Conventional monotherapy compared to a "sawtooth" treatment strategy in the radiographic progression of rheumatoid arthritis over the first eight years

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Abstract

Objective

To describe the treatment with disease-modifying antirheumatic drugs (DMARDs) in two inception cohorts of rheumatoid arthritis (RA) patients and to compare their radiographic outcomes.

Methods

A recent onset RA cohort was collected in Heinola in 1973-1975, and another in Jyväskylä in 1983-1989. The cohorts were followed up prospectively and treated with available DMARDs. The radiographic outcomes of 103 and 85 seropositive cohort patients from Heinola and Jyväskylä respectively were assigned Larsen scores (0 - 100) for their wrist, hand and foot radiographs in years 0, 1, 3, and 8, and compared with each other.

Results

In this study it was seen that DMARD treatment for RA became more extensive over time. The earlier cohort patients were treated with gold sodium thiomalate, chloroquine and D-penicillamine, while 8 additional DMARDs and various DMARD combinations were used for the later cohort patients. At the 8 year visit, 23%, 33%, and 2% of the Heinola patients, and 6%, 45%, and 21% of the Jyväskylä patients respectively were being treated with chloroquine, other single DMARDs, or DMARD combinations. Destruction in the peripheral joints remained lower in the more extensively treated cohort; from 0 to 8 years the median Larsen score increased from 1 to 25.5 and from 0 to 12 ($p = 0.001$) for the Heinola and the Jyväskylä patients, respectively.

Conclusion

Our result supports a role of DMARDs in preventing joint destruction in RA in the long-term.

Key words
Early rheumatoid arthritis, DMARD, follow-up study, Larsen score.

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Introduction

For several reasons, the treatment strategy for rheumatoid arthritis (RA) with disease-modifying antirheumatic drugs (DMARDs) has become more aggressive over the last decade. First, clinical RA has been demonstrated to be a serious disease with increased mortality and reduced functional and working capacity (1-3). Second, the available choice of DMARDs for RA has grown. Third, the relative toxicity of nonsteroidal anti-inflammatory drugs (NSAIDs) compared to DMARDs has been recognized (4). In addition, preliminary data show that DMARD therapy offers the potential for a better long-term outcome of RA (5-8).

In the present paper we describe the treatment with DMARDs of two prospective early RA patient cohorts collected in Finland in the 1970s and 1980s. In particular, we followed the progression of radiographic joint damage over the first eight years to see whether treatment with DMARDs had any effect.

Patients and methods

During 1973-1975 a total of 121 patients with recent (less than 6 months) RA were diagnosed at the Rheumatism Foundation Hospital in Heinola. The selection criteria, data collection strategy and details of the patients have been documented earlier (9-11). A total of 8 patients have since died, 7 have been lost to follow-up, and 3 have remained seronegative. All 103 patients with rheumatoid factor positive (RF+) RA seen by KK at their 8-year check-up were the subjects of this study.

A different cohort of 135 early RA patients were originally recruited into two separate RA studies at Jyväskylä Central Hospital. The first group comprised 58 and the second 77 early RA cases collected in the periods 1983 - 1985 and 1988 - 1989, respectively. The first group was assembled to study early erosiveness in recent onset RA (12), and the second to investigate the efficacy and tolerability of sulphasalazine (SASP) in early RA (13). For this study, the data of 85 patients who were RF+ at any time during the follow up period and who survived for 8 years were analysed. Before the eight-year control, 14 RF+ patients had died, and other 36 had remained seronegative.

Of the Heinola and Jyväskylä patients 42 (41%) and 22 (26%) respectively were erosive at the first visit. The mean age at diagnosis increased slightly from the 1970s to the 1980s, which is consistent with the findings of Kaipiainen-Seppänen *et al*. (14) (Table I). All patients in both cohorts met the American Rheumatology Association criteria (15) for definite or classical RA at the time of diagnosis and also the American College of Rheumatology 1987 criteria (16) for RA during some time of the study.

The 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 the diagnosis.

The Heinola cohort patients were clinically evaluated by means of radiographs at onset and at years 1, 3, and 8, whereas the patients in the Jyväskylä cohort were

Table I. Demographic and clinical characteristics of the cohort patients at the first visit.

