997 or in two cases until death, with the emphasis on permanent work disability due to at least in part to RA before the normal retirement age of 65 years. The date of permanent work disability was confirmed against disability certificates.

Sociodemographic variables including age, gender, race (all were Caucasians), marital status, as well as type and physical demands of occupation were documented at the first visit. Working capacity and possible job changes were documented at every check-up. At an extra outpatient visit in January 1997, the patients were interviewed with regard to their formal educational level and the type as well as physical demands of their present or the last occupation (in cases the patient had retired). For the statistical comparisons, occupation was classified into three categories, 1) white collar, 2) blue collar and 3) self-employed. Formal educational level was categorized according to length of education: 1) >12, 2) 9-12, and 3) <9 years. The physical demands of the jobs were graded as 1) light (sedentary work), 2) moderately demanding (sales and service workers) and 3) demanding (manual workers in manufacturing and agriculture).

4.6 Assessment of mortality

Causes of death were identified from death certificates and patient files. Age and gender specific person-years at risk were computed from the date of diagnosis to November 30, 1998, or until to death. Expected numbers of deaths were calculated for the person-years at risk by applying the time and age adjusted mortality rates for the population of Central Finland. Population estimates were taken from the Official Statistics of Finland (Helsinki, 1997). Mortality was expressed as a standardized mortality ratio (SMR) with 95% confidence intervals (CI95%).

5. STATISTICAL METHODS

SPSS/PC+ programs (SPSS Inc., Chigaco) were used to perform the statistical analyses. The Mann-Whitney test was used for unpaired comparisons, and the Chi-Square test for the categorical variables.

The Kaplan-Meier analysis (Kaplan and Meier 1958) was used to illustrate the development of work disability (IV).

To determine possible baseline factors predicting permanent work disability, the Cox regression analysis (Cox and Oakes 1984) was used with the following covariates: patients' age in years, gender (male vs. female), marital status (married vs. not-married), serology (seropositive vs. negative), swollen joint count, occupation (blue collar, and self-employed compared to white collar), length of formal education (<9 years, and 9-12 years compared to >12 years), and physical stress at work (physically medium and heavy work compared to light work) (IV).

The Cox regression analysis (Cox and Oakes 1984) was applied to determine baseline factors predicting mortality, with the following covariates: patient's age in years, gender (male vs. female), serology (seropositive vs. seronegative), occupation (blue collar and self-employed compared to white collar), and length of formal education (<12 years compared to <12 years) (V).

6. ETHICS AND PERMISSIONS

The Ethical Committee of the Jyväskylä Central Hospital approved the study. All the patients gave an informed consent. The Ministry of Health granted permission to use official registers to analyze data on patients and hospital records. The Statistical Office of Finland granted permission to obtain copies of death certificates. The Journal of Rheumatology and Professor Fries gave their permissions to use Figure 1.

7. RESULTS

7.1 Utility of DMARDs in the 'sawtooth' strategy (I)

During a total of 1,401 person years, the 135 patients were challenged 606 times with a single DMARD or a COMBO. The median (range) number of DMARD periods was six (1-16) and three (0-12, one patient never needed DMARDs due to self-remitting arthritis) in groups I and II, respectively. GST and SASP were the most commonly used DMARDs followed by COMBOs (with or without MTX) (Sokka et al. 1997), MTX, HCQ, AURA, and AZA. The median survival of the DMARD periods was ten months, ranging from six to 18 months for individual DMARDs when both the 528 discontinued and 78 periods ongoing were included.

A total of 528 (87.1%) out of the 606 DMARD periods were discontinued. Respectively, 270 (51.1%), 149 (28.2%), and 77 (14.6%) DMARD periods were terminated due to inefficacy, adverse reactions and other reasons, while in only 32 (6.1%) cases a DMARD period was stopped due to clinical remission. A DMARD was stopped due to clinical remission only during the three first rank order DMARD periods, while inefficacy remained the leading reason for discontinuation throughout the follow-up. Expectedly, the adverse effects were manifested as skin and/or mucosal and gastrointestinal symptoms and signs, and miscellaneous symptoms without objective findings accounted for 74% of all adverse reactions leading to discontinuation of DMARDs. Serious adverse reactions were rare: one reversible agranulocytosis due to SASP and one GST induced pneumonitis were seen. Less severe cytopenias led to discontinuation of an additional seven DMARD periods. Further, none of the deaths during the observation period were related to the use of DMARDs.

