Only high disease activity and positive rheumatoid factor indicate poor prognosis in patients with early rheumatoid arthritis treated with "sawtooth" strategy

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Abstract

***Objectives*—To investigate the prognostic significance of clinical and genetic markers on the outcome of patients with recent-onset rheumatoid arthritis (RA) treated actively with slow acting antirheumatic drugs (SAARDs).**

***Methods*—A total of 142 consecutive patients with early RA (median disease duration of 7 months) were treated according to the "sawtooth" strategy and prospectively followed up for an average of 6.2 years. Several clinical parameters at start as well as genetic markers were related to the functional outcome (ARA Functional class and HAQ disability score) and radiographic joint damage (Larsen's score) at the latest visit.**

***Results*—In logistic regression analysis only Mallya score (including morning stiffness, pain scale, grip strength, Ritchie's articular index, haemoglobin, and erythrocyte sedimentation rate) at baseline, and Mallya score and rheumatoid factor (RF) positivity at one year were found to be of significance with respect to the radiographic outcome of the patients. Furthermore, at the latest visit HAQ score was related to radiographic score. At baseline the mean ages of the DR4 positive patients and the patients with RA associated DR alleles were statistically significantly lower than those without the above mentioned risk factors (44 *v* 49, p=0.03 and 41 *v* 53, p=0.04, respectively). However, these genetic markers had no prognostic significance on the functional or radiographic outcome of the patients.**

***Conclusion*—High clinical disease activity at baseline and RF positivity especially at one year after the institution of SAARD treatment are the best predictors of poor prognosis in early RA. However, from the clinical point of view, the disease outcome of an individual patient with early RA, cannot be predicted accurately enough by present means.**

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Rheumatoid arthritis (RA) is an autoimmune disorder with unknown cause and characterised by a varying course of the disease. Early RA rarely remits spontaneously but in most cases the disease shows a resistant course with progressive joint damage and disability.[1–3] Slow acting antirheumatic drugs (SAARDs) may change the short-term course of RA.[4–7] However, more effective treatments are needed and new strategies for the SAARD treatments have been suggested.[8 9]

Optimal management of RA requires early diagnosis and immediate aggressive treatment.[10] The costs of new antirheumatic treatments in the future may be high, and only a proportion of the patients will probably have the best benefit from the treatment. Thus, there is an obvious need to develop methods to identify the rapidly deteriorating patients and to save others from toxic or expensive treatments, or both.

Numerous clinical and laboratory indices have been tested as predictive outcome markers but the results have been neither convincing nor consistent.[11–16] Genetic susceptibility markers have been claimed to be able to predict persisting arthritis, but their role as markers for disease severity in established disease has remained conflicting.[17–23] The controversies may be caused by the differences in the selection of patients, variations in the duration of disease, and in the designs of the studies.[12 24] Furthermore, active use of SAARDs as early treatment may have influenced the results.

We have recently found that the outcome of 142 patients with early RA after a mean of 6.2 years was widely variable. During the study, each patient was treated with SAARDs according to the set of principles for "sawtooth" strategy—that is, (1) SAARD treatment was begun early; (2) the use of one or multiple SAARDs was virtually uninterrupted; (3) if no positive effect could be established during 3–6 months or if an initial adequate effect disappeared or a clinically meaningful untoward adverse effect occurred, the SAARD was replaced with another one.[9] Despite the treatment strategy, one quarter of the patients failed to respond and deteriorated to ARA Functional classes III-IV and Health Assessment Questionnaire (HAQ) disability score > 1. On the other hand, one third of the patients were in remission at the end of the follow up.[25]

In this paper we have further tested the prognostic significance of clinical and genetic factors and the impact of SAARD treatment on the functional outcome and radiographic joint destruction in the cohort of early RA patients. In addition, the relations between the clinical disease activity, structural joint damage, and functional disability of these patients were examined.

