Prognostic Factors of Radiological Damage in Rheumatoid Arthritis: A 10-year Retrospective Study

THEODORA E. MARKATSELI, PARASKEVI V. VOULGARI, YANNIS ALAMANOS, and ALEXANDROS A. DROSOS

ABSTRACT. ***Objective.*** To describe the longterm clinical and radiological outcomes in rheumatoid arthritis (RA) in a cohort in northwestern Greece; and to investigate predictive factors of radiological damage at the 10-year followup in patients with RA.

Methods. We studied the disease course and outcome of 144 patients with RA and radiographs of the hands and wrists available at baseline and at 10 years. Baseline measurements and time-averaged measures of swollen joint count (SJC) and inflammatory markers [erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)] were tested in univariate analysis, and then those presenting a statistically significant association with either Larsen score at 10 years or annual progression rate were included in 2 logistic regression models in order to determine relevant independent prognostic factors.

Results. A significant clinical improvement was noted, associated with a decrease of inflammatory markers along the timepoints. Larsen score and the number of erosive joints were increased. In the univariate analysis, both final Larsen score at 10 years and accelerated annual radiological progression rate were significantly associated with baseline radiographic measurements (Larsen score and number of erosive joints), the presence of autoantibodies [anticyclic citrullinated peptide antibodies (anti-CCP) and rheumatoid factor of IgA and IgM isotype], disease duration, and time-averaged measures of ESR, CRP, and SJC. In the logistic regression analysis, the baseline Larsen score, anti-CCP antibodies, and time-averaged CRP presented significant and independent associations with Larsen score at 10 years. An accelerated annual radiological progression rate was also predicted by baseline Larsen score and time-averaged measures of SJC and CRP.

Conclusion. Despite clinical improvement, the radiologic progression of RA continues over time, because of the underlying inflammatory process. Baseline radiographic damage, anti-CCP antibodies, and time-averaged CRP constitute the main predictive factors of poor radiologic outcome in the long term. (J Rheumatol First Release Oct 15 2010; doi:10.3899/jrheum.100514)

Key Indexing Terms:
RHEUMATOID ARTHRITIS RADIOLOGIC DAMAGE LARSEN SCORE
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Rheumatoid arthritis (RA) is a widespread autoimmune disease characterized by chronic joint inflammation resulting in severe structural damage and loss of the patient's functional capacity[1,2]. In addition, RA is often characterized by the presence of extraarticular manifestations, which are responsible for the disease's morbidity and mortality[3]. The course and the outcome of RA may range from mild to severe, and are unpredictable, thus making therapeutic decisions challenging. Ideally, the intensity of treatment should be based on reliable prognostic factors of disease outcome, especially now that aggressive treatment with biologic agents is available[4,5,6].

The progressive joint damage reflected in radiographs constitutes the most objective outcome variable, while radiographs of the hands and the wrists are representative of the total damage that a patient with RA has sustained[7]. Regardless of the scoring method, the appearance and the number of erosions are considered the most important features of the radiographic changes and many studies focus on them[8,9,10].

Studies have been conducted to identify prognostic factors of poor radiographic outcome[8,9,10,11,12,13,14]. They have shown that various factors, including patients' demographic characteristics, clinical measures at baseline, markers of inflammation, serum autoantibodies [rheumatoid factor (RF), anticyclic citrullinated peptide (anti-CCP) antibodies, and others], genetic background (HLA-DRB1 genotype), and early imaging damage in hands, are associated with

From the Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina; and the Department of Public Health, Medical School, University of Patras, Patras, Greece.

T.E. Markatseli, MD, Fellow in Rheumatology; P.V. Voulgari, MD, Assistant Professor of Rheumatology; A.A. Drosos, MD, FACR, Professor of Medicine/Rheumatology, Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina; Y. Alamanos, MD, Associate Professor of Hygiene and Epidemiology, Department of Public Health, Medical School, University of Patras.

Address correspondence to Dr. A.A. Drosos, Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece. E-mail: adrosos@cc.uoi.gr

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worse radiographic outcome. However, there is no absolute agreement between studies.

The aim of our retrospective study was to determine baseline prognostic factors of radiographic damage, and to describe the longterm clinical and radiological outcome in an RA cohort in northwestern Greece.

MATERIALS AND METHODS

Patients. A total of 717 patients, who had a definite diagnosis of RA according to the American College of Rheumatology (ACR) disease criteria[15], and age at disease onset > 18 years, attended the Rheumatology Department of the University Hospital of Ioannina, Greece, during the inclusion period, between 1990 and 1998. From these, 407 patients had disease duration < 5 years at baseline (defined as the time of initial presentation at our department). Of the 407 patients, 186 had radiographs available only at baseline (Group 1), 77 at baseline and at 5 years but not at 10 years (Group 2), while 144 patients had radiographs available at baseline, 5, and 10 years (Group 3). These 3 groups of patients did not differ in their baseline characteristics ($p > 0.05$ for all comparisons; Table 1). We present the clinical and radiological course and outcome of the 144 patients in Group 3 (10-year cohort). However, in order to investigate predictive factors of annual radiological progression, we evaluated all patients who, in addition to baseline radiograph, also had a second radiograph, at either 5 or 10 years (in total, 221 patients).

Clinical assessment. Records of the patients were reviewed and demographic, clinical, laboratory, and radiological characteristics at baseline, at the end of the followup period, and at regular intervals in between were recorded.

The following measurements were recorded for each patient: sex, age, lifestyle characteristics (cigarette smoking, alcohol consumption), type of joint distribution, and autoantibody profiles. Additionally, these factors were noted at all timepoints: morning stiffness (in minutes), grip strength, numbers of tender and swollen joints, global evaluation of the disease by both patient and physician graded on a visual analog scale, and the Disease Activity Score for the 28-joint indices (DAS28)[16]. Data were also recorded concerning the treatment with various disease-modifying antirheumatic drugs (DMARD), steroids, nonsteroidal antiinflammatory drugs (NSAID), and biologic agents. The clinical improvement was measured according to the ACR criteria for response to treatment[17]. The time-averaged measures of swollen joint count (SJC) were calculated.