Not a single DMARD/COMBO stood out favourably from the others with respect to inefficacy, toxicity or drug survival.

7.2 Radiographic progression of 'sawtooth' treated seropositive patients compared to patients treated more sparsely with DMARDs (II)

We compared the progression of the erosion rate of 85 seropositive RA patients in the Jyväskylä cohort to that of 103 patients in the historical control cohort. From the onset to year eight, the median (IQR) Larsen score increased from 1 (0, 4) to 25.5 (8, 43) for the historical cohort patients, and from 0 (0, 2) to 12 (4, 28.5) for the Jyväskylä cohort patients. The progression of Larsen score over the eight years was statistically significantly higher for the historical cohort patients than for the Jyväskylä patients ($p=0.001$). Furthermore, radiographic damage remained under 20% of the maximum in 44 (43.1%), and in 55 (64.7%) cases in the historical cohort and the Jyväskylä cohort, respectively.

The historical control cohort patients were treated with GST, HCQ, and DPA, while eight additional

DMARDs and various DMARD combinations were used for the Jyväskylä cohort patients. At the eight year visit, 23%, 33%, and 2% of the historical patients, and 6%, 45%, and 21% of the Jyväskylä cases were treated with HCQ, other individual DMARDs, and DMARD combinations, respectively. During the observation period of eight years, 56% of the Heinola cohort patients and 55% of the Jyväskylä cohort patients used systemic glucocorticoids at least periodically.

7.3 Long-term functional capacity of the cohort patients compared to historical control cohorts (III)

7.3.1 The present cohort

The mean (median) HAQ scores were 0.75 (0.63) for group I and 0.55 (0.25) for group II patients after an average duration of disease of 13.0 and 8.5 years. A total of 39 (35.1%) patients had a HAQ score of 0, while 86 (77.5%), 21 (18.9%) and 4 (3.6%) patients scored 0-1.0, 1.01-2.0 and 2.01-3.0, representing mild, moderate and severe functional impairment, respectively.

Patients with at least moderate functional disability (HAQ>1) were statistically significantly older and suffered from more active and erosive disease, had more pain, and had more DMARD starts and more joint replacements than patients with normal or slightly deteriorated functional capacity (HAQ≤1). No significant differences were seen between the groups in frequency of seropositivity, gender, and presence of extra-articular disesease.

The median amount of time the patients were treated with DMARDs out of the total follow up time was 88%.

7.3.2 Historical control cohorts

Altogether 57 RA cohorts totaling 13,591 patients with more than five years disease duration were found in 30 reports published in English from the year 1988 onwards. In the cohorts whose disease duration was between 5 and 10 years the mean (n=13) or median (n=9) HAQs and the mean MHAQs (n=3) ranged from 0.5 to 1.8 or from 1.3 to 2.3 and from 0.5 to 1.0, respectively. The corresponding figures in cohorts with disease duration >10 years were respectively 0.8 - 2.4 (n=27), 1.8 (n=1) and 0.6 - 1.3 (n=3). A statement regarding DMARD treatment was found in 24 out of the 57 referred cohorts.

7.4 Development of work disability in the cohort patients during the first ten years of RA (IV)

Of the 135 patients, 82 (61%) were in paid work, 49 (36%) had retired, and 4 (3%) were housewives at the time of diagnosis. After two and ten years from the diagnosis, 19/82 (19%) and 36/82 (44%) patients had retired wholly or partially due to RA. In January 1997, 42/82 (51%) patients were still gainfully employed, while the proportion of patients in full-time work under the general retirement age of 65 years was 58% (42/72). The Kaplan-Meier analysis demonstrated that the decline in the probability of continuing in full-time work was at its fastest during the two first years following diagnosis.

The univariate analysis of the baseline factors indicated that the 36 subsequently work disabled patients were older, less educated, and had been engaged in physically more demanding work compared to the 46 patients who were able to continue in paid work. Ten years after the onset of the disease, however, the work disabled patients suffered from more severe disease than those who had continued in paid work. Cox regression analysis showed that physically heavy work at the baseline was the strongest independent factor predicting permanent work disability. Other statistically significant and independent risk factors were patient's age and disease activity.

