Predictive Factors of 5-Year Health Assessment Questionnaire Disability in Early Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine prognostic factors of disability in early rheumatoid arthritis (RA) and to investigate the radiological and functional course of the disease.

Methods. A total of 191 patients with early RA (diagnosed for less than one year) according to American College of Rheumatology criteria were followed prospectively for 5 years. At baseline and at endpoint, Stanford Health Assessment Questionnaire (HAQ) scores and radiological scores (Sharp's score modified by van der Heijde) were performed. Correlations between numerous baseline data and HAQ score at endpoint were analyzed, using nonparametric tests. A multilinear regression model was performed to select independent prognostic factors of HAQ disability.

Results. During the 5-year followup, mean HAQ decreased from 1.3 (± 0.7) to 0.6 (± 0.6). There were 98 (65.3%) patients with a score > 1 point at baseline, but only 46 (27.4%) after 3 years and 34 (21.8%) after 5 years. Moreover, 90% of the patients had an improvement of the disability score. Final HAQ disability was associated with baseline values of HAQ score, Pain, Ritchie index, tender joint count, Disease Activity Score, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and erosion. Multivariate analysis selected baseline HAQ score, Ritchie index, ESR, CRP, and presence of erosion as independent prognostic factors of HAQ disability. The probability cutoff in the logistic model was selected to minimize the sum of false positive and false negative values: negative predictive value = 92.71%, positive predictive value = 46.15%, p = 0.408. Sex, age, IgM and IgA rheumatoid factors, other tested autoantibodies, and HLA class II genes did not contribute significantly to prediction of the disability after 5 years. At baseline, mean scores were 3.6 units (± 7.7) for total radiological score, 1.7 (± 4.5) for erosion score, and 1.9 (± 3.7) for joint space narrowing score. After 5 years, they were 17.9 ± 22.3, 6.9 ± 9.5, and 11.0 ± 15.4, respectively. No erosion was present at the start in 58.0% of patients, compared to 24.2% and 22.4% at 3 and 5 years. Global radiographic progression concerned 87 patients (55.8%) during the 5 years.

Conclusion. During the first 5 years of RA, radiological damage increased progressively in half of the patients, whereas HAQ disability improved in most of them during the same period of time and could be predicted by baseline values of HAQ score, Ritchie index, ESR, CRP, and presence (or absence) of erosion. (J Rheumatol 2003;30:2344–9)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DISABILITY RADIOGRAPHIC EVOLUTION PROGNOSIS

Rheumatoid arthritis (RA) is a potentially severe but very heterogenous disease[1]. Disability can be rapidly extensive or almost absent, even after longterm followup. Nevertheless, close to 50% of patients with RA were work-disabled after 10 years of disease duration and 10% will develop severe functional impairment in the first 2 years of the disease[2,3]. Further, 25% of patients with RA will undergo joint replacement within 20 years of disease onset[4]. Radiological damage usually affects patients, but some have limited or even no joint destruction even after a long period of time[5]. The progression of damage seems to occur mainly during the first years of the disease[6-9]; however, a recent report by Hulsmans, *et al*[10] showed a rather stable and linear rate of progression of radiologic damage. The relationship between the severity of joint damage and the development of disability is controversial. A few studies have addressed this issue and their conclusions were discordant. Some investigators suggest that handicap and radiological damage

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increase together[11]. Others observed improvement of disability despite joint destruction[12,13]. Indeed, it seems that the effect of joint destruction on functional capacity changes over the course of the disease[14,15]. A number of short and longterm studies have attempted to identify predictive factors of disability in RA, but the results are conflicting[13,16–24]. Factors that have been suggested include initial functional status, sex, education, socioeconomic data, mode of onset, morning stiffness, Disease Activity Score (DAS), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), positive rheumatoid factor (RF), and baseline radiological damage. It has been suggested that prognostic factors and determinants of disability in RA could be different at each stage of the disease; inflammation processes could be the predominant determinant of disability in early RA and strucural abnormalities could generate functional impairment after many years of disease duration[25].

We recently reported prognostic factors of joint damage and radiological progression in early RA[26]. In the present study, we tried to identify predictive factors of the Stanford Health Assessment Questionnaire (HAQ) disability after 3 and 5 years of disease duration, and evaluated radiographic and functional evolution in the same cohort of community based patients. Self-report of functional impairment has become the standard in RA, and the HAQ is the most common assessment tool.