Table 1 Clinical data of the patients in this study enrolled originally in two separate cohorts

	Cohort 1 (Möttönen)	*Cohort 2 (Paimela et al)*
Patients (n)	57	85
Age, median (range)	50 (17–79)	46 (19–65)
Female/male, %	68/32	80/20
Disease duration at entry, months, median (range)	7 (2–24)	8 (2–12)
Rheumatoid factor found at entry, %	58	67
HLA-DR4 present, %	56	64
Mallya score at entry, median (range)	2.7 (1.5–3.7)	2.5 (1.3–3.6)
Larsen's score at entry, median (range)	0 (0–28)	2 (0–22)
Followup period at the latest visit, months, median (range)	91 (18–111)	60 (36–84)
% Treated with SAARDs during the study	100	100
Maximum symptomatic time before the start of SAARD treatment, months	24	12
Patients with joint replacements during the study	5	5

Methods

The study population consisted of 142 consecutive early RA patients of white origin (107 women, 35 men, median disease duration of 7 months) enrolled in two separate cohorts. The inclusion criteria included symptoms of RA less than 24 months and no previous SAARD and systemic corticosteroid treatment. The patients were referred to specialists from primary health care centres or private outpatient clinics. During the study period, all patients met the American College of Rheumatology (ACR) 1987 criteria for RA.[26] Initially, the two cohorts were assembled to study the early erosiveness of recent onset RA.[27 28] Table 1 shows the clinical data of the patients included in this study.The patients older than 65 years of age were excluded from the cohort 2[28]). Most importantly, all the patients in both groups were treated in the same country and with continuous use of SAARDs from the beginning of the study. Subsequently, the patients were combined in this prospective, longitudinal study. A more detailed description of the patients has been reported previously.[25]

Patients were followed up for a mean of 6.2 years (range 1.5–9.2, SD 1.6 years); 133 (94%) patients have been followed up for at least five years, and 84 (59%) for at least six years.

Clinical variables of disease activity were assessed at study entry and thereafter at intervals of 6–12 months. The count of swollen (66 joints) and tender (68 joints) joints and the index of disease activity (Mallya score)[29] were recorded at entry and after one year. The Mallya score includes two subjective measures (morning stiffness, pain scale), two semi-objective measures (grip strength, Ritchie articular index[30]), and two objective measures (haemoglobin, erythrocyte sedimentation rate (ESR)). Remission was defined according to the ACR preliminary criteria for clinical remission, but duration criterion was excluded. Thus the frequency of remissions represent the cross sectional situation.[31]

Posteroanterior radiographs of both hands, wrists, and feet were obtained at entry, once a year for the next two years, and at the end of the follow up. Serial radiographs were read by the same experienced rheumatologists. The number of eroded joints were counted and radiographs were scored according to the method introduced by Larsen and coworkers.[32]

The development of patients functional disability was assessed by the ARA Functional class[33] and by the HAQ disability indices.[34]

LABORATORY EXAMINATIONS

RF was determined at onset, and at one and two years by the Waaler-Rose test; titres >1:64 were regarded as positive. The presence of HLA-DR1 and -DR4 including subspecificities associated with RA susceptibility was defined by combining serological and cellular typing methods. HLA-DR typing was performed in 140 patients by standard microlymphocytotoxicity test using commercial panels of antisera (Biotest AG, Dreieich, Germany). HLA-DR4 subspecificities Dw4 and Dw14 corresponding DRB1*0401 and DRB1*0404/0408 alleles were defined in the cohort 1 (57 consecutive patients) using homozygous typing cells in mixed lymphocyte cultures as described earlier.[35]

STATISTICAL ANALYSIS

Outcome variables were assessed using the end point analysis. The prognostic value of the demographic and clinical features studied at the onset of the follow up and the genetic markers were related to several measures of outcome as determined at the latest visit. Outcome variables analysed included ARA Functional class, HAQ disability score, remission, and Larsen's score. Descriptive values of the variables with a normal (Gaussian) distribution were expressed as means and standard deviations (SD); statistical comparison between the groups was performed by using *t* test or analysis of variance (ANOVA). If the variables did not have a Gaussian distribution or they were

Table 2 The presence of HLA DR4 in 140 patients and shared epitopes (SE) in 57 patients with early RA and the course of RA

