Comparison of the baseline disease activity of early oligo- and polyarthritis in sequential years

L.M.A. Jansen[1], I.E. van der Horst-Bruinsma[2], D. van Schaardenburg[1,2], L.R. Lard[3], J.M.W. Hazes[4], T.W.J. Huizinga[3], B.A.C. Dijkmans[2]

[1]Jan van Breemen Instituut, Amsterdam;
[2]Department of Rheumatology, Vrije Universiteit Medical Centre, Amsterdam;
[3]Department of Rheumatology, Leiden University Medical Center, Leiden;
[4]Department of Rheumatology, Erasmus University, Rotterdam, The Netherlands

Abstract

Objective

Many early arthritis clinics (EACs) have been started in the last decade in order to detect and treat rheumatoid arthritis early. The present study evaluates whether the disease activity at admission of patients with early oligo- and polyarthritis changed during the period 1993-1998 in two EACs in the Netherlands.

Methods

Patients were selected who were diagnosed after one year as having rheumatoid arthritis (RA) or oligo- or polyarthritis (UPA), had a symptom duration of less than 2 years, and were referred from two Dutch EACs between 1993 and 1998. The data from the two clinics were combined and stratified by referral year. Differences in baseline disease characteristics as well as changes in radiological and functional scores after two years of follow-up between referral years were analysed by ANOVA using Bonferroni corrected p levels.

Results

A total of 405 patients (66% females; median age 57 yrs (18–93); 80% diagnosed as RA, the remainder as UPA) were included in the study. The year-groups did not differ significantly in demographic characteristics or in the duration of complaints (median 6 months). The number of patients with a diagnosis of RA declined over the years, as did the mean baseline erythrocyte sedimentation rate (ESR), in RA and UPA patients. The functional status (Health Assessment Questionnaire: HAQ) was enhanced in 1998 compared with the previous years ($p < 0.001$). Radiographic progression (Sharp/van der Heijde score) after the 2-year follow-up decreased ($p < 0.001$) in the later referral years compared to the referral group of 1994. Disease modifying anti-rheumatic drugs (DMARDs) were started in an earlier stage and the prescription rate of sulfasalazine and methotrexate increased over the years, whereas the number of patients not treated with DMARDs declined.

Conclusion

The pattern of patient referral changed over 6 years towards fewer patients who fulfilled the RA diagnosis and a lower ESR (among UPA as well as RA patients), whereas the number of swollen joints and the duration of complaints remained the same. The radiological progression declined over time, probably due to less inflammation at the first visit and the increased use of DMARDs.

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L.M.A. Jansen, PhD; D. van Schaardenburg, MD, PhD; I.E. van der Horst-Bruinsma, MD, PhD; B.A.C. Dijkmans, MD, PhD; L.R. Lard, MD; T.W.J. Huizinga, MD, PhD; J.M.W. Hazes, MD, PhD.

Please address correspondence to: B.A.C. Dijkmans, MD, Vrije Universiteit Medical Centre, Department of Rheumatology, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands.
E-mail: secr.reumatologie@vumc.nl

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Introduction

During the last decade the management of RA has changed tremendously (1). Nowadays treatment strategies are increasingly based on the assumption that early, rapid and effective pharmacotherapy is important for controlling disease. Therefore, disease-modifying anti-rheumatic drugs (DMARDs) are prescribed as soon as the diagnosis of RA is established. Currently combinations of DMARDs are increasingly used and appear to be successful (2-4) and agents such as anti-tumor necrosis factor alpha (TNFα) (5) are used more often.

Early aggressive therapy improves the outcome of RA at least during the first five years (6). Therefore, early referral and diagnosis is necessary. In order to stimulate early referral and start adequate treatment in an early stage and to limit joint destruction and disability, 'Early Arthritis Clinics' (EACs) were started worldwide (7-21). Moreover, research on disease characteristics and risk factors for the outcome of RA was facilitated by the start of EACs.

The present study evaluates whether the disease activity at admission of patients with early oligo- or polyarthritis has changed and whether the pattern of disease has changed during the period 1993-1999 in two EACs in the Netherlands.

