Predictors of radiographic joint damage in patients with early rheumatoid arthritis

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Abstract

Objective—To determine factors at diagnosis, associated with radiographic damage at diagnosis and after one year, in patients with early rheumatoid arthritis (RA).

Methods—New patients with early RA were followed up for one year. Possible prognostic factors were duration of complaints, morning stiffness, disease activity score (DAS28), functional status (Health Assessment Questionnaire (HAQ) score), rheumatoid factor (IgM RF), and C reactive protein (CRP). Outcome was defined as radiographic damage of the hands and feet (Sharp/van der Heijde score). For the statistical analysis, one way analysis of variance and a forward stepwise logistic regression model was used.

Results—130 patients with RA (68% female; median age 64 years, range 21–86) were included. Despite the fact that the median duration of complaints was short (15 weeks, range 2–106) the radiographic damage at diagnosis was significantly correlated with the duration of complaints (p<0.05). Patients with a duration of complaints of >34 weeks had significantly more radiographic joint damage at diagnosis than patients with a shorter duration of complaints. Radiographic progression at one year was correlated with high radiographic joint damage, high CRP level, and a positive IgM RF at entry.

Conclusions—In early RA, the number of radiographic lesions was correlated with a longer duration of complaints at the first visit. Progression of these lesions was predicted by a high baseline joint damage, high CRP level, and a positive IgM RF. Further reduction of the delay in referral and early treatment may further decrease joint damage in patients with recent onset polyarthritis.

(Ann Rheum Dis 2001;**60**:924–927)

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Accepted 27 February 2001

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes joint damage in an early stage, even within two years after disease onset in the vast majority (70–93%) of patients.[1–4] The rate of appearance of erosions is high in the early years of RA.[5 6] In the long term, joint damage may lead to functional disability.[4 7] In a study by Corbett *et al* the onset of erosions in hands and feet during the first two years of disease was the strongest predictive feature of a poor functional outcome after 15 years.[7]

If, at an early stage, those patients who will deteriorate rapidly could be recognised, a more appropriate treatment could be given. Several recent studies suggest that fast and aggressive treatment of RA by combining disease modifying antirheumatic drugs (DMARDs) will suppress the inflammation process and result in less joint destruction.[8–12] In the long term, this may preserve the functional outcome as well.[4] Many studies have examined the course and outcome of disease in patients with established RA and investigated the role of variables measured at the patient's initial visit as prognostic factors. Factors at initial presentation which are reported as predictors for joint damage in patients with RA are female sex[13]; serum IgM rheumatoid factor (RF) positivity[3 4 13–22]; the C reactive protein (CRP) level[15 16 21 23 24]; radiographic damage[14 17 18 21 25]; number of swollen joints[16 18]; disease activity;[4 20] and the presence of the genetic marker HLA-DR4.[17 20] The definition of early arthritis varies in these studies because the interval between symptom onset and presentation to the rheumatologist ranges from three months to six years. Difference in study design is probably the most important reason for the conflicting results found in published reports.

In this study a cohort of patients with early RA with a median duration of complaints of 15 weeks was followed up for one year. The purpose of the study was: (*a*) to determine which parameters correlate with radiographic damage at the time of the diagnosis RA, and (*b*) to identify variables at the first visit that can predict radiographic progression after one year.

Methods

PATIENTS

As part of a prospective cohort study[26] all patients with RA, fulfilling the American College of Rheumatology criteria for RA[27] within one year after presentation, were followed up at a large rheumatology outpatient clinic. They were referred between September 1995 and September 1996. The duration of symptoms was at most two years. All patients gave informed consent. The medical ethical committee approved the study protocol. Patients who had been previously treated with a DMARD were excluded.

DISEASE PARAMETERS

After receiving the diagnosis RA by a rheumatologist, the patients were seen by a research nurse who performed a structured interview and physical examination. Follow up assessments were performed at 3, 6, 9, and 12 months.

Table 1 Baseline and one year characteristics of 130 patients with early rheumatoid arthritis

Variable	Baseline	1 Year
Age (years), median (range)	64 (21–86)	—
Female (No (%))	88 (68)	—
Disease duration (months), median (range)	3 (0–24)	—
IgM RF* positive (No (%))	66 (51)	62 (54)
Erosive (No (%))	100 (77)	98 (86)
Radiographic score (S/H score), median (range)	4 (0–61)	9 (0–112)
DAS*, mean (SD)	5.4 (1.2)	3.8 (1.4)
ESR* (mm/1st h), mean (SD)	40 (24)	20 (17)
CRP* (mg/l), mean (SD)	34 (42)	15 (22)
Morning stiffness (min), mean (SD)	100 (150)	38 (102)
No of tender joints (38 joint count), median (range)	9 (0–30)	5 (0–32)
No of swollen joints (38 joint count), median (range)	12 (1–33)	7 (0–26)
HAQ*, mean (SD)	1.0 (0.8)	0.5 (0.6)

*RF = rheumatoid factor; DAS = disease activity score; ESR = erythrocyte sedimentation rate; CRP = C reactive protein; HAQ = Health Assessment Questionnaire.