	HLA DR4			*SE*			
	Not found (n=55)	*Found (n=85)*	*p Value*	*No SE found (n=12)*	*Single SE found (n=25)*	*Double dose of SE found (n=20)*	*p Value*
At the onset							
age, year, mean (SD)	49 (13)	44 (14)	0.029	53 (10)	51 (17)	41 (15)	0.042
disease duration, months, median (range)	6 (2–24)	8 (2–20)	NS	6.5 (3–24)	7 (2–18)	7 (2–20)	NS
rheumatoid factor positivity, %	58	66	NS	33	64	65	NS
swollen joint count, median (range)	6 (1–35)	5 (1–30)	NS	13 (1–34)	8 (1–35)	9.5 (1–20)	NS
tender joint count, median (range)	16 (3–40)	15 (2–36)	NS	22.5 (8–37)	17 (3–40)	13.5 (4–30)	NS
Mallya score, median (range)	2.6 (1.6–3.7)	2.5 (1.3–3.6)	NS	2.8 (1.7–3.5)	2.7 (1.7–3.7)	2.2 (1.5–3.0)	0.047
Larsen score, median (range)	0 (0–27)	2 (0–28)	NS	0 (1–16)	0 (0–28)	0 (0–11)	NS
At the latest visit							
In remission, (%)	31	32	NS	33	32	40	NS
Larsen score, median (range)	28 (0–180)	39 (0–146)	NS	59 (11–123)	41 (0–180)	47.5 (4–146)	NS
with nodules, (%)	15	11	NS	17	12	15	NS
SAARDs used, median (range)	3 (1–7)	3 (1–8)	NS	4 (1–7)	3 (1–8)	4 (1–8)	NS

Table 3 Rheumatoid factor (RF) seropositivity and prognosis of 142 patients with early RA during the follow up period of a mean of six years

	RF at baseline			*RF at one year*			*RF at baseline and one year*		
	RF+ (n=90)	*RF− (n=52)*	*p Value*	*RF+ (n=76)*	*RF− (n=66)*	*p Value*	*RF+ (n=62)*	*RF− (n=38)*	*p Value*
At onset									
swollen joint count, median (IQR)	5 (3–10)	5.5 (2–14)	NS	6 (4–14)	3 (2–7)	<0.001	6 (4–12)	4 (2–8)	NS
tender joint count, median (IQR)	15 (8–21)	16 (9–24)	NS	16 (9–24)	13.5 (8–20)	NS	16 (8–24)	15 (7–24)	NS
Mallya score, median (IQR)	2.4 (2.1–2.8)	2.6 (2.2–3.0)	NS	2.5 (2.1–2.8)	2.4 (2.1–2.8)	NS	2.5 (21–28)	2.6 (2.1–3.0)	NS
At one year									
swollen joint count, median (IQR)	1 (0–6)	1 (0–7)	NS	2 (0–8)	0 (0–2)	<0.001	2 (0–7)	0 (0–2)	0.01
Mallya score, median (IQR)	1.8 (1.5—2.1)	1.8 (1.5–2.4)	NS	2.0 (1.5–2.5)	1.8 (1.3–2.2)	0.011	2.0 (1.5–2.5)	1.8 (1.3–2.3)	NS
At two year									
in remission, %	24	33	NS	17	39	0.003	19	42	0.014
At the latest visit									
nodules found, %	14	8	NS	22	0	<0.0001	21	0	0.002
ARA Functional Class III-IV, %	28	17	NS	36	11	<0.001	36	11	0.006
HAQ >1, %	22	26	NS	27	19	NS	27	25	NS
in remission, %	29	37	NS	26	38	NS	27	42	NS
SAARDs used, median (IQR)	3 (1–5)	3 (2–5)	NS	4 (2–5)	2 (1–4)	0.0066	3 (2–5)	2 (1–4)	NS
Discontinuations of SAARD treatment because of inefficacy, median (IQR)	1 (0–2)	0.5 (0–3)	NS	1.5 (0–3)	0.5 (0–2)	0.013	1 (0–2)	0 (0–2)	0.022

HAQ = Health Assessment Questionnaire.

ordinal, then descriptive values were expressed as medians and interquartile ranges (IQR) or ranges; statistical comparison between the groups was performed by using Mann-Whitney or Kruskal-Wallis tests. Measures with a discrete distribution were expressed as counts (%) and analysed by χ^2 or Fisher's exact test.