Patients and methods

Patients

Patients were included from two outpatient clinics in the Netherlands, the JBI (Amsterdam) and the LUMC (Leiden), which are geographically situated close to each other. The Amsterdam EAC is an outpatient clinic for early oligo- and polyarthritis patients. It was initiated with the idea of enrolling not only patients with RA, but also patients who did not yet fulfill the 1987 ACR revised criteria for RA(22). In this way patients with a mild disease onset, often denoted as having undifferentiated polyarthritis (UPA) and who may develop progressive disease at a later stage, were monitored as well. In Amsterdam those patients referred between September 1995 and December 1998 were included, and in Leiden those patients who had been referred between January 1993 and December 1998. EAC inclusion criteria were: age 18 years or more, peripheral arthritis of at least 2 joints and less than a 2-year symptom duration. After one year of follow up the diagnosis of rheumatoid arthritis [according to the 1987 ACR criteria (22)] or oligo- or polyarthritis (UPA) (based on the clinical judgement of an experienced rheumatologist) was made.

Excluded from both EACs were patients previously treated with a DMARD or patients with bacterial, psoriatic and crystal-induced arthritis, as well as patients with osteoarthritis.

Pharmacotherapy

All patients from the Amsterdam EAC referred between 1995 and 1998 received NSAIDs at their first visit to the clinic. At the second visit, 2 weeks after inclusion, patients were treated with either hydroxychloroquine (HCQ) or sulphasalazine (SASP). The sequence of subsequent therapy was methotrexate (MTX) followed by aurothioglucose.

In Leiden (23), all patients referred between 1993 and 1995 received NSAIDs, and after approximately 4 months those RApatients who fulfilled the criteria of active disease received HCQ or SASP. The diagnosis of active disease demanded fulfillement of at least three of the following criteria: 1) morning stiffness > 30 minutes, 2) >5 swollen joints, 3) Ritchie score > 15, and 4) ESR> 28 mm/h. Patients with mild disease were not treated with DMARDs (23-25). All patients in Leiden referred from 1996 to 1998 were promptly treated with the same DMARDs as the Amsterdam group 2 weeks after their referral, in addition to NSAIDs.

In both clinics, prednisone was prescribed as required according to the judgement of the rheumatologist.

Disease parameters

At baseline we recorded: demographic characteristics, the time of onset of complaints (defined as persistent pain and/or swelling of a joint), the erythrocyte sedimentation rate (ESR), C-reactive-protein (CRP), IgM-rheumatoid

Table I. Comparison of baseline characteristics of patients from the EACs in Amsterdam and Leiden (n = 356).

Parameter	Amsterdam (n = 257)	Leiden (n = 99)	P
% female	68%	72%	n.s.
Age, years: median (range)	57 (18-86)	56 (18-93)	n.s.
% RA	75%	89%	**
Symptom duration (months): median (range)	3.8 (0 - 24)	5 (0 - 24)	n.s.
% IgM-RF positive	38%	57%	***
ESR, mm/h: mean (SD)	32 (24)	43 (31)	**
CRP, mg/dl: mean (SD)	28 (37)	31 (33)	n.s.
% max. swollen joint count[1]	28%	26%	n.s.
% max. tender joint count[2]	24%	16%	***
% erosive[3]	24%	19%	n.s.
Radiographic score (Sharp): median (range)	1 (0-136)	1 (0-103)	n.s.
HAQ-score: mean (SD)	0.8 (0.8)	1 (0.7)	***

**p < 0.01, ***p < 0.001 for differences between groups.
[1]Maximal swollen joint count = a percentage-score of the maximum achievable score (Amsterdam: 28 joint count, Leiden: 53 joint count [Ritchie-score])
[2]maximal tender joint count = a percentage-score of the maximum achievable score (Amsterdam: 28 joint count, Leiden: 44 joint count)
[3]erosive = Sharp/ van der Heijde score > 4.

factor, and the number of swollen and tender joints. In the Amsterdam EAC a 28-joint count was used for both the painful and swollen joints. In the Leiden EAC a 53-joint count for painful joints (Ritchie score) and a 44-joint count for swollen joints was used. Because of these differences in the joint count, a percentage of the maximum achievable score was determined for both the swollen and tender joint counts in order to make the scores comparable.

Outcome variables after 2 years were radiographic damage and functional status. Radiographic damage was evaluated for erosion and joint space narrowing according to the Sharp/van der Heijde method (range 0 – 448) (26). Erosive disease was defined as a Sharp/ van der Heijde score > 4, the remainder was denoted as non-erosive (27). An experienced rheumatologist who was blind to the clinical status of the patients scored the radiographs in chronological order. Functional status was measured by the validated Dutch version of the Health Assessment Questionnaire (HAQ) (range 0 – 3) (28).