MATERIALS AND METHODS

Patients. All consecutive outpatients fulfilling American College of Rheumatology (ACR) criteria for RA[27] of less than one year duration who were referred from primary care physicians for the purpose of this study, who had not been treated with disease modifying antirheumatic drugs (DMARD), and who agreed to be enrolled in a 5-year followup study (and gave signed informed consent) were included between March 1993 and October 1994 in 4 French centers (Montpellier, Paris-Cochin, Toulouse, Tours). They were all treated with DMARD [usually methotrexate (MTX) or sulfasalazine (SSZ)] that could be modified during the study according to efficacy and side effects. The study was approved by the ethical review board in Montpellier.

Clinical and biological assessment. The following evaluation data were collected at baseline: age, sex, body mass index (BMI), disease duration, morning stiffness, pain (visual analog scale), number of swollen and tender joints, DAS, presence or absence of nodules and extraarticular manifestations, ESR, CRP, antinuclear antibodies [ANA; immunofluorescence (IF) technique], IgA and IgM rheumatoid factor (RF; anti-human Fc IgG-ELISA), anti-keratin antibodies (indirect IF on cryostat sections of rat esophagus), antiperinuclear antibodies (IF on buccal epithelial cells), anti-RA-33 antibodies (immunoblotting), anti-HSP-90 antibodies (ELISA)[28,29], anticalpastatin antibodies (ELISA, Progen®, Heidelberg, Germany), and YKL-40 (radioimmunoassay, Chondrex® Metro Biosystem, CA, USA) and ANA (IF, HEp-2). HLA-DRB1* and DQB1* genotyping were performed as described[6]. Each patient was followed up by the same investigator, 6 months after inclusion and once a year for 5 years.

Functional assessment. Functional disability was assessed by HAQ at baseline and at 3 and 5 years. This instrument has been adaptated and validated in French[30]. A continuous scale from 0 to 3.0 was used to relate the score of the functional state of the patients. Patients could be classified as mildly disabled (score 0–1), moderately disabled (score 1–2), or severely disabled (score > 2).

Radiographic measurement. Hand, wrist, and foot radiographs were taken at baseline and at 3 and 5 years. They were evaluated blindly and in chronological order by 2 independent observers, according to the Sharp method modified by van der Heijde[31]. For each patient, an erosion score, a narrowing score, and a total damage score were noted for hands and feet. Before the conclusive evaluation, the intraclass, intraobserver, and interobserver coefficients of correlation were calculated on 30 chosen pairs of radiographs of hands and feet, and were always > 0.85. No systematic differences were found in any of the scores. Then we used the mean of the 2 observer scores for erosions, joint space narrowing, and total damage scores (hands and feet).

To determine a cutoff value for changes in joint space width that would define individual radiological progression of RA unrelated to measurement errors (smallest detectable difference), we calculated the mean of differences between 2 analyses as described[32,33]. We thus selected 30 pairs of radiographs of hands and feet representative of the study population. The mean ± standard deviation of the differences between the 2 analyses performed by the 2 observers were calculated for each score.

Radiological progression was therefore defined by a change in radiological scores greater than the upper bound of the 95% confidence interval of the differences, i.e., a change of at least 5.0, 4.9, and 4.1 in the erosion score, narrowing score, and total damage score, respectively.

Statistical methods. Statistical analysis was performed using the BMDP statistical software[34].

Univariate analysis of the relationship between all baseline continuous variables and functional outcome (HAQ scores) used as a continuous variable was undertaken using nonparametric correlation tests. Spearman's test was chosen because baseline variables did not have a Gaussian distribution as shown by the the Shapiro-Wilks test. The nonparametric Kruskal-Wallis test was performed to compare baseline categorical variables and continuous HAQ scores at 3 and 5 years.

Significant levels for the changes over time on radiographic and HAQ scores have been displayed using the Friedman test (non-Gaussian variables).

A multilinear regression model with variance–covariance analysis entering continuous and categorical variables at the same time was used to find relevant independent prognostic factors of 3- and 5-year HAQ scores used as continuous variables. The significance level was set at 0.05.