	Heinola cohort	Jyväskylä cohort
Number of patients	103	85
Assembly years	1973 - 1975	1983 - 1989
Mean age	45.0	48.2
Female/male ratio	70/33	59/26
RF+	103	85
Disease duration, months, mean (range)	5 (2-6)	7 (2-24)
ESR, median (IQR)	32 (18, 55)	35 (23, 45)
Number of swollen joints, median (IQR)	6 (3, 10)	7 (4, 11)
Number of erosive joints	42	22

IQR = interquartile ranges

clinically assessed at least yearly and radiographs were taken once every one to two years.

A Larsen score of 0 - 100 was applied to grade the structural damage of the wrists, MCP I-V and MTP II-V joints (11, 17, 18). Normal joints and joints with only swelling of the soft tissues or osteoporosis were assigned a Larsen grade 0, and joints with pre-erosive changes or manifest narrowing of the joint space were assigned Larsen grade 1. In cases of MTP or wrist reconstruction, the latest preoperative radiographs were assessed. Resection of the processus styloideus ulnae did not contribute to the score, the wrist being assigned a score based on the reference films. All radiographs were read by the same rheumatologist (KK).

Statistical analyses were carried out using the Statistical Package for the Social Sciences (SPSS) (19). The Mann-Whitney test was used for unpaired comparisons, and the chi-square test was used for categorial variables.

Results

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 cases of GST and/or DPA toxicity, patients were obliged to continue with CHQ or without DMARDs.

In the Jyväskylä cohort, GST was started immediately after the diagnosis in the earlier group of patients (n = 41), whereas in the second group (n = 44), SASP was started at the first visit in 21 cases, and GST within the first year (mean 4.5, range 1-12 months) in the other 23 cases. Since then, the Jyväskylä cohort patients have been treated with DMARDs continually and serially, an approach later designated by Fries as the "sawtooth" strategy (20). If clinical remission (21) or significant clinical improvement was not achieved within six months, or if the patient clinically, functionally or radiograhpically deteriorated, it was considered mandatory to change the DMARD to another or to combine it with (an)other DMARD(s). During the first eight years after the diagnosis, the Jyväskylä patients were treated for a median (IQR) of 7.5 (5.6, 8.0) years with DMARDs.

The median daily maintenance doses of DMARDs were: 300 mg for CHQ, 2,000 mg for SASP, 450 mg for DPA, 150 mg for azathioprine (AZA), 200 mg for cyclosporin-A (CYA), 6 mg for auranofin (AURA), 300 mg for podofyllotoxine derivatives (CPH82), 4 mg for chlorambucil (KB), and 150 mg for cyclophosphamide (CYP). The respective median doses for GST and methotrexate (MTX) were 50 mg monthly and 10 mg weekly. With the exception of 1,000 mg daily dose for SASP, the same median doses were used in the combination therapies (COMBOs) as well.

Figures 1 and 2 show the point prevalences of the DMARD recipients and those not receiving DMARDs at 0 to 8 years to visualize the profile of DMARD use in the two cohorts. In the Heinola cohort the proportion of GST recipients decreased and the proportion of non-DMARD-recipients grew at the later check-ups (Fig. 1). A constantly increasing proportion of the Jyväskylä patients