7.5 Mortality of the cohort patients during 8-14 years following diagnosis (V)

A total of 25 (14 women and 11 men) of the 135 patients died during the 1422 person-years before November 30, 1998. The total SMR (95%CI) was 1.28 (0.83-1.89); 1.69 (0.92-2.82) for the women and 0.98 (0.49-1.74) for the men. The length of the follow-up period ranged from eight to 14 (mean 11) years.

Ten patients died from cardiovascular (including cerebrovascular) diseases, three from cancer, two from infections, two from gastrointestinal morbidities, and another two from Alzheimer's disease. Additional causes of death in individual cases were suicide, alcohol and drug intoxication, chronic uraemia, chronic bronchitis, amyotrophic lateral sclerosis, and RA related vasculitis. Compared to the causes of death of the Finnish population, the proportions of infections and gastrointestinal morbidities were slightly higher, while the proportions of cardiovascular diseases and malignancies appeared to be comparable. In five cases death was considered to be closely related to RA or the medication. Those patients died from systemic vasculitis, septicemia, pneumonia, perforation of the sigmoid colon, and strangulation of the ileum. There were no deaths either from amyloidosis, nor DMARDs in spite of the extensive use of these drugs.

8. DISCUSSION

A randomized (placebo) controlled double-blind clinical trial has geneally been considered the most reliable method of assessing the efficacy of treatments. However, the limits of traditional clinical trials have also been recognized, and the atmosphere is becoming conducive to reports based on longitudinal observational studies. Furthermore, all the important findings concerning both the long-term outcomes of RA and effectiveness of treatments in the long-term have been derived from longitudinal observations in a clinical setting (Pincus and Stein 1995).

Longitudinal observational studies have known limitations. The most notable limitation compared to clinical trials is, naturally, the absence of a randomized control group. In our study, the radiographic findings of the study cohort were compared to the only hitherto available Finnish cohort of patients with early RA over a long observation period. The HAQ scores were compared to those of 50 cohorts consisting of both cross sectional studies and longitudinal observational studies of patients with recent-onset RA. The work disability rates and mortality of our patients were compared with those reported in the literature.

The study cohort consisted of well-documented patients with recent-onset RA. The patients were treated early, continually and serially with the available DMARDs or COMBOs according to the policy traditional in Finland (Luukkainen et al. 1978, Sokka et al. 1997). Our study is, however, the first detailed description of the longitudinal 'sawtooth' strategy in a cohort of patients with RA. The long-term benefits of the extensive use of antirheumatic drugs are clearly evident in our results.

8.1 Utility of DMARDs in the 'sawtooth' strategy (I)

This study confirmed our earlier findings that the use of DMARDs is also safe in the long run (Sokka et al. 1997).

Inefficacy was the leading reason for the cessation of DMARD periods in the majority of cases. The finding is in contrast to reports from the 1980s indicating that toxicity was the most common reason for the discontinuation of DMARDs in long-term clinical use. Situnayake et al. (1987) reported that adverse effects led to withdrawal of GST, DPA, and SASP in 57%, 41.2%, and 27% of cases, respectively, over a five-year period. In another retrospective study involving several DMARDs (Thompson et al. 1985), adverse effects accounted for 60% of all discontinuations. Furthermore, in two large patient databases from the US, adverse reactions were a more common reason for termination of DMARD use than inefficacy (Wolfe et al. 1990, Pincus et al. 1992). On the other hand, in accordance with the present study, in two other European patient cohorts, from Spain (de la Mata et al. 1995) and from the Netherlands, (Wijnands et al. 1992) inefficacy rather than toxicity led to

termination of the use of DMARDs. Furthermore, Jessop and coworkers (1998) reported that the proportion of patients who remained on their first DMARD or who were in remission at five years was 53% for DPA, 34% for GST, 31% for AURA, and 30% for HCQ. Obviously, there has been no change in the toxicity of DMARDs. The shift from toxicity to inefficacy as the leading reason for the discontinuation of the use of DMARDs more likely mirrors a change of attitude towards treatment with DMARDs. When, earlier, few DMARDs were available and DMARDs were regarded as toxic drugs, some clinical activity of RA was acceptable providing the patient tolerated the drug, whereas we are nowadays taught to treat patients up to the point where they have 'no signs of the disease' (Pincus et al. 1997).