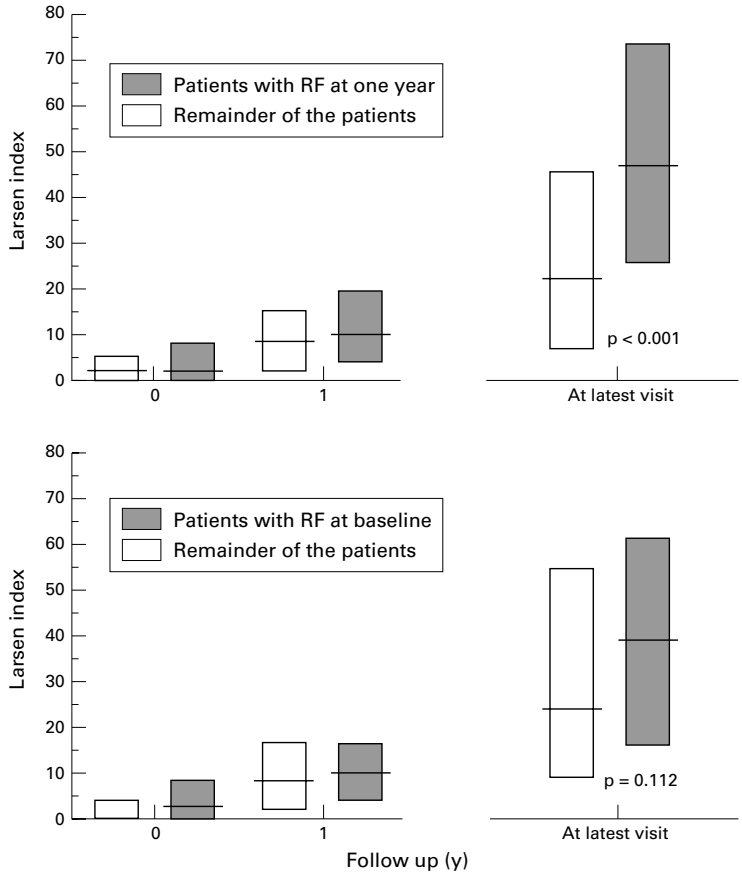

Figure 1 Larsen's score over time in the seronegative and seropositive patients followed up for a median of seven years and RF detected at baseline and at one year. Horizontal bars indicate the median values; boxes indicate the first through third quartiles.

The normality of variables was evaluated by the Kolmogorov-Smirnov statistics, with a Lilliefors significance or Shapiro-Wilk statistics. No adjustment was made for multiple testing, but this information can be obtained by multiplying the actual p value by the number of comparison made. Correlations were estimated with Spearman's correlation coefficient method. For estimation of prediction we used a logistic regression model and determined which variables at entry and at one year were predictive for the most progressive joint destruction. Because 34% of the patients (48 of 142) had deteriorated to Larsen's score more than 50 at the latest visit, we chose to compare them with the remaining two thirds of the cases and used in the analysis that cut off point.

Results

EFFECT OF SEX ON OUTCOME

Disease remission at the latest visit was observed more frequently in men (54%) than in women (24%) (p<0.01). No significant differences were found between the sexes in the values of disease duration or clinical activity of RA at baseline. However, in the men without remission the course of RA was more severe than in the women on average. No significant difference was observed between the sexes in median values of the final Larsen's and HAQ scores, in the number of SAARDs used during the follow up, or in the frequencies of the patients with nodular disease.