RESULTS

Demographic, clinical, and biological features of the patient cohort. Baseline characteristics of the patients are shown in Table 1. One hundred ninety-one patients (140 women, 51 men) were enrolled for study. The mean age at diagnosis was 50.5 ± 14.7 years and the mean disease duration at inclusion was 3.6 ± 2.6 months. One hundred thirty-nine patients (80.8%) were IgM or IgA RF-positive (< 20 IU/ml and < 7 U/ml, respectively) at baseline; 12.8% were only IgA RF-positive and 7.2% only IgM RF-positive; 86 (47%) had at least one RA-associated DRB1*04 allele (DRB1*0401, 0404, 0405, 0408). During the 5-year followup, a mean of 1.95 DMARD (range 1–5) were prescribed (MTX, 175; SSZ, 147; gold, 41; hydroxychloroquine, 25; D-penicillamine, 14; cyclosporine, 1). Eighty-six patients received the same DMARD or the same combination of DMARD during the 5-year followup. Sixty-three patients (34.6%) received low dose prednisone at least once (5–15 mg/day).

Twenty-six patients (13.6%) were lost to followup (6 patients died, 8 refused further followup, 12 moved out of

Table 1. Baseline characteristics of 191 patients with early RA.

	No. (%) of Patients Mean ± SD
Female, %	140 (73)
Age, yrs	50.5 ± 14.7
Mean disease, mo	3.6 ± 2.6
Pain, 0–100 mm VAS	57.5 ± 22.00
Morning stiffness, min	84.9 ± 79.4
Ritchie index	17.5 ± 8.5
Tender joints, n	21.7 ± 10.5
Swollen joints, n	9.0 ± 5.9
Nodules, %	11 (5.7)
ESR, mm/h	40.2 ± 28.5
CRP	34.1 ± 43.2
IGA or IgM RF positivity, %	154 (80.6)
DAS	4.1 ± 0.8
HLA-DRB1*04[†]	86 (47)
HLA-DRB1*01	54 (29.5)

[†] RA associated DRB1*04 genes: 0401, 0404, 0405, 0408.

the area or were otherwise lost to followup). The 5-year radiographs were incomplete or missing for 9 additional patients. Data for 156 patients were available for both functional and radiological analysis at 5 years. The baseline data for the 45 patients that were not available for the 5-year analysis did not differ from those of the whole cohort.

Functional outcome. HAQ disability was less severe after 3 and 5 years of disease than at baseline (Table 2). Median HAQ score decreased from 1.25 to 0.37 during this period (mean 1.3 ± 0.7 to 0.6 ± 0.6) ($p < 0.001$). Most patients (78.2%) had HAQ score lower than 1 (mild disability) after 5 years compared to 34.7% at baseline. By contrast, 19.1% of patients had severe HAQ disability (HAQ > 2) at the start, compared to 5.8% at 3 years and 4.5% at the 5-year followup. Finally, 90% of the patients had an improvement of the HAQ score.

Predictive factors for functional outcome. When univariate analysis was undertaken, baseline HAQ score at 5 years was associated with baseline values of HAQ ($p < 0.0001$), pain ($p = 0.001$), Ritchie index ($p = 0.008$), tender joint count ($p = 0.009$), DAS ($p = 0.009$), ESR ($p = 0.01$), CRP ($p = 0.04$), erosion score ($p = 0.03$), and total radiological score (Table 3). Only baseline HAQ score ($p = 0.0001$) and DAS ($p = 0.04$) were correlated with HAQ disability at 3 years. Age, sex, extraarticular manifestations, IgM RF, IgA RF, antikeratin, antiperinuclear, anti-HSP-90, anti-RA33, anticalpastatin and antinuclear antibodies, YKL-40, and HLA-DRB1* genes were not associated with 3-year or 5-year HAQ score.

Multivariate analysis revealed that the only independent baseline variables that were able to predict 5-year HAQ disability were HAQ score, ESR, CRP, Ritchie index, and presence (or absence) of erosion (Table 4). HAQ scores at 3 years were predicted only by baseline HAQ score (data not shown).

To determine positive and negative predictive values (PPV and NPV), we needed to choose a probability cutoff in the logistic model. When this cutoff was selected to minimize the sum of false positive and false negative values, $p = 0.408$, PPV = 46.15%, and NPV = 92.71%; $p = 0.408$ was the probability in this model to have a 5-year HAQ score higher than 1; "1" was chosen as the cutoff point because HAQ disability is usually considered to be mild when the score is lower than 1.