Laboratory measurements. Laboratory measurements recorded included erythrocyte sedimentation rate (ESR; mm/hour), C-reactive protein (CRP; mg/l), hemoglobin (Hb; g/dl), IgM RF (latex test ≥ 1:80), and antinuclear antibodies (ANA; ≥ 1/160). In addition, using stored serum samples, IgA RF and anti-CCP antibodies were measured by ELISA (BL Diagnostika, Mainz, Germany, and Aesku Diagnostics, Wendelsheim, Germany) and were considered positive at a cutoff value > 20 and > 25 units/ml, respectively, as suggested by the manufacturer. The ELISA method used for the detection of anti-CCP antibodies was a second-generation anti-CCP test.

Radiographic measurement. The sets of the anteroposterior radiographs of the hands and the wrists at the 3 timepoints were reviewed by the same examiner, who was blind for patients' identity, and were scored using Larsen's criteria in chronological order[18]. The following joints were assessed: 4 proximal interphalangeal, 5 metacarpophalangeals, and the wrist bilaterally. Scoring of each joint was by 6 stages from 0 (normal) to 5. The wrist was considered as a unit and the score was multiplied by 5. Thus, the scores range from 0 to 140. The number of erosive joints from the total of 20 joints, which the Larsen scoring system assesses, was also evaluated.

Statistical methods. Statistical analysis was performed using SPSS Statistics, version 17.0. Because of their non-normal distributions, the outcome continuous variables were sorted into categorical variables: higher or lower than the median value for the final Larsen score and the annual radiographic progression seen on radiographs. Annual radiographic progression was calculated for all patients who, in addition to baseline radiograph, also had a last radiograph (at either 5 or 10 years). A 2-step analysis was applied to test the possible association of baseline measurements and time-averaged measures of SJC, ESR, and CRP with these radiographic measurements. The association of possible predictor factors of radiographic progression with the final radiographic measurements was initially tested in univariate analysis. For this purpose, all baseline variables, as well as the time-averaged measures of SJC, ESR, and CRP, were related to the out-

Table 1. Baseline characteristics of 407 patients with RA in groups according to the availability of their radiographs. For all variables, the number of evaluated patients is given. Group 1: patients with radiographs available only at baseline; Group 2: patients with radiographs available at baseline and at 5 years but not at 10 years; Group 3: patients with radiographs available at baseline, 5 and 10 years. No significant differences among the baseline characteristics of the patients of the 3 groups were found ($p > 0.05$).

Characteristics	Group 1 (186 Patients)	Group 2 (77 Patients)	Group 3 (144 Patients)
Sex, male, n (%)	46 (24.7 (186)	20 (26.0) (77)	34 (23.6) (144)
Female, n (%)	140 (75.3) (186)	57 (74.0) (77)	110 (76.4) (144)
Disease duration, mo, mean (SD)	21.1 (20.6) (186)	18.9 (20.5) (77)	20.0 (20.2) (144)
Age at disease onset, yrs (range 18–79), mean (SD)	53.0 (12.5) (186)	52.8 (13.6) (77)	51.4 (12.9) (144)
Age at baseline, yrs (range 18–79), mean (SD)	54.7 (14.2) (186)	54.2 (13.4) (77)	52.9 (12.7) (144)
DAS28, mean (SD)	5.78 (1.09) (186)	5.93 (1.11) (77)	5.84 (1.16) (144)
ESR, mean (SD)	48.3 (24.2) (186)	49.3 (26.9) (77)	51.1 (28.4) (144)
CRP, mean (SD)	26.9 (28.1) (186)	26.7 (26.7) (77)	25.9 (27.4) (144)
Anti-CCP positivity, n (%)	78 (53.8) (145)	35 (52.2) (67)	76 (55.9) (136)
IgA RF positivity, n (%)	63 (44.7) (141)	27 (41.5) (65)	57 (43.5) (131)
IgM RF positivity, n (%)	96 (51.6) (186)	38 (49.4) (77)	72 (50.0) (144)
Extraarticular manifestations, n (%)	93 (50.0) (186)	40 (51.9) (77)	70 (48.6) (144)
Rheumatoid nodules, n (%)	13 (7.0) (186)	5 (6.5) (77)	10 (6.9) (144)
Larsen score, mean (SD)	15.7 (11.3) (186)	15.6 (11.7) (77)	15.3 (11.5) (144)

DAS28: 28-joint count Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CCP: cyclic citrullinated peptide; RF: rheumatoid factor.

come radiographic variables using the chi-squared test. For this purpose, the continuous variables were transformed into categorical variables with the median value used as the cutoff. Variables presenting a statistically significant association with Larsen score at 10-year followup or with annual progression rate were included in 2 separate multivariate logistic regression models as independent variables. In these models, they were inserted again as categorical variables.

Area under the curve methods based on the trapezoid rule were applied to determine the time-averaged measures of SJC, ESR, and CRP collected at all visits over the observational period[19]. A systematic time interval of 3 months between 2 visits was followed. Changes over time were analyzed with the Friedman test. For this specific test, in case of missing clinical and laboratory data at years 5 and 10, data were extrapolated based on surrounding values of the variable of the same year. Thus, there were no missing data. Comparisons between groups were made with the chi-square test for categorical variables and Mann-Whitney U test and Kruskal-Wallis test for the continuous variables. Correlation analysis between continuous measurements was performed using Spearman's rank order correlation test. All tests were 2-sided and the significance level was set at 0.05.

RESULTS

Demographic, clinical, and immunological characteristics of patients. From the 717 patients with RA, 144 were selected for inclusion in our study because they fulfilled the study criteria; their baseline characteristics are shown in Table 1. One hundred ten patients (76.4%) were women. The mean age at baseline was 52.9 ± 12.7 years and the mean disease duration was 20 ± 20.2 months. IgM RF, IgA RF, and anti-CCP antibodies were positive for 50%, 43.5%, and 55.9% of patients, respectively. Of note, 24% of the patients with RA were both IgM and IgA RF-positive, while 34% were both IgM RF-positive and anti-CCP-positive. Further, 10% of the patients with RA were IgM RF-positive/anti-CCP-negative, and 18% were anti-CCP-positive/IgM RF-negative. Regarding smoking, 26 patients (18.1%) were current smokers, 9 (6.3%) were ex-smokers, and 109 (75.7%) had never smoked.