EFFECT OF AGE ON OUTCOME

At baseline 118 patients (83%) were < 60 and 24 (17%) > 60 years of age. The median (IQR) Mallya and Larsen's scores were significantly higher at baseline in the older patient group than in the younger one (2.8, (2.3–3.0) *v* 2.5, (2.1–2.8); p=0.01 and 4 (0–14) *v* 2, (0–5); p=0.0007, respectively). Despite the comparable intensity of SAARD treatment and in the rate of achieved remissions the older patients

Table 4 Baseline characteristics and clinical data in the patients with slow and fast rate of radiographic progression during follow up period of a mean of six years. Cut off point >50 (fast) and ⩾50 (slow) Larsen score at the latest visit

	Radiographic progression		
	Slow (Larsen score ⩽50)	*Fast (Larsen score >50)*	*p Value*
Patients (n) (%)	94 (66)	48 (34)	
At onset			
age, year, mean (SD)	46 (13)	44 (14)	NS
disease duration, months, median (IQR)	8 (5–11)	6 (4–9)	NS
female/male, %	73 / 27	79 / 21	NS
RF positivity, %	60	70	NS
DR4 positivity, % (studied in 140 patients)	63	55	NS
DRB1 *0101/*0401/4/8 positivity, % (studied in 57 patients)	84	72	NS
swollen joint count, median (IQR)	4 (2–8)	7 (3–14)	0.015
tender joint count, median (IQR)	14.5 (7–22)	16.5 (12–23)	NS
ESR, median (IQR)	25.5 (14–52)	35 (24–55)	0.033
Mallya score, median (IQR)	2.3 (2.1–2.8)	2.8 (2.4–3.0)	<0.001
HAQ score, median (IQR) (studied in 134 patients)	0.1 (0–0.4)	0.3 (0.1–0.5)	<0.001
Larsen score, median (IQR)	2 (0–7)	2 (0–8)	NS
At the latest visit			
disease duration, median (IQR)	76 (60–84)	84 (60–95)	0.01
HAQ score, median (IQR) (studied in 130 patients)	0 (0–0.5)	1.0 (0.5–1.8)	<0.001
SAARDs used, median (IQR)	2 (1–4)	5 (4–6)	<0.001
SAARDs discontinuations			
because of inefficacy, median (IQR)	0 (0–1)	3 (2–3)	<0.0001
because of adverse event, median (IQR)	0 (0–1)	1 (0–2)	0.0036

HAQ = Health Assessment Questionnaire.

developed more often a nodular disease (29% *v* 9%, p=0.01) and progressed more often to ARA Functional classes III-IV than the younger patients (42% *v* 20%, p=0.026). At the latest visit also the median (IQR) Larsen's score was significantly higher in the older patients than in the younger patients (42.5, (27–84) *v* 30, (11–59); p=0.004). However, in logistic regression analysis age was not found to be a significant predictor of further joint damage.

EFFECT OF SYMPTOMATIC PERIOD AT STUDY ENTRY ON OUTCOME

In 62 patients (44%) the time period between symptoms at onset and institution of SAARD treatment was less than six months. At the baseline the median (IQR) Mallya score of these patients was significantly higher (2.8, (2.3–3.0)) than that of the rest of the patients (2.3, (2.0–2.8)) (p=0.002). However, at one year the clinical disease activity was comparable in both patient groups. The number of RF positive patients at baseline, as well as those with HLA-DR4 or some of the alleles with the so called "shared epitope" (SE) were also found in comparable frequencies in both groups. The relatively short delay in the institution of SAARD treatment at baseline did not influence the further response to the treatment, the development of joint destructions or the rate of remissions (data not shown).

Table 5 Logistic regression analysis with total radiographic progression Larsen score more than 50 at the latest visit in 140 early RA patients treated with "sawtooth" strategy for a mean of six years

	Model	
Variable	*At onset OR (95% CI)**	*At one year OR (95% CI)*
Sex (female)	1.7 (0.7 to 4.5)	2.3 (0.8 to 6.2)
Age (⩾60)	1.5 (0.5 to 4.1)	1.3 (0.4 to 3.8)
DR4 found	0.7 (0.3 to 1.7)	0.8 (0.4 to 1.8)
RF positivity	2.3 (1.0 to 5.3)	3.9 (1.7 to 9.2)
Mallya score	4.7 (2.0 to 11.0)	2.8 (1.4 to 5.6)
Presence of erosion	0.9 (0.4 to 2.1)	—
Disease duration (months) at the latest visit	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.1)

* Odds ratio and 95% confidence intervals. Odds ratios are adjusted for all the other variables in the model.