The median duration of individual periods of DMARDs or COMBOs ranged from six to 18 months only. In contrast to earlier reports (Wolfe et al. 1990, Pincus et al. 1992, Bologna et al. 1997), MTX did not stand out favourably from the other DMARDs, but rather appeared to be comparable. On the other hand, our result is in line with that obtained in a Dutch early RA patient cohort (van Gestel et al. 1997). As with other DMARDs, the major reason for MTX discontinuations in our series was inefficacy. Whether the diverging results depend on a different choice of patients (early vs. advanced RA), different dosage of the drug (median 10 mg weekly vs. not reported), type of study (prospective vs. retrospective), differences in the rank order of the DMARDs prescribed, differences in the use of folic acid as co-medication (our patients have used folic acid routinely from 1995 onwards), or possible different attitudes and expectations of the treating physicians remain to be shown. Our aim, according to the 'sawtooth' strategy, was to treat the patients to achieve clinical remission; in 70% of cases ineffective MTX was replaced by a COMBO including MTX.

Long-lasting remission in RA is exceptional (Wolfe and Hawley 1985). In our series 32 (6.1%) DMARD periods were stopped due to clinical remission. Our figure is in accordance with other early RA cohorts indicating that DMARD treatment can be terminated in 4-6% of early RA cases due to remission (Wijnands et al. 1992, Suarez-Almazor et al. 1995). In some of these patients the course of the disease may have been self-remitting, since 5-12% of patients have achieved remission with placebo treatment (Young et al. 1987, Eberhardt et al. 1990). On the other hand, remissions seen during the first few DMARD periods may reflect an optimal therapeutic window during the early stages of RA.

In the present study, the safety of the long-term use of continual and serial DMARDs was confirmed. However, the results also undisputably indicated that the drugs presently used to treat progressive RA are insufficient and that more powerful therapies are needed.

8.2 Radiographic progression (II)

In this study we found that radiographic damage in early seropositive patients developed at a lower rate and remained lower in the Jyväskylä patients treated actively with DMARDs according to the 'sawtooth' strategy than in the historical cohort patients who were treated more sparsely with DMARDs.

The median Larsen scores at the baseline were low in both cohorts (1 for the Heinola, and 0 for the Jyväskylä patients) compared to the scores earlier reported in cases of recently diagnosed RA patients. In the previous studies the respective median baseline Larsen scores of the maximum were 4.5% (Eberhardt et al. 1990), 1.0% (Paimela et al. 1995), 3.8% and 4.5% (Peltomaa et al. 1995), and 2.6% and 2.2% (Pasero et al. 1996). Some of this variation in the baseline Larsen scores may be attributable to differences in the scoring system. In the present study, only joints with pre-erosive changes or a manifest narrowing of joint space were assigned as grade 1, while in earlier studies swelling of soft tissue and para-articular osteoporosis were also included in the grade 1.

Several reports based on cross-sectional studies suggest that radiographic damage scores for peripheral small joints are as high as from one third to a half of the theoretical maximum during the first five to ten years of the disease (Larsen and Thoen 1987, Fuchs et al. 1989, Lassere et al. 1997). In longitudinal studies with early RA patients the radiographic damage scores also reached 20-50% of the maximum five to ten years from the onset of the disease (Salaffi and Ferraccioli 1989, Fex et al. 1996, Plant et al. 1998). The eight-year median Larsen score of 25.5 (25.5% of the maximum) for the Heinola patients was comparable to that obtained in these reports.

The final median Larsen score of the Jyväskylä cohort patients was low (12% of the maximum) in relation to the Heinola cohort as well as to the other previous reports (Fex et al. 1996, Plant et al. 1998). On the other hand, the result of the Jyväskylä cohort was in line with the report by Wolfe and Sharp (1998). The eight year erosion score of their recent onset RA patients was about ten per cent of the maximum score. All the latter patients had received treatment for RA: 40.2% had received prednisone and 78.5% had received DMARDs. Our findings as well as the findings by Wolfe and Sharp seem to reflect the history of actively treated RA rather than the history of sparsely treated or even natural history of RA. We assume that the extensive use of DMARDs was a major reason for these favourable results.