The treatment strategies for the patients with RA after initial presentation are shown in Table 2. For most patients, traditional therapy with DMARD was administered. Biologic agents were not prescribed in our patients, because they have been available for only a few years. At the fifth year, 72 patients (50%) were receiving the same DMARD (independent of dosage changes), while at the end of the observational period only 46 patients (31.9%) had not substantially modified their RA treatment. During the observational period, 73.5% of the patients received at least 2 different DMARD.

Table 2. Drugs prescribed to 144 patients with RA after initial presentation.

DMARD/Biologics	N (%)
Methotrexate	66 (45.8)
Cyclosporine A	27 (18.8)
D-penicillamine	13 (9)
Hydroxychloroquine	11 (7.6)
Leflunomide	3 (2.1)
Gold intramuscular	3 (2.1)
DMARD combination therapy	19 (13.2)
Steroids	105 (72.9)

DMARD: disease-modifying antirheumatic drug.

Clinical outcome. A statistically significant improvement ($p < 0.0001$) in clinical measurements, DAS28 score, and levels of acute-phase reactants was observed over time (Table 3). Additionally, 103 (71.5%), 41 (28.5%), and 11 (7.6%) patients satisfied the ACR 20%, ACR 50%, and ACR 70% response criteria at 5 years, respectively. At 10 years, the respective percentages of the patients were 72.2%, 45.8%, and 16.7%. Thirty-two (22.2%) and 41 (28.5%) patients were in remission (DAS28 < 2.6) at the fifth and tenth year, respectively.

Radiographic outcome. The Larsen score was increased from 15.3 ± 11.5 at baseline to 25.9 ± 13.7 and 35 ± 17.3 at 5 and at 10 years, respectively. The median progression in Larsen score during the first 5 years of the observational period was 10, and from year 5 to 10 it was 7. When the patients were stratified into 2 groups according to the presence of radiographic progression of ≥ 10 Larsen units during years 0–5 and 5–10, respectively, we obtained the following results: during the first 5 years, 51.4% of the patients had a progressive disease, while during the following 5 years the percentage of patients with radiographic progression was 34%. The average annual progression rate was 2.13 ± 1.28 points/year between baseline and 5 years, and 1.81 ± 1.34 points/year between 5 and 10 years (statistically significant difference, $p = 0.001$). The number of erosive joints was increased from 1.6 ± 2.3 at baseline to 3.3 ± 2.9 at 5 years and 4.8 ± 3.9 at 10 years (Table 3). At baseline, 36 patients (25%) did not show any erosions compared with 26 patients (18.1%) at 5 years. At the fifth year, 118 patients (81.9%) had at least 1 eroded joint, while 41 patients (28.5%) had at least 5 eroded joints. At 10 years, 18 (12.5%) patients had no erosions, even though other abnormalities were seen in their radiographs, such as joint space narrowing, periarticular osteopenia, or subluxations. Thus, 126 patients (87.5%) had at least 1 eroded joint at 10 years, while 63 (43.8%) presented with at least 5 eroded joints.

Relation between time-averaged disease activity markers and final radiographic measurements. Although none of the clinical variables or the markers of inflammation at baseline was predictive of the radiological outcome, the time-averaged values of SJC ($r = 0.35$, $p < 0.0001$), ESR ($r = 0.18$, $p = 0.034$), and CRP ($r = 0.27$, $p = 0.001$) over the 10-year period were correlated with the final Larsen score. These variables were also correlated with the final number of erosive joints (data not shown).

Predictive factors of radiographic outcome. Univariate analysis was performed to determine predictive factors of radiologic damage at 10 years and the accelerated annual radiological progression rate. Baseline variables and time-averaged measurements presenting a statistically significant

Table 3. Clinical, laboratory, and radiographic changes over time in 144 patients with RA. Values represent mean (± SD). All variables presented a statistically significant change over time ($p < 0.0001$) except for hemoglobin ($p = 0.144$).

Measurements	Baseline	5 Years	10 Years
Morning stiffness, min	81.32 (90.211)	14.65 (42.936)	13.96 (32.338)
TJC	14.53 (10.282)	3.38 (4.935)	2.83 (4.336)
TJC (28)	10.65 (6.687)	2.71 (3.916)	2.37 (3.641)
SJC	7.84 (6.978)	1.03 (2.458)	0.87 (2.102)
SJC (28)	6.93 (5.497)	0.88 (2.278)	0.73 (1.93)
DAS28	5.84 (1.16)	3.48 (1.3)	3.3 (1.21)
ESR	51.05 (28.388)	32.73 (24.021)	30.74 (20.352)
CRP	25.92 (27.399)	9.24 (13.898)	7.54 (13.509)
Hemoglobin	12.568 (1.528)	12.757 (1.451)	12.822 (1.608)
Larsen score	15.29 (11.476)	25.93 (13.716)	34.99 (17.316)
No. erosive joints	1.56 (2.252)	3.33 (2.928)	4.83 (3.919)

TJC: total joint count; SJC: swollen joint count; DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

association with these radiographic outcome measurements in univariate analysis are shown in Table 4. These measurements were all associated with both final Larsen score at 10 years and accelerated annual radiological progression rate: baseline Larsen score, baseline number of erosive joints, the presence of anti-CCP antibodies, IgM RF and IgA RF, disease duration at baseline, and time-averaged measures of ESR, CRP and SJC. Rheumatoid nodules showed a borderline correlation with final Larsen score.