Radiological outcome. By 5 years of followup, the total damage score, erosion score, and joint space narrowing score increased from 3.6 ± 7.7 to 17.9 ± 22.3 ($p < 0.001$), from 1.7 ± 4.5 to 6.9 ± 9.5 ($p < 0.001$), and from 1.9 ± 3.7 to 11.0 ± 15.4 ($p < 0.001$), respectively (Table 2). Median values of the total score were 1.0 at the start, 4.0 at 3 years, and 10.0 at 5 years.

Total score was null for 80 patients (42.8%) at baseline, for 30 (17.4%) patients at 3 years, and for 27 (17.3%) at 5 years. No erosion was present at the start in 58.0% of the patients, compared to 24.2% at 3 years and 22.4% at 5 years. Absence of joint space narrowing was noted in 54.5% of the patients at baseline, in 32.4% at 3 years, and in 26.3% at 5 years.

During the 3 and 5 year followup, a significant radiographic progression was observed in 71 (41.3%) and 87 (55.8%) patients for total damage score, in 55 (31.8%) and 75 (48.1) patients for erosion score, and in 46 (26.6%) and 62 (39.7%) patients for joint space narrowing score, respectively.

Table 2. Radiographic scores (hands and feet) and HAQ scores at baseline and after 3 and 5 years of followup.

	At Baseline	At 3 Years	At 5 Years
Erosion score, mean (range)	1.7 (0–33.0)	4.8 (0–46.0)[†]	6.9 (0–51.0)[†]
Patients without erosion, n (%)	109 (58.0)	42 (24.2)	35 (22.4%)
Joint space narrowing score, mean (range)	1.9 (0–26.5)	2.9 (0–48.0)[†]	11.0 (0–80.0)[†]
Patients without JSN, n (%)	102 (54.5)	56 (32.4)	41 (26.3%)
Total score, mean (range)	3.6 (0–59.5)	9.7 (0–72.5)[†]	17.9 (0–95.0)[†]
Patients without radiographic damage (total Sharp score = 0), n (%)	80 (42.8)	30 (17.4)	27 (17.3%)
HAQ score, mean (range)	1.3 (0–2.75)	0.5 (0–2.50)[†]	0.6 (0–3.0)[†]

[†] $p < 0.0001$ compared to baseline; Friedman test.

Table 3. Association between baseline continuous variables and 5-year HAQ score.

Baseline Variable	Spearman Correlation Coefficient	p*
Pain	0.317	0.001
Morning stiffness	0.211	0.045
Ritchie index	0.292	0.008
Tender joints	0.265	0.009
Swollen joints	0.0025	0.45
DAS	0.263	0.009
ESR	0.217	0.01
CRP	0.174	0.04
Erosion score	0.186	0.03
Total Sharp score	0.167	0.04
HAQ	0.468	0.0001

* Spearman test.

Table 4. Multilinear regression model with variance-covariance analysis of predictive factors of 5-year HAQ score.

Baseline Variable	Coefficient	p
HAQ score	0.3943	0.0001
ESR	0.008	0.006
CRP	0.005	0.001
Ritchie index	0.0214	0.045
Equality of adjusted mean* (erosion)		0.047

* The grouping variables were presence or absence of erosion at baseline.

DISCUSSION

This multivariable prospective study of 191 patients with early RA, who were DMARD-naive at entry, confirmed that most patients with early RA have a fairly good 5-year prognosis for functional outcome despite progression of joint destruction evaluated on modified Sharp score, and that the best prognostic factors of 5-year HAQ disability were baseline HAQ score, ESR, CRP, Ritchie index, and presence (or absence) of erosion. Our cohort of patients was similar (sex ratio, age, biological and clinical disease activity variables) to other prospective cohorts[12,13,17,18,20,22,23,35,36-39]. Some studies have described lower acute phase reactants, but their mode of recruitment (public campaign) or the absence of information about continuing treatments or prestudy treatment prevents a comparison.

Positive rheumatoid factor was more frequent than usually described — 80% of our population had one or 2 isotypes of RF (IgA or IgM). This could be due to differences in technical methods. ELISA tests are more sensitive than latex or Waaler-Rose methods frequently used in previous studies. However, these data were similar to those obtained by van Leeuwen, *et al*[36], who reported that 81.2% of their patients had IgM RF and only 12.8% had no RF when different isotypes (A, G, M) were examined in a cohort of patients with early RA. The proportion of patients with disease-associated DRB1*04 alleles was lower than described in early RA[18,37], but was similar to other studies from the south of France[6,38].