EFFECT OF HLA DR1- AND DR4-ALLELES AND SHARED EPITOPE ON OUTCOME

At baseline the mean age of the DR4 positive patients and of the patients with a double dose of SE was lower than in the rest of the patients (table 2). The frequencies of DR1- and DR4-alleles and SE were comparable in women and men (data not shown).

The presence of DR4-allele or SE had no significant influence on the rate of achieved remissions, the development of joint damage, or a nodular disease, or on the number of SAARDs used during the follow up (table 2). Furthermore, none of the patients with joint replacement had a double dose of SE and most of these patients were without any SE.

EFFECT OF RF ON OUTCOME (TABLE 3)

The genetic markers (HLA-DR1, -DR4, SE) were not related to the presence or absence of RF at any time point during the study (data not shown). At start of the study RF was found in 71% of the women and 61% of the men, but at one year men were significantly more frequently RF positive than women (73 % *v* 47 %, p<0.01).

The Mallya and Larsen's scores at the study onset were comparable in the seropositive and seronegative patients whether the RF was detected at baseline or one year later (table 3). However, Mallya score remained at higher level in those patients with RF at one year than in seronegative patients. Moreover, the Larsen's score, the frequency of the patients with nodules, and the proportional number of patients in ARA Functional classes III-IV were higher in patients seropositive at one year (fig 1 and table 3). Also, these patients had used higher number of SAARDs and discontinuation of treatment because of inefficacy (table 3).

Twenty eight patients turned seronegative during the first year after the institution of SAARD treatment. Their median (IQR) Larsen's score at the latest visit was 21.5 (7–50) and 9 of 28 (32%) had reached remission. On the other hand, 14 patients turned RF positive during the first year and their corresponding

Table 6 Correlations (Spearman) with 95% confidence limits of disease clinical activity of RA, radiographic joint damage (Larsen score), and HAQ disability score at the onset of the treatment and at the end of the study in the patients with early RA treated with "sawtooth" strategy for a mean of six years

	HAQ score at onset (n=134)	*HAQ score at end (n=130)*
At onset		
swollen joint count	0.33 (0.17 to 0.48)	0.15 (−0.02 to 0.32)
tender joint count	0.39 (0.24 to 0.52)	0.25 (0.08 to 0.40)
ESR	0.22 (0.05 to 0.37)	−0.00 (−0.17 to 0.17)
Mallya score	0.42 (0.28 to 0.56)	0.14 (−0.03 to 0.30)
Larsen score	−0.03 (−0.20 to 0.14)	0.01 (−0.16 to 0.18)
disease duration	−0.23 (−0.39 to −0.06)	−0.04 (−0.21 to 0.13)
HAQ score	—	0.32 (0.15 to 0.47)
At the latest visit		
Larsen score	0.31 (0.15 to 0.46)	0.51 (0.37 to 0.63)
disease duration	0.06 (−0.11 to 0.23)	0.23 (0.05 to 0.38)

Larsen's score was 61 (38–78) and only 3 of 14 (21%) of them were in remission.

EFFECT OF THE NUMBER OF SWOLLEN JOINTS AT BASELINE ON OUTCOME

At baseline 52 patients (37%) had less than four swollen joints. Twenty of them (38%) were in remission at two years while the frequency of remissions was 21% in the rest of the patients (p=0.04). The patients with initially lower number of swollen joints were in remission at the end of the follow up in similar frequencies as the rest of the patients (33% *v* 31%, NS). Furthermore, patients with initially low number of swollen joints (<4) had lower proportion of those with ARA Functional classes III-IV at the end compared with patients with higher number (13 % *v* 30 %, p<0.05). No such trend was observed for HAQ scores > 1 (19% *v* 26 %, NS). The median (IQR) Larsen's scores in corresponding groups at the latest check up were 16 (4–49) and 42 (23–66) (p<0.01).