In the logistic regression analysis, the baseline Larsen score and the presence of anti-CCP antibodies presented a significant and independent association with Larsen score at 10 years (Table 5). Time-averaged CRP also showed a borderline significant and independent association with Larsen score at 10 years. More specifically, the final Larsen score was predicted independently by baseline Larsen score (OR 18.060, 95% CI 6.576 to 49.597), the presence of anti-CCP antibodies (OR 3.794, 95% CI 1.325 to 10.859), and the time-averaged CRP (OR 2.667, 95% CI 0.920 to 7.731). An annual radiological progression rate greater than the median was predicted by baseline Larsen score (OR 2.616, 95% CI 1.286 to 5.322), the time-averaged CRP (OR 1.996, 95% CI 0.994 to 4.007), and the time-averaged SJC (OR 2.251, 95% CI 1.189 to 4.259).

Clinical and radiological outcome in anti-CCP-positive and anti-CCP-negative patients. Because the presence of anti-CCP antibodies and of RF was found to predict radiological outcome (anti-CCP antibodies in an independent manner), it was of interest to compare the clinical and radiological outcome in the following subgroups of patients: anti-CCP-positive/IgM RF-negative patients (n = 26) vs anti-CCP-negative/IgM RF-positive patients (n = 14). Regarding the clinical outcome, the group of anti-CCP-positive/IgM RF-negative patients presented a higher number of swollen joints (28) ($p = 0.006$) and a higher DAS28 score ($p = 0.001$) at the tenth year than anti-CCP-negative/IgM RF-positive patients. However, the 2 groups did not differ statistically significantly in final Larsen score ($p = 0.173$), radiological progression ($p = 0.442$), or in the time-averaged measures of ESR ($p = 0.478$), CRP ($p = 0.097$), and SJC ($p = 0.571$). These results need to be interpreted with caution because of the small number of patients in each group.

Table 4. Predictive factors of radiographic outcome (univariate analysis).

	Larsen Score at 10 Years (144 Patients)		Annual Progression Rate (221 Patients)	
	p	OR (95% CI)	p	OR (95% CI)
Baseline Larsen score	< 0.0001	17.123 (7.484–39.178)	< 0.0001	2.907 (1.671–5.060)
Baseline no. of erosive joints	< 0.0001	16.242 (7.035–37.498)	0.008	2.180 (1.260–3.774)
Anti-CCP positivity	< 0.0001	4.6 (2.187–9.677)	< 0.0001	4.337 (2.382–7.896)
IgA RF positivity	0.017	2.509 (1.232–5.109)	0.007	2.297 (1.284–4.110)
IgM RF positivity	0.03	2.212 (1.133–4.317)	< 0.0001	2.759 (1.6–4.758)
Disease duration at baseline	0.001	3.559 (1.77–7.143)	0.026	1.896 (1.11–3.236)
Rheumatoid nodules	0.055	5.241 (1.072–25.618)	0.003	3.523 (1.554–7.987)
Time-averaged CRP	0.004	2.8 (1.421–5.515)	< 0.0001	3.713 (2.11–6.534)
Time-averaged ESR	0.066	1.97 (1.013–3.831)	0.034	1.846 (1.081–3.153)
Time-averaged SJC	0.066	1.97 (1.013–3.831)	0.007	2.549 (1.475–4.404)

Anti-CCP: anticyclic citrullinated peptide; RF: rheumatoid factor; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SJC: swollen joint count.

Table 5. Logistic regression analysis.

Independent Variables	First Model: Dependent Variable, Larsen Score at 10 Years			Second model: Dependent Variable, Annual Progression Rate		
	p	OR	95% CI	p	OR	95% CI
Larsen score at baseline	< 0.001	18.060	6.576–49.597	< 0.01	2.616	1.286–5.322
Anti-CCP	0.01	3.794	1.325–10.859	NS	1.511	0.754–3.030
IgM RF	NS	1.276	0.445–3.659	NS	1.885	0.976–3.639
Disease duration at baseline	NS	1.589	0.616–4.097	NS	1.122	0.594–2.118
Time-averaged CRP	0.07	2.667	0.920–7.731	0.06	1.996	0.994–4.007
Time-averaged ESR	NS	1.338	0.488–3.665	NS	1.009	0.513–1.986
Time-averaged SJC	NS	1.877	0.727–4.844	< 0.01	2.251	1.189–4.259

Anti-CCP: anticyclic citrullinated peptide; RF: rheumatoid factor; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; SJC: swollen joint count; NS: not significant.

DISCUSSION

New, effective treatments have become available in RA, aimed at suppressing the inflammatory process and retarding structural joint damage. Reliable prognostic factors are warranted to help the clinician predict a possible severe disease course and outcome in a patient with RA and to subsequently choose a more aggressive treatment.

In our study, the median Larsen score at baseline was 12, while in the study by Lindqvist and colleagues[9], in which Larsen score was assessed by evaluating radiographs of both hands and feet (range 0–200), it was 6. This can be explained by the shorter disease duration in patients in the latest study. In our study, the median Larsen score reached 22 after 5 years and 30 after 10 years. These values are lower than those reported by Lindqvist, in which the median Larsen score reached 41 after 5 years and 54 after 10 years[9]. Comparisons with other longitudinal studies are difficult, because they use Sharp score or its modifications. The proportion of patients with no erosions at baseline was 25%, higher than the 16.9% in the report by Courvoisier and colleagues[8] or the 4% in the study by Lindqvist and colleagues[9]. However, the proportion of patients with erosive disease at 5 years was 81.9%, similar to that in other reports[20]. These lower radiographic scores in our patients are in agreement with observations coming from epidemiological reports, that in Mediterranean European populations the RA course is milder, with less severe radiologic damage than in North European populations[21]. This may be because of genetic differences among ethnicities[22,23,24,25,26,27] or because of exposure to different environmental factors such as climate, diet, and so on[28,29]. Additionally, in our study, the average annual progression rate was higher during the first 5 years than during the following 5 years (p = 0.001). This is in agreement with the results of previous reports[9,30,31].