At baseline, demographic characteristics, the time of onset of complaints (persistent pain and swelling), serum rheumatoid factor (IgM RF), and radiographs of hands and feet were recorded. Every three months the following variables were assessed: the 28 joint disease activity score (DAS28: a composite score based on erythrocyte sedimentation rate (ESR), number of painful and number of swollen joints (both by 28 joint count), and patient global assessment by visual analogue scale (VAS)),[28] the number of painful and number of swollen metatarsophalangeal joints, pain (VAS), CRP, and functional status by the validated Dutch version of the Health Assessment Questionnaire (HAQ).[29]

Outcome was assessed by counting the number of erosions and grading the joint space narrowing according to the van der Heijde modification of Sharp's method.[25 30] The main difference from the original Sharp method was the inclusion of the feet in the scoring system. The maximum number of erosions in the hands is 160 and in the feet 120, and the maximum scores for joint space narrowing for hands and feet are respectively 120 and 48. The maximum total score is 448. All radiographs were scored by a trained researcher, who was unaware of the clinical data of the patients. The x ray pictures were read in pairs with unknown time sequence. Radiographic progression, expressed as delta (δ) damage, was computed by subtracting the initial Sharp van der Heijde score from the one year Sharp/van der Heijde score.

STATISTICAL ANALYSIS

Patients were split into five centile groups according to the duration of complaints: 0–7 weeks, 8–13 weeks, 14–19 weeks, 20–33 weeks, and 34–104 weeks. Because of a skewed distribution the joint damage score was log transformed. One way analysis of variance was used to test whether the groups differed in baseline joint damage.

At one year the patients were divided into two groups, "slowly progressive" or "rapidly progressive", using the median of the δ damage. Subsequently, clinically relevant baseline characteristics were entered into a forward stepwise logistic regression analysis using the δ damage between the baseline and one year as dependent variable. The initial Sharp/van der
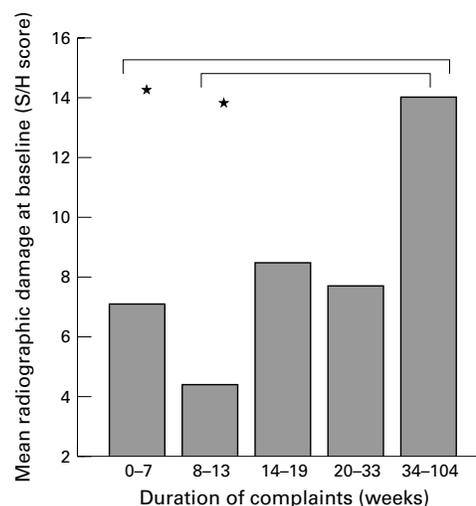

Figure 1 Radiographic damage at baseline in five centile groups by duration of complaints. *p<0.05 (one way analysis of variance). S/H score = Sharp/van der Heijde score.

Heijde score, age, sex, duration of complaints, DAS28 score, number of tender and swollen joints (38 joint count), HAQ score, IgM RF positivity, ESR high (≥28 mm/1st h)/low, and CRP high (≥20 mg/l)/low were considered as independent variables. For the statistical methods used we refer to Altman.[31] All analyses were carried out with SPSS 9.0.

Results

One hundred and forty two patients were eligible for the study. Twelve patients were excluded because they moved away at the start (n=7), had a language problem (n=3), or refused to participate (n=2). Thus 130 patients were included in the study.

Complete data after one year's follow up were obtained from 114 (88%) of the 130 patients. Three patients died (two from malignancy and one from renal failure), four patients refused to participate, and nine had incomplete follow up data—namely, insufficient radiographic data, clinical data, or the questionnaires were incomplete. The baseline disease characteristics of the 16 patients lost to follow up were similar to those of the 114 who completed the trial (data not shown).

Table 1 presents demographic and baseline clinical data on the 130 patients with RA studied. The median disease duration at entry was three months (range 0–24).

The baseline joint damage correlated significantly with age (p<0.01), ESR, swollen joint count, and duration of complaints (p<0.05). Patients were categorised according to the duration of complaints into five centile groups: 0–7 weeks, 8–13 weeks, 14–19 weeks, 20–33 weeks, and 34–104 weeks. By one way analysis of variance it was illustrated that the mean joint damage score at baseline was higher among the patients with a longer duration of complaints ($F_{4,123}$ =2.75; p<0.05). The mean difference in baseline joint damage score between the group with 0–7 weeks' and more than 34 weeks' duration of complaints was −7.0 (p=0.027, confidence interval (CI) −13.2 to −0.82), and

Table 2   Summaries of logistic regression analysis of baseline variables to predict severely progressive joint damage (Sharp/van der Heijde) at one year