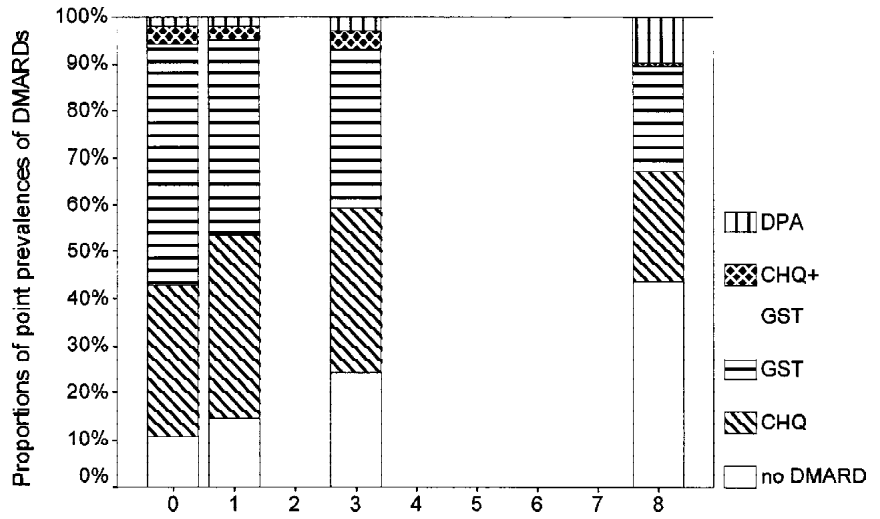

Fig. 1. Proportion of the Heinola cohort patients on single or combination DMARD therapy at 0, 1, 3 and 8 years. Proportions represent point prevalences at each time point. DPA: d-penicillamine; CHQ: chloroquine; GST: gold sodium thiomalate.

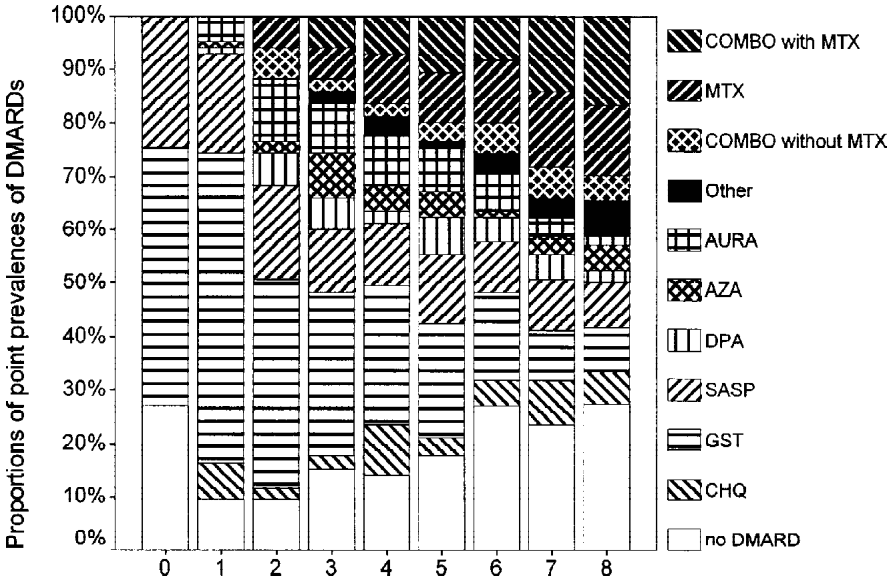

Fig. 2. Proportion of the Jyväskylä cohort patients on single or combination DMARD therapy at 0 to 8 years. Proportions represent point prevalences at each time point. COMBO: combination of DMARDs; MTX: methotrexate; AURA: auranofin; AZA: azathioprine; DPA: d-penicillamine; SASP: sulphasalazine; GST: gold sodium thiomalate; CHQ: chloroquine; Other: cyclosporin-A, podophyllotoxine derivatives, chlorambucil and cyclophosphamide.

Table II. Progression of the Larsen scores (0 - 100) during the follow-up of eight years.

Year	Larsen score for the Heinola cohort			Larsen score for the Jyväskylä cohort		
	No.	Median (IQR)	Mean (SD)	No.	Median (IQR)	Mean (SD)
0	103	1 (0, 4)	2.5 (3.6)	85	0 (0, 2)	1.5 (3.2)
1	102	6 (3, 10)	7.0 (6.4)	85	2 (0, 8.5)	5.1 (6.4)
3	103	11 (5, 20)	13.9 (11.2)	84	6 (1, 16)	10.1 (11.2)
8	102	25.5 (8, 43)	27.1 (20.0)	85	12 (4, 28.5)	18.8 (20.6)

IQR = interquartile ranges, SD = standard deviation

were treated with MTX or various combinations of DMARDs, as well as with other DMARDs including CYA, CPH82, KB and CYP (Fig. 2).