8.3 Long-term functional capacity (III)

We found well preserved functional capacity (HAQ) in both groups of patients with RA treated with DMARDs according to the 'sawtooth' strategy. On the other hand, in the majority of the comparator

cohorts with at least five years of RA the HAQ scores exceeded 1.0, reflecting moderate or even severe loss of function.

Fries (1990) sketched the figure (Figure 1) on different courses of RA to illustrate the failure of the traditional 'pyramidal' use of DMARDs to alter the development of long-term disability in patients with RA. Despite negligible data, the proposed 'sawtooth' strategy with early, continual, and serial use of DMARDs was expected to offer better long-term outcomes for RA patients. The results of the present study suggest that the theory of the 'sawtooth' strategy works.

Our favourable results raise doubts. Since the course of epidemiological RA is more favourable than that of the clinical disease (Wolfe 1996), it is important to know how the patient cohort is assembled and how the disease is defined (Kirwan and Quilty 1997). A conspicuous shortcoming of most of the comparator studies was the lack of clinical data at the outset, which hampers adequate comparisons. Only three other cohorts, except ours, consisted of patients with early RA with complete baseline data (Corbett et al. 1993, Fex et al. 1998, Munro et al. 1998). In comparison to our results, the most striking differences were the noticeably higher HAQ scores and very modest use of DMARDs in two of them. While all but one of our patients have been treated with DMARDs with a median coverage of 88% of the total follow-up time, only 65% and 55%, respectively, of the patients in the studies by Fex (1998) and Corbett (1993) and their coworkers had ever been treated with DMARDs.

Another concern is that those who died might have been severely disabled and would have worsened the final HAQ scores. However, we assume that this bias would not differ from that present in other reported clinical cohorts. Moreover, our cohorts are also exceptional owing to negligible dropout rates.

The observation of the improved (in comparison to historical controls) functional outcome of our 111 patients treated according to the 'sawtooth' strategy from diagnosis onwards for up to average of 13 years is promising but preliminary. We assume, that more aggressive therapy with traditional DMARDs had an impact on the better long-term functional outcome of our patients.

8.4 Work disability (IV)

Our results indicated that the working capacity of RA patients is at risk from the very start of the disease. This finding is in line with every published prospective study concerning early RA (Kaarela et al. 1987, Borg et al. 1991, Mau et al. 1996, Fex et al. 1998, Eberhardt et al. 1993, Häkkinen et al. 1998). On the other hand, Pincus and Callahan (1994) assumed that work disability occurs infrequently in early RA.

Our finding that work rather than disease related factors at the baseline appear to predict permanent

work disability in RA accords with earlier reports (Borg et al. 1991, Mau et al. 1996, Fex et al. 1998). Patient's higher age and clinical disease activity at the baseline also increased the risk of permanent work disability. However, after an average of ten years from the onset of the disease the work disabled patients were physically much more impaired than the others. This finding indicates a more severe disease process in these patients, too, and is consistent with all previous reports regarding the working capacity of RA patients (Table 3).

The observed prevalence of full-time employed RA patients in the present study is in accordance with the report by Mau et al. (1996), but higher than that reported by Kaarela et al. (1987) and Fex et al. (1998). In the Swedish cohort, however, an additional 25% of the patients were part-time employed. Table 6 presents a comparison of the baseline characteristics as well as the available final HAQ and Larsen's scores of the results of the prospective studies published so far. The commonly applied disease outcome measures, HAQ and Larsen's score, of our patients tended to be more favourable than those of other early RA cohorts. Working capacity was also better preserved, although a greater proportion of our patients had worked in physically heavier jobs. On the other hand, our patients were younger, but had suffered from RA for two years longer. Our patients were also treated actively with DMARDs from the very early phases of the disease onwards according to the 'sawtooth' strategy. Their median time on DMARDs was 88% out of the total follow up period while only 65% of the patients of Fex et al. (1998) had ever been treated with DMARDs. No unequivocal conclusions can be drawn, but we presume that the active treatment strategy may have been beneficial to the preservation of the working capacity of our patients. However, despite early and relatively aggressive DMARD therapy, a total of 44% of RA patients became work disabled over an average of ten years. The figure is high, and indicates that more effective treatment and rehabilitative modalities are needed.

Table 6. Comparison of demographic and clinical variables at the baseline and at the latest visit in the published prospective early RA studies. If not otherwise explained the figures represent medians.