Criterion predictor (n=114)	Coefficient (β)	Standard error	Odds ratio (exp β)	95% CI	Multiple R²
(Constant)	−3.08	0.78			72%
Joint damage at entry	0.07	0.03	1.07	1.02 to 1.12	
CRP* high/low	1.28	0.43	3.59	1.53 to 8.39	
IgM RF* positivity	0.95	0.43	2.58	1.11 to 5.97	
Variables not in the equation	*Score*	*p Value*			
Disease duration	2.01	0.16			
Age	0.19	0.67			
ESR* high/low	0.48	0.49			
DAS*	1.08	0.29			
Female sex	2.59	0.11			
No of tender joints	0.37	0.54			
No of swollen joints	0.02	0.89			
HAQ*	0.43	0.51			

*CRP = C reactive protein; RF = rheumatoid factor; ESR = erythrocyte sedimentation rate; DAS = disease activity score; HAQ = Health Assessment Questionnaire.

the difference in baseline joint damage between the 8–13 weeks and the 34–104 weeks group was −9.65 (p=0.002, CI −15.6 to −3.8) (fig 1).

During the one year follow up, 85% of the patients were treated with DMARDs: sulfasalazine (47%), methotrexate (22%), hydroxychloroquine (13%), and auranofin (2%). Prednisone was used by nine patients as well.

Table 2 shows the results of the logistic regression analysis of radiographic progression at one year. The median radiographic progression rate was 3 Sharp/van der Heijde score units a year (range –7 to 77). Radiographic progression at one year was independently associated with high joint damage, high CRP level, and a positive IgM RF at initial presentation. The duration of complaints and the ESR were significantly correlated (p<0.05) with radiographic progression but had no additional value for the prediction of progression and were therefore not included in the regression model.

Discussion

In this cohort of patients with very early RA, patients with a delay in referral of more than nine months had a higher joint damage score at entry than patients with a shorter delay. After one year of follow up the duration of complaints was also significantly correlated with the rate of radiographic progression in that year. In the predictive model of radiographic progression within one year the baseline joint damage score, CRP score, and IgM RF positivity proved to have a higher association with radiological progression than the duration of complaints at first visit. Patients with a long duration of complaints had more erosions at diagnosis and also showed more radiographic progression during the first year. In contrast, patients with a low number of erosions at entry had a short period of complaints and had little radiographic progression during the first year.

In this study, the Sharp/van der Heijde method was preferred to the Larsen scoring method. According to Giovagnoni et al, the Sharp/van der Heijde score index can be considered as the best tool for evaluating patients with early RA because of its sensitivity in detecting early disease signs and the possibility of expressing anatomical damage

progression quantitatively.[32] To avoid bias as a result of the fact that the observer may expect progression of damage over time (that is, over-estimation), it was decided to read the radiographs in pairs with unknown time sequence. In the present cohort radiographic damage showed an improvement in 9% of the patients, which may be due to intraobserver variability, different positioning, or smoothing of the surface.

Our findings about the effects of treatment delay are in accordance with the results of Irvine *et al*.[33] They concluded that 73% of patients who had a one year delay from symptom onset until the first visit to the rheumatologist already showed erosive changes, compared with 34% of patients seen within one year.

In the present study, patients were categorised into five centile groups according to disease duration. The group with the longest duration of complaints showed the highest score in radiographic joint damage and a higher percentage of patients with RF positivity compared with the shortest delay group (68% *v* 29%). However, this does not imply that the IgM RF level is causally related to duration of complaints.

Most studies agree that a positive IgM RF is an important predictor for joint damage in the first years of disease.[3 4 14–17] Also for the long term, IgM RF positivity is associated with an unfavourable prognosis. Kaarela *et al* concluded that 99% of patients, fulfilling four 1987 American Rheumatism Association criteria for RA, including a positive IgM RF, had developed erosive disease after 17 years of disease duration.[34] In the present study as in that of van der Heijde *et al*,[25] the baseline joint damage was a stronger predictor of progression then the IgM RF. Van der Heijde concluded that patients with little radiographic progression could already be identified at one year of follow up. Moreover, it was found that an already damaged joint is more prone to become seriously damaged than an unaffected joint. In contrast with this, Coste *et al* found, in a two year follow up study, that only disease duration and age were predictive of joint damage progression.[35]

In our study, the duration of complaints correlates with baseline joint damage. This correlation was not found when correlating the baseline HAQ score with patient delay in the same cohort.[26] Others have also found that joint damage and HAQ scores are not related in the earliest phases of RA.[36] The link between damage and disability is strongest in late (>8 years) RA. This is confirmed by Drossaers-Bakker *et al*, who found the correlation between the Sharp/van der Heijde score and the HAQ score to be weak at study start but strong after 12 years.[37] According to Guillemin *et al*, physical disability in early RA is mainly determined by disease activity, whereas joint damage becomes more important in a later stage of the disease.[38]

In conclusion, patients should be referred to a rheumatologist as soon as possible in order to initiate treatment with DMARDs rapidly,

especially in case of RF positivity and a high CRP level.

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