EFFECT OF EARLY EROSIVENESS ON OUTCOME

Joint erosions were found at the study entry and after one year in 47% and 82% of the patients, respectively. The presence of erosions at baseline had no significant influence either on the further functional outcome (HAQ score, ARA Functional class) or the development of new erosions. The respective frequencies of achieved remissions in initially non-erosive and erosive patients were 36% and 27% (NS). Neither did the values of Larsen's score or the number of used SAARDs at the latest visit differ significantly from each other in initially non-erosive and erosive patients. However, when the patients were divided into erosive and non-erosive disease at one year, more joint damage developed in erosive patients during the follow up than in the non-erosive patients (final median (IQR) Larsen's scores: 41 (17-61) *v* 11 (2-41), p<0.05), but no statistically significant difference was found in functional outcome measures (HAQ score, ARA Functional class) and the number of the patients in remission between these groups (data not shown).

PREDICTION OF STRUCTURAL JOINT DAMAGE PROGRESSION (TABLES 4 AND 5)

At the latest visit the Larsen's score of 48 patients (34%) was more than 50. At baseline the parameters measuring disease activity (swollen joint count, ESR, Mallya score) and functional disability (HAQ score) of these patients were statistically significantly higher than in the rest of the patients. On the other hand, the Larsen's scores at the baseline were comparable between these groups. In addition, a higher number of SAARDs were used in the treatment of the patients with extended joint destructions (table 4). In logistic regression analysis the independent variables consisted of sex, age, DR4, the presence of joint erosion at baseline, disease duration at the latest visit as well as RF and disease clinical activity (Mallya score) at onset and at one year. Only Mallya score at baseline and at one year, and RF at one year were variables of high significance with respect to the total joint destruction (table 5).

In 56 of 142 patients (39%) the disease clinical activity (Mallya score) was diminished by 30 per cent or more during the first year on SAARD treatment. Nevertheless, in 16 of these 56 patients (29%) the final Larsen's score exceeded 50.

PREDICTION OF FINAL REMISSION

No variable at baseline predicted reliably the patients with remission at the latest visit (data not shown).

RELATIONS OF DISEASE ACTIVITY AND EXTENT OF JOINT DESTRUCTIONS TO THE HAQ DISABILITY

At the study entry HAQ disability score was not related to Larsen's damage score (table 6). In contrast, the Mallya and HAQ scores correlated statistically significantly with each other. On the other hand, at the latest assessment HAQ and Larsen's scores had achieved highly significant correlation (table 6).

Discussion

Considerable debate has focused on whether genes bearing the alleles encoding SE are associated with an unfavourable outcome of RA.[17–19 20 22 23 36–40] In a cross sectional study Weyand and coworkers[18] found that patients homozygous for HLA-DRB1*04 had more severe disease when compared with patients with either DRB1*04/01 or with only a single DRB1*04 allele. All their patients typed as HLA-DRB1*04/04 had also nodular disease.[18] It has even been recommended that patients with early RA should be screened for HLA genotypes to guide treatment decisions.[42] However, in a recent prospective study from Sweden and in cross sectional studies from Norway and Finland the value of genomic typing to select patients for early aggressive treatment remained questionable.[20 21 36 41] Our data demonstrate that the DR4 positive patients developed RA at a significantly younger age than the rest of the patients, which is in agreement with the Swedish and Norwegian findings.[21 36] However, our patients with DR4 had lower initial clinical disease activity in comparison with the rest of the patients. During the follow up the progression of joint structural damage or functional disability of these patients did not differ significantly from the rest of the patients. Furthermore, the development of rheumatoid nodules or severe joint destruction reflected in the number of joint replacements was not associated with the

presence of these alleles. This study confirms the previous reports from Scandinavia and suggest that prognostic significance of SE to disease outcome in one population may not work in another.[21 36 41]