In our study, radiographic progression was defined as a change in the radiographic score greater than the median for the delta-Larsen score rather than the minimum clinically important difference (MCID). The mean MCID determined by the Outcome Measures in Rheumatology Clinical Trials study for the Scott-modified Larsen method, which is a minor variation of the original method, was equal to 2.3 points[32]. However, the median progression in Larsen score during the 10-year period in our cohort was 17. Subsequently, the majority of our patients presented a delta-Larsen score higher than the MCID. Thus, the median for the delta-Larsen score was selected as a threshold in order to stratify patients as progressors and nonprogressors for statistical analysis.

Analyzing our data we found that the stronger and simultaneously independent predictor factor of increased radiographic damage at 10 years was baseline Larsen score. Baseline number of erosive joints was also a predictor factor of poor radiological outcome in the univariate analysis, but it was not selected for inclusion in logistic regression analysis. In general, baseline Larsen score was predictive of the final Larsen score and of an accelerated annual progression rate. It is notable that early radiographic damage has been significantly associated with the likelihood of subsequent structural deterioration in many short-term studies[14,33,34,35] and in several longterm studies[8,9,11]. In a recent report, the baseline erosion score according to the van der Heijde-modified Sharp scoring system was determined as the best independent predictor of the 10-year radiographic score[8].

In our study, being positive for anti-CCP antibodies was strongly correlated with the final radiographic measurements. Logistic regression analysis determined anti-CCP antibodies as an independent predictive factor of increased Larsen score at 10 years. The presence of anti-CCP antibodies has been related to disease aggressiveness[36] and has been suggested as a strong and independent prognostic factor of radiologic damage by several studies[12,14,33,37,38,39,40,41,42]. To our knowledge, only 2 studies do not fully support this association[43,44]. Reasons for this discrepancy in one of them may be the use of the anti-CCP1 test (which is less sensitive than the newer anti-CCP2 and anti-CCP3 tests) or a different study design.

The presence of RF of either IgA or IgM isotype was correlated with poor radiological outcome in our cohort, but

IgM RF was not found to constitute an independent predictive factor in the logistic regression analysis. IgA RF was not selected for inclusion in the model. The predictive value of RF has been confirmed in many studies and it involves mainly these 2 RF isotypes[8,10,12,13,45,46,47,48,49,50,51,52]. However, Kaarela did not recognize RF as an independent prognostic factor[11], while Lindqvist and colleagues showed that RF independently of isotype did not predict radiological progression[39]. Studies comparing the predictive value of the 2 isotypes conclude that IgA is better than IgM RF[40,53,54]. We also noticed a small superiority of IgA RF.

Disease duration was strongly associated with the final radiographic measurements in the univariate analysis, but it was not identified as an independent predictive factor in the logistic regression analysis. Disease duration constitutes an important predictive factor of radiologic damage, and studies have shown that long-lasting untreated disease may become catastrophic, resulting in severe structural damage in joints and deformities[55,56].

In our study, demographic measurements such as age at disease onset, sex, and cigarette smoking were not correlated with the final radiographic measurements. There are conflicting results in the literature regarding the role of these factors in predicting the radiological outcome. Being female has been identified as an independent predictor of radiological progression in several studies[12,57], while being male has been suggested as a prognostic factor of remission[33]. These results have not been confirmed by others[58]. Old age at disease onset was correlated with radiological progression in the longterm study by Kaarela[11]; however, it was not correlated in other studies[8,12,59,60]. There are also conflicting results in the literature regarding the role of cigarette smoking in predicting the radiological outcome. Several investigators have suggested a time-dependent and dose-dependent association between radiologic damage and smoking[61,62,63,64,65]. In contrast, cigarette smoking was not correlated with radiologic damage in other studies[66,67,68].

None of the clinical measurements at baseline was found to be correlated with either the final radiographic measurements or the radiological progression. The predictive value of the clinical measurements remains unclear in the literature. For example, the number of swollen joints has been suggested as an independent predictive factor of radiological progression[11], but other studies have not confirmed that[8,37]. We also noticed that the mean number of swollen joints throughout the overall time period of observation was correlated with the final Larsen score. Time-averaged SJC was also an independent predictor factor of an increased annual radiological progression. These findings are in agreement with those of Machold and colleagues, who observed that, although none of the clinical variables at onset was predictive of radiological progression, cumulative clinical activity including time-averaged joint counts actually was predictive[37].

The presence of rheumatoid nodules at baseline was found to be correlated with the number of erosive joints (data not shown). Moreover, rheumatoid nodules were associated with the final Larsen score and radiological progression in univariate analysis. Among the extraarticular manifestations, rheumatoid nodules are considered to be predictive of the radiological progression in RA. Dixey and colleagues showed that nodules could predict erosions, with an OR similar to that of RF and the shared epitope[69], while Saraux and colleagues noticed that nodular patients presented an accelerated rate of radiological progression over nonnodular patients[70]. Although the relationship between erosive disease and rheumatoid nodules remains uncertain, it is suggested that RF is implicated in the pathogenesis of both in patients with RA[71]. Our results confirm the existence of such a relationship between nodules and erosive disease.

The baseline levels of acute-phase reactants were not associated with the radiographic outcome measurements in our study. Although ESR has been suggested as a predictive factor of radiographic deterioration in both short-term[34,35,69,72] and longterm[8,10,11,12] reports, our results were not in agreement. An explanation for this discrepancy may be that a significant proportion of our patients were already under therapy with DMARD at the time of initial presentation, which could have led to a reduction of ESR levels. These patients first visited our department to get a second opinion after already being under treatment with DMARD for < 1 year. Thus, the ESR levels measured at the initial presentation in our department and used as baseline levels do not reflect their initial inflammation status. This constitutes a limitation in our study. However, even after exclusion of these patients, we obtained similar results. CRP levels were also not found to be prognostic of the final Larsen score or the radiological progression. The predictive value of CRP levels has been suggested by several studies[14,34,73,74], but it has not been confirmed by others[8,11,75]. In a recent study, CRP levels were significantly associated with radiographic progression in the univariate analysis, but this association was not maintained in the logistic regression model[12]. However, in our cohort, the mean concentration of CRP over the 10-year period was correlated statistically significantly with the final Larsen score, as in reports by others[37,74,76,77].