All the patients were DMARD-naive at baseline, and then were mainly treated with SSZ, MTX, or a combination of both. Since the 18-month effects of these drugs on radiological outcome was shown to be similar[39], it is unlikely that drug regimen could have influenced the results we obtained. Progression of radiological scores during the 5-year followup was lower than the results obtained by Drossaers-Bakker, *et al*[12], but in this study, the disease duration at baseline was higher (0 to 5 years) and the DMARD regimen was not precise. In the report by van der Heijde, *et al*[9],the baseline score was also higher than in our study, but only 10% of the patients received MTX compared to 74% receiving drugs that have shown no significant ability to slow structural damage (nonsteroidal antiinflammatory drugs, hydroxychloroquine, auranofin), and 56 of their 146 patients did not have radiographic evaluation after 3 years of followup. By contrast, our radiological data are similar to recent results from Hulsmans, *et al*[10], where the median rates of progression of Sharp score, erosion score, and narrowing score were 4.0, 2.0, and 1.0 Sharp units per year, respectively. Further, we observed that 24% of the patients had no erosion after 3 years, in agreement with other studies[10,35,40]. Our study is the first to use individual structural RA progression not related to measurement method errors (statistically relevant change)[32] as outcome variable. Using this method, 55.8% of the patients had radiological progression of the total damage score on hands and feet.

Functional outcome in our patients after 5 years of RA duration was fairly good. The mean HAQ score decreased from 1.3 (± 0.7) to 0.6 (± 0.6). At baseline, 65.3% of patients had a score higher than 1, but only 21.8% did so after 5 years. The baseline HAQ disability score was slighty higher than in other reports, but in contrast to some reports[12,13,22–25,40] our patients with early RA were DMARD and steroid-naive. Compared to recent reports[12,18,22-25] our 3 and 5-year HAQ scores were low, and the HAQ disability during this 5-year study was weakly associated with radiographic damage on hands and feet. Most of the short or middle-term studies suggest that HAQ disability was mainly

explained by disease activity or pain scores[12,13] or psychosocial factors[41]. Improvement or absence of significant deterioration of functional capacity in the first year of RA may be due to different factors[24,42], including the effect of treatment strategies that are usually the most efficient in this period of the disease course, the "coping phenomenon" that is the result of patients that underestimate their functional abilities at the start of the disease and overestimate these abilities in established RA, or because HAQ score does not measure all dimensions of functional capacity.

Univariate analysis tested most of the clinical, biological, and immunological factors that were previously reported to be possibly related to RA outcome. This analysis showed that 3- and 5-year HAQ disability was mainly correlated to baseline HAQ score and to a lesser extent to baseline values of disease activity including pain, tender joint count, Ritchie index, CRP, and ESR. Previous studies focusing on the predictive factors of HAQ disability have also identified baseline HAQ score as the best prognostic indicator[11,13,17,19,22,23,25,40]. Pain[17,18,24,40], clinical variables of disease activity[22,25,40], ESR[13,16,25,43], and psychosocial factors[13,23,40] have also been selected in previous studies. Autoantibodies, including IgM and IgA RF, antikeratin and antiperinuclear antibody, HLA-DRB1*04 and 01 genes, that are good prognostic factors for joint damage in RA[26] have a low prognostic value in this study, and have rarely been evaluated as prognostic factors of functional disability in the literature. Finally, the presence of baseline erosion was also selected as an independent predictive variable of the 5-year HAQ, which is consistent with the fact that joint destruction can influence HAQ disability, but only in long-standing RA[12,13,25]. HAQ score, ESR, CRP, Ritchie index, and presence of erosions were the only variables selected by the multivariate analysis. The negative predictive value in the logistic model was 92.71%, with a probability cutoff of 0.408. This means that only a few patients (7.29%) with low values in the logistic analysis had a high 5-year HAQ score (> 1).

During the first 5 years of RA, radiological damage increased progressively in half of the patients, whereas HAQ disability improved in most of them during the same period of time and could be predicted by initial HAQ score, erosion score, and pain.

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