During the eight-year follow-up 56% of the Heinola cohort and 55% of the Jyväskylä cohort patients were at least periodically treated with prednisolone. A total of 27, 35, 34, and 39 Heinola patients and 3, 8, 13, and 23 Jyväskylä patients were using glucocorticoids at the 0, 1, 3, and 8 year visits, respectively. The median dose of prednisolone was 5.0 mg in both cohorts.

At eight years, five (4.9%) Heinola patients and 16 (18.8%) Jyväskylä patients remained non-erosive. Furthermore, radiographic damage remained less than 20% or exceeded 50% of the maximum in 44 (43.1%) and 14 (13.7%), and in 55 (64.7%) and 9 (10.6%) cases in the Heinola and the Jyväskylä cohorts, respectively.

From disease onset to eight years, the median (IQR) Larsen score increased from 1 (0, 4) to 25.5 (8, 43) for the Heinola cohort patients, and from 0 (0, 2) to 12 (4, 28.5) for the Jyväskylä cohort patients (Table II). Progression of the Larsen score over eight years was statistically significantly higher for the Heinola cohort patients than for the Jyväskylä cohort patients ($p = 0.001$) (Fig. 3).

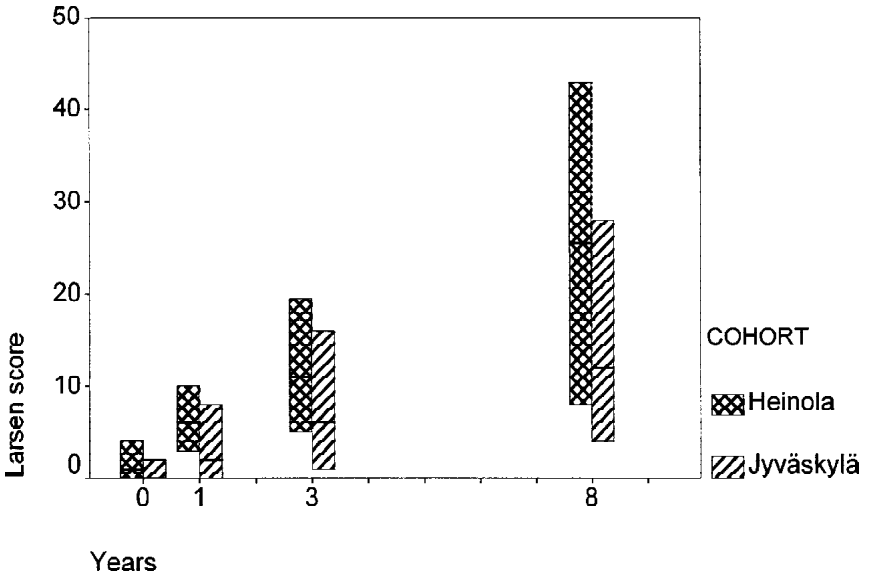

Fig. 3. Medians and interquartile ranges (IQR) of the Larsen scores in the patients with early RA over eight years.

Discussion

The present paper shows the development of DMARD treatment strategies for early RA patients in the 1970s and in the 1980s - 1990s in Finland. The historical Heinola Follow-up Survey of Arthritis represents the only 8-year study of patients with recent onset RA with radiographic assessment in the 1970s. The Jyväskylä cohort, collected ten years later, is the only available Finnish prospectively followed cohort for comparison.

In the 1970s intensive DMARD therapy was defined in Finland as starting treatment with a DMARD for RA patients at the time of diagnosis instead of waiting for the NSAIDs to take effect (22). Since few DMARDs were available (GST and CHQ; DPA since 1975; and SASP since 1963 but this was hardly ever used), patients, in the case of adverse effects of the available DMARDs, were obliged to manage without DMARDs, as shown by the Heinola cohort (Fig. 1). On the other hand, since the 1980s several new (23) DMARDs have become available for RA. The Jyväskylä cohort patients were treated with DMARDs according to the "sawtooth" strategy (20). A growing proportion of the patients were treated with MTX and combinations of DMARDs (Fig. 2).