	Age	Sex, F(%)	RF+ (%)	Baseline			Blue collar job (%)	High physical workload	At the latest visit			Prevalence of full time working
				Erosive (%)	ESR	HAQ				HAQ	Larsen's score	
Kaarela			97						working:		mean 29 / 0-200	≥36%
									disabled:		mean 74 / 0-200	
Borg	51	57			30-33	0.58	51					
Mau	49	73	62	33	26		30					
Fex, working	48	68				0.6		30%		1	42 / 0-200	40%
disabled	52	67				1.0		28%		1.5	52 / 0-200	
This study	41	73	67	29	33	0.25	61	44%	working:	0	17, mean 25 / 0-210	58%
									disabled:	0.9	52, mean 57 / 0-210	

8.5 Mortality (V)

Previous studies concerning the survival of RA patients show excess mortality rising up to three times that of the general population (Table 4). In our study, the total SMR of 1.28 did not differ statistically significantly from that of the general population.

The findings of Symmons et al. (1998) suggested that patients with early referral to hospital have a better outcome either because early presenters may include patients with milder RA or because early treatment improves prognosis, or both. Increased mortality, however, has also been found in two inception cohorts of patients seen within one year after RA onset (Reilly et al. 1990, Corbett et al. 1993). On the other hand, reports from Sweden (Lindqvist and Eberhardt 1999) and the Netherlands (Kroot et al. 1998) suggested that the mortality rate of early RA patients was not increased during the first 8 - 13 and 6 years, respectively. Our patients were seen in the hospital within a mean (range) of 6.4 (2-24) months after the onset of arthritis symptoms; for 72% of the patients the first DMARD was started at the first visit, while for the other patients it was started within a median of 3 months after diagnosis. Thus, our patients were early presenters with early DMARD treatment. However, the mortality rate of our patients was not as favourable as that in the Swedish and Dutch reports.

In the present study, death was closely related to RA in only five (20%) cases, while Reilly et al. (1990), Allebeck et al. (1981), Constable et al. (1978), and Benn and Wood (1972) reported respective RA-related mortality rates of 33%, 38%, 44%, and 50%. None of our patients died from amyloidosis, while in two earlier Finnish studies, amyloidosis was over represented among causes of death in RA patients. Mutru et al. (1985) reported that six per cent of men and 12% of women died from renal amyloidosis, while Myllykangas-Luosujärvi et al. (1995) found that 15% of excess mortality in RA was caused by amyloidosis. Active use of DMARDs and glucocorticoids may also have contributed to our positive result, possibly by suppressing the level of circulating serum amyloid-A protein (Berglund 1993).

Rheumatologists tend to believe that early and aggressive treatment with DMARDs diminishes comorbidity and even mortality in RA (Reilly et al. 1990). A couple of findings favour this hypothesis. Sustained GST (Lehtinen and Isomäki 1991) and MTX (Wolfe et al. 1998) treatments were associated with longer survival. Furthermore, an SMR of only 113 in the study by Lewis et al. (1980) has been considered to reflect the exceptionally aggressive medication of the patients (Isomäki 1992). Use of DMARDs has not been reported in detail in any of the previous papers concerning mortality in RA. However, for several reasons the use of DMARDs 10 to 30 years ago was sparse (Kaarela 1985, Ward and Fries 1998). In the case of our patients treated extensively with DMARDs the mortality rate was among the lowest so far reported.

8.6 Opportunities to assess the influence of DMARDs on the long-term outcome of RA

A randomized, placebo-controlled, double-blind clinical trial is the gold standard in obtaining information on the efficacy of a new therapy (Ingelfinger 1972). In chronic diseases such as RA clinical trials are a suitable method to separate inefficient therapies from effective treatments in the short-term. However, in determining long-term outcomes of RA, traditional clinical trials are unreasonable, unethical and even impossible (Pincus and Stein 1995).