Analysis

A comparison was made of the demographic characteristics and baseline disease activity between the patients from the two clinics. Data were compared for homogeneity by Student's t-test or, in cases of a skewed distribution, by the Mann-Whitney U test.

Secondly, the data from the two clinics were merged into one file, stratified by referral year. For each variable, the mean change was calculated by subtracting the baseline scores from the two-year follow-up scores. Baseline differences between the referral years, as well as the mean change after two years of follow up, were investigated by one-way analysis of variance (ANOVA). Bonferroni corrected p-levels were assessed for the referral year

Table II. Mean baseline characteristics of patients with early RAand oligo- and polyarthritis (UPA) stratified by referral year[1].

	Year	% RA at 1 yr	Symptom duration (mos.)	% IgM-RF positivity	ESR	% max. SJC	% max. TJC	% erosive	Sharp score	HAQ score
N = 405		*			***	*				***
Complete group (RA and UPA)	1993	100%	4.7	70%	54	24%	15%	20%	2.1	0.9
	1994	91%	7.9	71%	58	26%	19%	17%	3.0	1.1
	1995	81%	6.5	52%	42	25%	22%	27%	4.8	1.1
	1996	87%	4.9	50%	39	32%	22%	29%	4.4	0.9
	1997	72%	5.1	48%	31	27%	20%	17%	4.3	0.9
	1998	70%	6.1	39%	28	21%	20%	18%	4.8	0.5
N = 324					***	**				***
Subgroup (RA) 2	1993	100%	4.7	70%	54	26%	19%	20%	2.1	0.9
	1994		7.9	71%	61	27%	20%	18%	3.5	1.2
	1995		5.7	63%	49	29%	22%	29%	5.5	1.3
	1996		5.0	55%	42	35%	24%	32%	4.7	1.1
	1997		4.9	61%	36	33%	24%	20%	5.1	1.0
	1998		6.3	53%	27	25%	21%	27%	6.9	0.5

[1]Data are expressed as means or percentages; maximal SJC (swollen joint count) = a percentage score of the maximum achievable score (Amsterdam: 28 joint count, Leiden: 53 joint count [Ritchie-score]); maximal TJC (tender joint count) = a percentage score of the maximum achievable score (Amsterdam: 28 joint count, Leiden: 44 joint count); erosive = Sharp-score > 4.
* P< 0.05; ** P< 0.01; ***P< 0.001 for differences between referral years (ANOVA).
[2] No significant differences in baseline characteristics were seen between the year groups of patients diagnosed as UPA.

1998. Additional analyses were performed for a subgroup of patients clinically diagnosed by the rheumatologist as having RA after one year of follow-up.

Results

Between 1993 and 1998, a total of 556 patients were eligible for study, 209 patients (67% definite RAand 33% UPA) from Leiden and 347 patients (66% RA and 34% UPA) from Amsterdam.

The one-year follow up was completed by 464/556 patients (83%). The reasons for loss to follow-up were: remission (4%), death (3%), non-compliance (3%), changing residence (1%), and miscellaneous reasons (6%). Radiographs after two years of follow-up were available for 405 (73%) patients. The baseline characteristics of the patients who were lost to follow-up differed from the completers: the non-completers had a longer duration of complaints and more radiographic joint damage ($p < 0.001$), but were less frequently IgM-RF positive ($p < 0.01$) compared to the completers (data not shown).

The characteristics of the patients referred after 1995 to the two clinics were compared ($n = 356$) (Table I). Patients from Leiden were significantly more often rheumatoid factor positive, had a worse functional status (HAQ-score) ($p < 0.001$) and a higher ESR at entry, and were more often diagnosed as having RA ($p < 0.01$). However, the mean tender joint-count ($p < 0.001$) was lower compared to the patients from the Amsterdam EAC (Table II). The radiographic progression after 2 years was comparable between clinics (data not shown).

Secondly, the data from the two clinic series were merged into one file and stratified by referral year. The patient groups for the separate years of referral did not differ significantly in demographic characteristics (data not shown). In Table II, an overview of the baseline characteristics is shown. Over the years the percentage of patients admitted who were diagnosed as having RA decreased from 100% towards 70%, whereas the number of diagnoses of UPA increased. Furthermore, the baseline ESR showed a gradual decline ($p < 0.001$) in both RA and UPA patients. The functional status decreased in the last year ($p < 0.001$), as did the swollen joint count ($p < 0.05$). No significant differences were observed between the referral years in symptom duration.