One limitation to our report is that our analyses were applied only to hand and wrist radiographs and that radiographs of other joints were not investigated. The fact that our study lacks genetic data is also a limitation. However, HLA-DRB1 genotyping is time-consuming and costly and is not a routinely assessed examination in clinical practice. Additionally, the fact that our study was an open-observational design may have influenced our results. Patients with RA who did not have an adequate number of radiographs were excluded from the study, and therefore it is possible that we have overlooked patients with less or more severe radiological course. While there is no reason to suspect that

this happened, it cannot be excluded. However, it is notable that our 10-year cohort of 144 patients is considered representative of the total of 407 patients with RA with disease duration < 5 years at inclusion.

Despite clinical improvement, the radiologic damage in RA continues over time because of the underlying inflammatory process. Baseline radiographic damage, anti-CCP antibodies, and time-averaged CRP constitute the main predictive factors of poor radiologic outcome in the long term. Thus, new therapeutic strategies are needed to achieve clinical remission and inhibit progression of structural damage.

REFERENCES

1. Scott DL, Symmons DP, Coulton BL, Popert AJ. Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet 1987;1:1108-11.
2. Pincus T, Callahan LF. Taking mortality in rheumatoid arthritis seriously — predictive markers, socioeconomic status and comorbidity. J Rheumatol 1986;13:841-5.
3. Gabriel SE, Crowson CS, Kremers HM, Doran MF, Turesson C, O'Fallon WM, et al. Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years. Arthritis Rheum 2003;48:54-8.
4. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R, et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006;54:26-37.
5. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet 2008;372:375-82.
6. van der Heijde D, Klareskog L, Landewé R, Bruyn GA, Cantagrel A, Durez P, et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum 2007;56:3928-39.
7. Scott DL, Coulton BL, Popert AJ. Long term progression of joint damage in rheumatoid arthritis. Ann Rheum Dis 1986;45:373-8.
8. Courvoisier N, Dougados M, Cantagrel A, Goupille P, Meyer O, Sibilia J, et al. Prognostic factors of 10-year radiographic outcome in early rheumatoid arthritis: a prospective study. Arthritis Res Ther 2008;10:R106.
9. Lindqvist E, Jonsson K, Eberhardt K. Course of radiographic damage over 10 years in a cohort with early rheumatoid arthritis. Ann Rheum Dis 2003;62:611-6.
10. Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. Arthritis Rheum 1998;41:1571-82.
11. Kaarela K. Prognostic factors and diagnostic criteria in early rheumatoid arthritis. Scand J Rheumatol 1985;57:1-54.
12. Syversen SW, Gaarder PI, Goll GL, Ødegård S, Haavardsholm EA, Mowinckel P, et al. High anti-CCP levels and an algorithm of four variables predict radiographic progression in patients with rheumatoid arthritis: results from a 10-year longitudinal study. Ann Rheum Dis 2008;67:212-7.
13. Scott DL. Prognostic factors in early rheumatoid arthritis. Rheumatology 2000;39 Suppl 1:24-9.
14. Jansen LM, van der Horst-Bruinsma IE, van Schaardenburg D, Bezemer PD, Dijkmans BA. Predictors of radiographic joint damage in patients with early rheumatoid arthritis. Ann Rheum Dis 2001;60:924-7.
15. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
16. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44-8.
17. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727-35.
18. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by reference films. Acta Radiol Diagn 1977;18:481-91.
19. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. BMJ 1990;300:230-5.
20. Hulsmans HM, Jacobs JW, van der Heijde DM, van Albada-Kuipers GA, Schenk Y, Bijlsma JW. The course of radiologic damage during the first six years of rheumatoid arthritis. Arthritis Rheum 2000;43:1927-40.
21. Drosos AA, Lanchbury JS, Panayi GS, Moutsopoulos HM. Rheumatoid arthritis in Greek and British patients. A comparative clinical, radiologic, and serological study. Arthritis Rheum 1992;35:745-8.
22. Boki KA, Panayi GS, Vaughan RW, Drosos AA, Moutsopoulos HM, Lanchbury JS. HLA class II sequence polymorphisms and susceptibility to rheumatoid arthritis in Greeks. The HLA-DR beta shared epitope hypothesis accounts for the disease in only a minority of Greek patients. Arthritis Rheum 1992;35:749-55.
23. Boki KA, Drosos AA, Tzioufas AG, Lanchbury JS, Panayi GS, Moutsopoulos HM. Examination of HLA-DR4 as a severity marker for rheumatoid arthritis in Greek patients. Ann Rheum Dis 1993;52:517-9.
24. Balsa A, Minaur NJ, Pascual-Salcedo D, McCabe C, Balas A, Fiddament B, et al. Class II MHC antigens in early rheumatoid arthritis in Bath (UK) and Madrid (Spain). Rheumatology 2000;39:844-9.
25. Benazet JF, Reviron D, Mercier P, Roux H, Roudier J. HLA-DRB1 allelles associated with rheumatoid arthritis in southern France. Absence of extraarticular disease despite expression of the shared epitope. J Rheumatol 1995;22:607-10.
26. Ioannidis JP, Tarassi K, Papadopoulos IA, Voulgari PV, Boki KA, Papasteriades CA, et al. Shared epitopes and rheumatoid arthritis: disease associations in Greece and meta-analysis of Mediterranean European populations. Semin Arthritis Rheum 2002;31:361-70.
27. Gorman JD, Lum RF, Chen JJ, Suarez-Almazor ME, Thomson G, Criswell LA. Impact of shared epitope genotype and ethnicity on erosive disease: a meta-analysis of 3,240 rheumatoid arthritis patients. Arthritis Rheum 2004;50:400-12.
28. Goldberg RJ, Katz J. A meta-analysis of the analgesic effects of omega-3 polyunsaturated fatty acid supplementation for inflammatory joint pain. Pain 2007;129:210-23.
29. Sköldstam L, Hagfors L, Johansson G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. Ann Rheum Dis 2003;62:208-14.
30. Sharp JT, Wolfe F, Mitchell DM, Bloc DA. The progression of erosion and joint space narrowing scores in rheumatoid arthritis during the first twenty-five years of disease. Arthritis Rheum 1991;34:660-8.
31. van der Heijde DM, van Leeuwen MA, van Riel PL, Koster AM, van 't Hof MA, van Rijswijk MH, et al. Biannual radiographic

assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum 1992;35:26-34.
32. Bruynesteyn K, van der Heijde D, Boers M, Saudan A, Peloso P, Paulus H, et al. Determination of the minimal clinically important difference in rheumatoid arthritis joint damage of the Sharp/van der Heijde and Larsen/Scott scoring methods by clinical experts and comparison with the smallest detectable difference. Arthritis Rheum 2002;46:913-20.
33. Forslind K, Hafström I, Ahlmén M, Svensson B for the BARFOT Study Group. Sex: a major predictor of remission in early rheumatoid arthritis? Ann Rheum Dis 2007;66:46-52.
34. Combe B, Dougados M, Goupille P, Cantagrel A, Eliaou JF, Sibilia J, et al. Prognostic factors for radiographic damage in early rheumatoid arthritis; a multiparameter prospective study. Arthritis Rheum 2001;44:1736-43.
35. Guillemin F, Gérard N, van Leeuwen M, Smedstad LM, Kvien TK, van den Heuvel W; EURIDISS Group. Prognostic factors for joint destruction in rheumatoid arthritis: a prospective longitudinal study of 318 patients. J Rheumatol 2003;30:2585-9.
36. del Val del Amo N, Ibanez Bosch R, Fito Manteca C, Gutierrez Polo R, Loza Cortina E. Anti-cyclic citrullinated peptide antibody in rheumatoid arthritis: relation with disease aggressiveness. Clin Exp Rheumatol 2006;24:281-6.
37. Machold KP, Stamm TA, Nell VP, Pflugbeil S, Aletaha D, Steiner G, et al. Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. Rheumatology 2007;46:342-9.
38. Rojas-Villarraga A, Diaz FJ, Calvo-Páramo E, Salazar JC, Iglesias-Gamarra A, Mantilla RD, et al. Familial disease, the HLA-DRB1 shared epitope and anti-CCP antibodies influence time at appearance of substantial joint damage in rheumatoid arthritis. J Autoimmun 2009;32:64-9.
39. Lindqvist E, Eberhardt K, Bendtzen K, Heinegard D, Saxne T. Prognostic laboratory markers of joint damage in rheumatoid arthritis. Ann Rheum Dis 2005;64:196-201.
40. Berglin E, Johansson T, Sundin U, Jidell E, Wadell G, Hallmans G, et al. Radiological outcome in rheumatoid arthritis is predicted by presence of antibodies against cyclic citrullinated peptide before and at disease onset, and by IgA RF at disease onset. Ann Rheum Dis 2006;65:453-8.
41. Meyer O, Nicaise-Roland P, Santos MD, Labarre C, Dougados M, Goupille P, et al. Serial determination of cyclic citrullinated peptide autoantibodies predicted five year radiological outcomes in a prospective cohort of patients with early rheumatoid arthritis. Arthritis Res Ther 2006;8:R40.
42. Nielen MM, van der Horst AR, van Schaardenburg D, van der Horst-Bruinsma IE, van de Stadt RJ, Aarden L, et al. Antibodies to citrullinated human fibrinogen (ACF) have diagnostic and prognostic value in early arthritis. Ann Rheum Dis 2005;64:1199-204.
43. Kroot EJ, de Jong BA, van Leeuwen MA, Swinkels H, van den Hoogen FH, van 't Hof M, et al. The prognostic value of anti-cyclic citrullinated peptide antibody in patients with recent-onset rheumatoid arthritis. Arthritis Rheum 2000;43:1831-5.
44. Quinn MA, Gough AK, Green MJ, Devlin J, Hensor EM, Greenstein A, et al. Anti-CCP antibodies measured at disease onset help identify seronegative rheumatoid arthritis and predict radiological and functional outcome. Rheumatology 2006;45:478-80.
45. Morel J, Combe B. How to predict prognosis in early rheumatoid arthritis. Best Pract Res Clin Rheumatol 2005;19:137-46.
46. Papadopoulos IA, Katsimbri P, Katsaraki A, Temekonidis T, Georgiadis A, Drosos AA. Clinical course and outcome of early rheumatoid arthritis. Rheumatol Int 2001;20:205-10.
47. Isomaki H. Long-term outcome of rheumatoid arthritis. Scand J Rheumatol 1992;95 Suppl:3-8.
48. Plant MJ, Jones PW, Saklatvala J, Ollier WE, Dawes PT. Patterns of radiological progression in early rheumatoid arthritis: results of an 8 year prospective study. J Rheumatol 1998;25:417-26.
49. Uhlig T, Smedstad LM, Vaglum P, Moum T, Gerard N, Kvien TK. The course of rheumatoid arthritis and predictors of psychological, physical and radiographic outcome after 5 years of follow-up. Rheumatology 2000;39:732-41.
50. Brennan P, Harrison B, Barrett E, Chakravarty K, Scott D, Silman A, et al. A simple algorithm to predict the development of radiological erosions in patients with early rheumatoid arthritis: prospective cohort study. BMJ 1996;313:471.
51. Mattey DL, Hassell AB, Dawes PT, Cheung NT, Poulton KV, Thomson W, et al. Independent association of rheumatoid factor and the HLA-DRB1 shared epitope with radiographic outcome in rheumatoid arthritis. Arthritis Rheum 2001;44:1529-33.
52. van der Heide A, Remme CA, Hofman DM, Jacobs JW, Bijlsma JW. Prediction of progression of radiologic damage in newly diagnosed rheumatoid arthritis. Arthritis Rheum 1995;38:1466-74.
53. Manfredsdottir VF, Vikingsdottir T, Jonsson T, Geirsson AJ, Kjartansson O, Heimisdottir M, et al. The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis. Rheumatology 2006;45:734-40.
54. Houssien DA, Jonsson T, Davies E, Scott DL. Rheumatoid factor isotypes, disease activity and the outcome of rheumatoid arthritis: comparative effects of different antigens. Scand J Rheumatol 1998;27:46-53.
55. Voulgari PV, Drosos AA. Catastrophic rheumatoid arthritis. J Rheumatol 2008;35:2062-3.
56. Abu-Shakra M, Toker R, Flusser D, Flusser G, Friger M, Sukenik S, et al. Clinical and radiographic outcomes of rheumatoid arthritis patients not treated with disease-modifying drugs. Arthritis Rheum 1998;41:1190-5.
57. Sanmarti R, Gómez-Centeno A, Ercilla G, Larrosa M, Viñas O, Vazquez I, et al. Prognostic factors of radiographic progression in early rheumatoid arthritis: a two year prospective study after a structured therapeutic strategy using DMARDs and very low doses of glucocorticoids. Clin Rheumatol 2007;26:1111-8.
58. Voulgari PV, Papadopoulos IA, Alamanos Y, Katsaraki A, Drosos AA. Early rheumatoid arthritis: does gender influence disease expression? Clin Exp Rheumatol 2004;22:165-70.
59. Peltomaa R, Leirisalo-Repo M, Helve T, Paimela L. Effect of age on 3 year outcome in early rheumatoid arthritis. J Rheumatol 2000;27:638-43.
60. Papadopoulos IA, Katsimbri P, Alamanos Y, Voulgari PV, Drosos AA. Early rheumatoid arthritis patients: relationship with age. Rheumatol Int 2003;23:70-4.
61. Saag KG, Cerhan JR, Kolluri S, Ohashi K, Hunninghake GW, Schwartz DA. Cigarette smoking and rheumatoid arthritis severity. Ann Rheum Dis 1997;56:463-9.
62. Mattey DL, Dawes PT, Clarke S, Fisher J, Brownfield A, Thomson W, et al. Relationship among the HLA-DRB1 shared epitope, smoking, and rheumatoid factor production in rheumatoid arthritis. Arthritis Rheum 2002;47:403-7.
63. Wolfe F. The effect of smoking on clinical, laboratory, and radiographic status in rheumatoid arthritis. J Rheumatol 2000;27:630-7.
64. Masdottir B, Jónsson T, Manfredsdóttir V, Víkingsson A, Brekkan Á, Valdimarsson H. Smoking, rheumatoid factor isotypes and severity of rheumatoid arthritis. Rheumatology 2000;39:1202-5.
65. Papadopoulos NG, Alamanos Y, Voulgari PV, Epagelis EK, Tsifetaki N, Drosos AA. Does cigarette smoking influence disease