An interesting question is whether antirheumatic treatment neutralises the contribution of genetic markers as determining the course of RA. The placebo treated white patients with DR4 epitope developed in a 48 week minocycline trial more erosions than the DR4 negative patients, but the gradient was not observed in the minocycline treated patients.[22] The conflicting results in the studies of the predictive value of SEs may also be influenced by the intensity of SAARD treatment. Our patients with early RA were treated intensively with SAARDs from the beginning of the follow up. However, in contrast with an earlier report[40] the SAARD treatment intensity in our patients was comparable in the patient with or without SE. Thus, our finding suggests that, rather than a marker of severity, SE is a marker of susceptibility contributing to the development of RA at a younger age.

Since the introduction of the RF test, RF has been considered strongly predictive for an unfavourable disease outcome.[12] Nevertheless, in some studies the correlation of the presence of RF and the development of radiographic damage has not been shown.[20 43–45] This study clearly shows the critical importance of the disease duration at the time of RF detection as a predictor of disease progression. In our patients with very early disease and intensive SAARD treatment, RF positivity at study entry was a weak predictor of the outcome. On the other hand, the seropositivity at one year was of highly significant prognostic value.

Variations in the duration of disease and follow up of the studied populations and in the selection criteria for study inclusion are fundamental pitfalls in prognostic studies.[12 24] Our cohort comprises 142 consecutive patients with very early RA. Although the disease duration of our patients at the latest visit was higher in cohort 1 than cohort 2, all patients were followed up and checked up at regular intervals by the rheumatologists. Moreover, the patients were treated with SAARDs according to the "sawtooth" strategy. Thus, this study fulfils the criteria required for an adequate design to study the predictive factors of RA.[12 46]

Most previous studies claim that men show a more favourable outcome than women.[12] In this study both sexes were treated as actively with SAARDs, and the mean joint damage developed in parallel during the follow up in women and men. Moreover, our results indicate that in the majority of men the course of RA is favourable but in a few men it is very serious.

Older age at onset of RA has been considered to associate with a less favourable outcome but the results have been inconclusive.[20 38 47–51] In our patients the disease activity at baseline was higher in older patients than in younger ones and the joint damage progression was more pronounced in the older patients. However, in logistic regression analysis, age was not the variable of significance to extended joint destruction.

An interesting question is "how early" we actually have to start SAARD treatment to achieve the best results by using "sawtooth" strategy. In this study the further progression of joint damage was not related to the disease duration at baseline. However, the results do not exclude the possibility that the earlier SAARD institution would be of greater benefit in the patients with shorter disease duration.

Many earlier studies have stated that the patients with several clinically active joints at baseline are those who most likely will have a progressive disease course.[20 48 52–55] Also in this study the high clinical disease activity at baseline was the most important single prognostic factor for the further joint destructions. On the other hand, in contrast with several earlier reports[47–49 56] the presence of joint erosions at baseline had no significant influence on the further development of structural joint destruction during the follow up.

The reports of the development of functional disability of RA patients have found a poor initial functional capacity to be of predictive value for future disability.[49 57–60] This study clearly indicates that in the early phases of RA HAQ disability index and the measures of RA clinical activity correlate significantly, while HAQ disability and joint damage score do not. The result is consistent with two earlier Dutch studies, in which the number of painful joints was statistically significantly correlated to HAQ disability index.[55 59] At the later phases of the disease, however, HAQ disability index reaches highly significant correlation with structural joint damage index. Our result are in accordance with previous findings.[61–63] Furthermore, it is important to observe that disease duration at the latest visit is one of the major variables reflecting on HAQ score.

We conclude, that from the clinical point of view, the disease outcome of an individual patient with very early RA cannot be predicted accurately enough by present means. Initially high disease clinical activity is the best marker for poor prognosis. In addition, after one year from the institution of SAARD treatment, the patients with unfavourable outcome are prone to be RF seropositive. Furthermore, in the patients treated according to "sawtooth" strategy, DR4 and SE seem to associate with a younger onset disease but not with an unfavourable outcome.

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