The baseline characteristics of the subgroup of patients who were diagnosed as having RA after one year (Table II) showed that the baseline ESR as well as the functional status exhibited the same pattern as in the total cohort. No significant differences in baseline characteristics were seen between the year groups of patients diagnosed as having UPA(data not shown).

Radiographic progression after 2 years decreased over the years (Table III) in the total cohort ($p < 0.001$) as well as in the subgroup of patients diagnosed as having RA ($p < 0.01$). A post hoc test demonstrated a significant ($p < 0.001$) decline in radiological progression in the 1998 referral group compared to the year 1994 group (Fig.1).

The percentage of patients not treated with a DMARD during the first year decreased significantly ($p<0.001$) from 40% to 0% between 1993 and 1998 (Table III). The prescribed DMARD during the first year was mainly hydroxychloroquine (Fig. 2). The prescription of sulfasalazine and methotrexate increased during the years. These trends remained after two years of follow-up.

Table III. Disease progression after 2 years in patients with early RAand oligo- and polyarthritis (UPA) stratified by referral year (n = 405).

	Year	% Erosive 2 yrs ***	Sharp score 2 yrs **	Delta Sharp score 0-2 yrs ***	% without DMARDs 1st yr ***
Complete group (RA and UPA)	1993	70%	14.3	12.2	40%
	1994	79%	31.8	26.8	50%
	1995	61%	16.3	11.5	32%
	1996	55%	14.7	10.2	10%
	1997	43%	10.9	6.6	7%
	1998	28%	10.7	5.9	0%
		**	*	**	***
Subgroup (RA)	1993	70%	14.3	12.2	40%
	1994	86%	35.6	30.0	43%
	1995	69%	19.7	14.3	23%
	1996	58%	16.2	11.5	5%
	1997	51%	13.8	8.9	2%
	1998	38%	14.7	7.9	0%

Data are expressed as means or percentages. ** P< 0.01; ***P< 0.001 for differences between referral years (ANOVA).

Discussion

The pattern of disease activity of patients with oligo- and polyarthritis who did not fulfil any other diagnoses than UPA or RA changed during the referral years. Fewer patients with RA were sent to the rheumatologist and more were sent with the diagnosis of undifferentiated polyarthritis (UPA). Moreover, the baseline ESR, as well as the swollen joint count, declined in both RAand UPA patients, and the functional status at entry improved over the years, whereas the symptom duration before referral remained the same.

The fact that patients with milder RA are being referred to EACs at a later stage in their disease might be due to a naturally occurring decrease in disease severity at onset. However, it could also be explained by a lower threshold for the general practitioners (GPs) to refer their patients to a rheumatologist. Perhaps they became more motivated to send patients because of the improvement in outcome with new DMARDs strategies (2, 6, 23).

After 2 years of follow-up, it can be concluded that the radiographic progression decreased and fewer patients with erosive disease were found in patients referred in the later years. This pattern was present in the whole group