expression, activity and severity in early rheumatoid arthritis patients? Clin Exp Rheumatol 2005;23:861-6.
66. Finckh A, Dehler S, Costenbader KH, Gabay C on behalf of the Swiss Clinical Quality Management project for RA (SCQM). Cigarette smoking and radiographic progression in rheumatoid arthritis. Ann Rheum Dis 2007;66:1066-71.
67. Westhoff G, Rau R, Zink A. Rheumatoid arthritis patients who smoke have a higher need for DMARDs and feel worse, but they do not have more joint damage than non-smokers of the same serological group. Rheumatology 2008;47:849-54.
68. Mikuls TR, Hughes LB, Westfall AO, Holers VM, Parrish L, van der Heijde D, et al. Cigarette smoking, disease severity and autoantibody expression in African Americans with recent-onset rheumatoid arthritis. Ann Rheum Dis 2008;67:1529-34.
69. Dixey J, Solymossy C, Young A; Early RA Study. Is it possible to predict radiologic damage in early rheumatoid arthritis (RA)? A report on the occurrence, progression, and prognostic factors of radiological erosions over the first 3 years in 866 patients from the Early RA Study (ERAS). J Rheumatol 2004;31 Suppl 69:48-54.
70. Saraux A, Allain J, Guedes C, Valls I, Baron D, Youinou P, et al. Clinical, laboratory, and radiographic features of rheumatoid arthritis with and without nodules. Rev Rhum Engl Ed 1997;64:11-7.
71. De Rycke L, Peene I, Hoffman IE, Kruithof E, Union A, Meheus L, et al. Rheumatoid factor and anticitrullinated protein antibodies in rheumatoid arthritis: diagnostic value, associations with radiological progression rate, and extra-articular manifestations. Ann Rheum Dis 2004;63:1587-93.
72. Valenzuela-Castano A, Garcia-Lopez A, Pérez-vilches D, Rodriguez-Pérez R, Gonzalez-Escribano MF, Nunez-Roldan A. The predictive value of the HLA shared epitope for severity of radiological joint damage in patients with rheumatoid arthritis. A 10-year observational prospective study. J Rheumatol 2000;27:571-4.
73. Amos RS, Constable TJ, Crockson RA, Crockson AP, McConkey B. Rheumatoid arthritis: relation of serum C-reactive protein and erythrocyte sedimentation rates to radiographic changes. Br Med J 1977;22:195-7.
74. Plant MJ, Williams AL, O'Sullivan MM, Lewis PA, Coles EC, Jessop JD. Relationship between time-integrated C-reactive protein levels and radiologic progression in patients with rheumatoid arthritis. Arthritis Rheum 2000;43:1473-7.
75. Green M, Marzo-Ortega H, McGonagle D, Wakefield R, Proudman S, Conaghan P, et al. Persistence of mild, early inflammatory arthritis: the importance of disease duration, rheumatoid factor, and the shared epitope. Arthritis Rheum 1999;42:2184-8.
76. Aletaha D, Nell VP, Stamm T, Uffmann M, Pflugbeil S, Machold K, et al. Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796-806.
77. Roux-Lombard P, Eberhardt K, Saxne T, Dayer JM, Wollheim FA. Cytokines, metalloproteinases, their inhibitors and cartilage oligomeric matrix protein: relationship to radiological progression and inflammation in early rheumatoid arthritis. A prospective 5-year study. Rheumatology 2001;40:544-51.