The best known Finnish observational study is the Heinola follow-up survey which has provided important data on the outcome of RA for 20 years (Kaarela, Kautiainen 1997). The world's largest microcomputer based follow-up system of RA is probably that of Wolfe (Wolfe and Pincus 1995). However, long-term data collection should not be the prerogative of just a few authorities. Microcomputer technology with advanced software allows the collection, management and analysis of extensive clinical data in routine care. In fact, rheumatologists are encouraged to collect long-term data in routine rheumatologic care to obtain information on long-term outcomes of RA (Pincus 1995). Rationale and instructions have already been established (Wolfe and Pincus 1995, Rao and Callahan 1995, Wolfe 1995). In addition, as a result of the 1998 OMERACT 4 conference, a core set of domains for longitudinal observational studies in rheumatic disorders have been published (Table 2).

The health care system in Finland provides good facilities for studying long-term outcomes of RA and the influences of DMARDs on them. Patients with rheumatic symptoms seen by general practitioners are sent to the rheumatology clinics of local or central hospitals for accurate diagnosis, multidisciplinary patient education, and the start of therapy. Owing to the defined patient catchment areas of hospitals in Finland, all rheumatoid patients living in an area are seen at the same center. The statistics of the Social Insurance Institution can be used to ensure that all patients in the area diagnosed as RA can be reached.

Rheumatology care in Finland has traditionally been based on a multidisciplinary process: patient education, use of DMARDs, and surgery, as well as their scientific analysis. Much has been achieved; in 1995, the ratio between the number of published papers on rheumatology and the population of the country in millions of inhabitants was 10.2 for Finland, which was the best world score (Mela and Cimmino 1998).

Our study clearly shows that long-term outcomes of RA can be improved by using DMARDs early, continually and serially. In addition, it confirms that longitudinal observational studies have an important role to play in increasing our knowledge about rheumatology.

Although no cure for RA is within sight, it is hoped that the indications obtained in the present study favouring the extensive long-term use of DMARDs encourage rheumatologists to collect long-term

data on RA patients in routine clinical setting. It is my sincere belief that this is the right way to remove obstacles and to provide better outcomes for patients with RA in the future.

9. SUMMARY

The purpose of the present study was to obtain information on the influence of early, continual and serial use of DMARDs, known as the 'sawtooth' strategy, on the long-term outcomes of patients with RA.

A total of 135 RA patients were originally assigned to two early RA cohorts; I) n= 58 (mean symptomatic period 8 months, mean age 48 years), and II) n=77 (mean symptomatic period 5 months, mean age 52 years) during 1983-84 and 1988-89, respectively. Seventy-three percent of the patients were seropositive. The patients were prospectively followed with regular clinical check ups and treated according to the 'sawtooth' strategy from the onset of the disease. Radiographs of wrists, hands and feet were taken at intervals of one to two years, and assessed according to the Larsen score. Functional disability was assessed by the HAQ. DMARD treatment, employment status and deaths were documented.

The serial and continual treatment with DMARDs and COMBOs was safe. Serious drug related adverse events were exceptional. Inefficacy was the leading reason for discontinuation of DMARDs or COMBOs. Not a single DMARD/COMBO stood out favourably from the others with respect to inefficacy, toxicity or drug survival.

Radiographic damage of 85 seropositive cohort patients progressed over the observation period of eight years, but developed at a lower rate and remained at a lower level than that of a historical cohort of 103 early seropositive RA patients with more sparse DMARD treatment.

Patients' functional capacity was rather well preserved. The mean HAQ scores were 0.75 for group I at 13 years, and 0.55 for group II at 8.5 years of RA, while in several historical control cohorts with a follow-up period of >5 years the mean HAQ scores exceeded 1.

Nevertheless, a total of 44% out of those 82 patients who were gainfully employed at the time of diagnosis became work disabled on an average period of ten years. Most of them became work disabled during the first two years after diagnosis.

Twenty-five patients died during the observation period. Five of these deaths were closely related to RA. The mortality rate of 1.28 (95%CI 0.83-1.89) did not differ from that of the population in Central Finland at that time.

Long-term outcomes of clinical RA have been severe. Our present study suggests that the long-term outcomes of patients with early RA treated according to the ’sawtooth’ strategy were better than those of historical controls.

10. CONCLUSIONS

1. DMARD treatment according to the ’sawtooth’ strategy is safe in the long-term.

2. Early, continual and serial use of available DMARDs alters the course of RA in the long-term.
a) Progression of radiographic damage can be retarded.
b) Functional capacity can be better preserved.
c) A positive influence on preservation of working capacity is possible.
d) Mortality rate can be reduced.

3. The present means to treat RA are not curative.

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