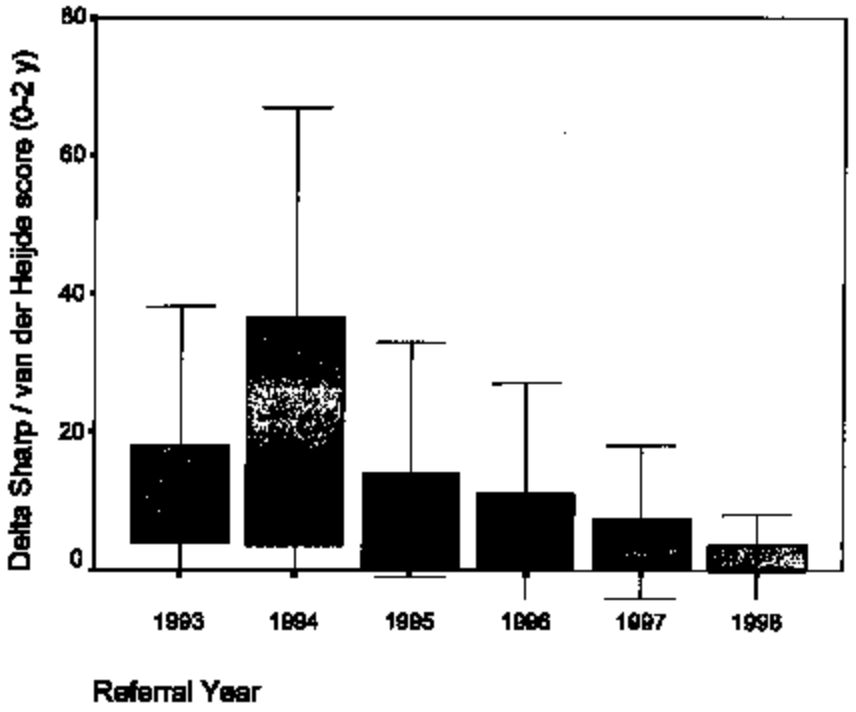

Fig. 1. Radiographic progression after 2 years of follow-up in patients with early RAand oligo- and polyarthritis (UPA) stratified by referral year (n = 405).

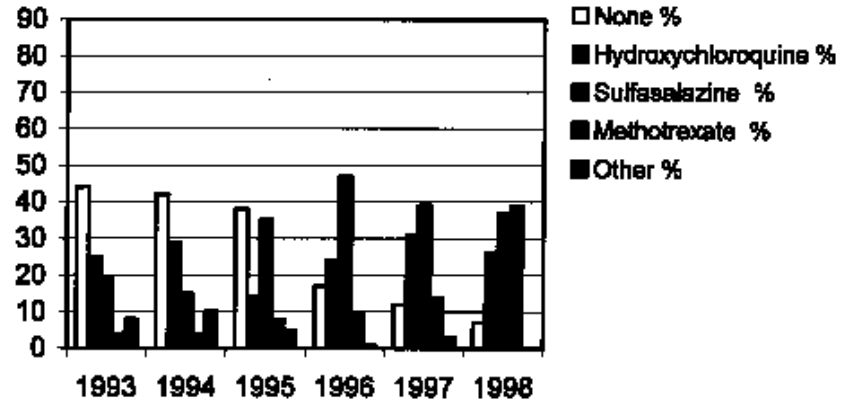

Fig. 2. Comparison of prescribed DMARDs during the first year of follow up in patients with early RAand oligo- and polyarthritis stratified by referral year (n = 405).

as well as in the subgroup of patients diagnosed with RA. The decline in radiological progression in the later referral years can be explained by the increasing application of effective DMARDs and the lower disease activity at entry.

The diminished disease activity at entry could not simply be explained by the increased number of UPA patients being referred compared with RA patients, because the decline in ESR was observed in the subgroup of RA patients as well. Moreover, the median symptom duration before admission to the EAC remained short, i.e. 6 months, over the years. The prescription rate of sulfasalazine and methotrexate increased over the years, whereas the patients not treated with DMARDs declined.

The beneficial effect of this changed DMARD strategy in the patients deriving from the Leiden EAC was already discussed by Lard *et al.* (23), who demonstrated a significant decline in the number of erosions. Early treatment with DMARDs was also propagated by Emery *et al*. (29), who showed in a review that early referral to a rheumatologist as well as early DMARD treatment improved the long-term outcome in RA. Sokka *et al.* studied the treatment of two inception cohorts of patients with early RA recruited between 1973-1975 and 1983-1989. It was seen that DMARD treatment for RAbecame more extensive over time and it was concluded that DMARDs played an important role in preventing joint destruction in RAin the long term (30).

Furthermore, the enhanced starting point for treatment observed in this study because patients showed less inflammation (lower ESR) at the first visit despite the same duration of complaints (6 months), is in accordance with an earlier study performed by Porter *et al.* (31). He concluded that patients being enrolled into second-line drug trials had milder disease in the 1990s compared to the 1980s whereas their disease duration was similar. However, Porter *et al*. studied only patients with RA, while UPA patients were also included in the present study. The aim of Early Arthritis Clinics is to minimize the delay in referral in order to start adequate treatment in an early stage and to limit joint destruction and disability. The EAC policy appears to be proving increasingly successful over the years as it has gradually led to an improvement in the starting point for the treatment of early RA, whereas the median symptom duration remained less than 6 months; it has also led to the referral of more patients with UPA who should be treated early as well. It appears that the decreased disease activity at entry and the increased use of DMARDs resulted in an improved radiological outcome after 2 years.

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