Several DMARDs including MTX (23-28), CYA (29-30), SASP (28, 31), injectable gold (28, 32), and CYP (33), have been shown to slow the radiographic progression of RA in short-term studies, while there is little and only circumstantial evidence to suggest that DMARDs change the long-term radiographic outcome in RA. Luukkainen *et al.* (5) found that the progression of radiological destruction was statistically significantly less marked in those patients who could continue intra-muscular gold therapy compared to those who could not. Heikkilä and Isomäki (6) analysed hand and foot radiographs of RA patients admitted to the Rheumatism Foundation Hospital in Heinola in 1962, 1972, 1982 and 1992. They found a decline in erosions over time, and concluded that these finding might have been due to the improved therapy. In a prospective study of early RA patients (40 of which patients were included in the present study), Möttönen *et al*. (7) found that the rate of peripheral joint erosiveness was remarkably slower in Finnish patients who had been treated actively with DMARDs than the rate in Swedish patients with more sparse DMARD therapy. Rau and Herborn have found reparative changes in the joints of RA patients treated with DMARDs over long periods (34). Finally, a recent paper from Israel indicated that the radiographic outcome of patients never treated with DMARDs was poorer when com-

pared to DMARD recipients (35).

The median Larsen scores at baseline were low in both of the cohorts (1% for the Heinola, and 0% of the maximum score for the Jyväskylä patients) compared to the scores reported in previous studies of recently diagnosed patients with RA (30, 36-38). The respective median baseline Larsen scores in those studies were 2.6% and 2.2% (Pasero *et al*.), 4.5% (Eberhardt *et al*.), 1.0% (Paimela *et al*.), and 3.8% and 4.5% (Peltomaa *et al*.) of the maximum. Variation in the Larsen scores may arise from differences in the scoring system. According to Larsen's original procedure (17), soft tissue swelling and para-articular osteoporosis were also assigned grade 1. As these findings are prominent in early phases of the disease, the total Larsen score would be higher than that obtained using Larsen's later modified method (18). In the new version these findings are assigned grade 0, and only joints with pre-erosive changes or manifest narrowing of the joint space are assigned Larsen grade 1. We used the latter modification, while in the earlier reports the former method had been applied.

Several reports based on cross-sectional studies suggest that radiographic damage scores may reach from one-third to one half of the theoretical maximum during the first 5 to 10 years of the disease (39-42). Furthermore, in prospective early RA studies from Sweden (43) and the UK (44) the radiographic damage scores reached 20 - 40% of the maximum at 5 and 8 years. The eight-year Larsen score of 25.5% of the maximum seen in the Heinola patients is in line with the results of these reports.

The final median Larsen score of 12 (12% of the maximum) for the Jyväskylä patients was low in relation to that of the Heinola cohort, as well as in comparison to the early cohorts from Sweden (43) and the UK (44). In the present study, a clear difference in DMARD treatment strategy could be seen between the cohorts. Though not precisely described, the treatment strategy in the cohorts from Sweden and the UK also seemed to be sparse compared to that in the Jyväskylä cohort. Two-thirds of the Swedish patients had been treated with DMARDs for longer than 6 months; cytotoxic drugs were not used in either of the cohorts. On the other hand, the results for the Jyväskylä cohort are in line with the report by Wolfe and Sharp (45). The eight-year erosion score for their recent onset RA patients was about 10% of the maximum score, and reached one-third of the maximum only after 19 years. All of their patients had received treatment for RA: 40.2% received prednisone and 78.5% DMARDs. Our findings, as well as those of Wolfe and Sharp, seem to reflect the actively treated history of RA rather than the sparsely treated or even the natural history of RA.

The comparison of separate follow-up studies can involve several pitfalls. Unfortunately, already at the onset a greater proportion of the Heinola patients than the Jyväskylä patients had erosive damage (41% vs. 26%, $p = 0.023$) and thus the Heinola patients could represent cases of more severe RA than the Jyväskyä patients. Furthermore, early RA cohorts may include patients without progressive RA, a fact which could to some extent explain the favourable results of the Jyväskylä cohort. However, at the eight-year visit, only 3 Heinola patients and 8 Jyväskylä patients had experienced a long-term remission without DMARDs and remained non-erosive.

We conclude that DMARD treatment for RA has become more extensive over the last decades, and that the radiographic outcome of RA patients has contemporaneously improved.

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