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ORIGINAL ARTICLE

First-Year Radiographic Progression as a Predictor of Further Progression in Early Arthritis: Results of a Large National French Cohort

GABRIEL TOBÓN,[1] ALAIN SARAUX,[2] CEDRIC LUKAS,[3] FREDERIQUE GANDJBAKHCH,[4] J. E. GOTTENBERG,[5] XAVIER MARIETTE,[6] BERNARD COMBE,[3] AND VALERIE DEVAUCHELLE-PENSEC[2]

Objective. **A major goal in the treatment of recent arthritis is the prevention of joint destruction. The value of radiographic progression in the first year for predicting further radiographic progression has not been evaluated comparatively with conventional predictive factors.**

Methods. **Patients with arthritis of <6 months' duration were included in the prospective French ESPOIR cohort. Radiographs were obtained and modified Sharp scores were determined by a blinded reader. The rate of progression was determined over the first year, then over the second and third years. Rapid progression was defined as a >5-point annual increase in the total Sharp score.**

Results. **In total, 500 patients had complete data available after 3 years and were included. The total Sharp score indicated rapid progression in 123 patients (25%) in year 1 and 92 patients (18%) in years 2/3. By logistic regression, the variables independently associated with rapid progression in years 2/3 were year 1 rapid progression of the erosion and total Sharp scores, baseline erosion Sharp score, the serologic American College of Rheumatology/European League Against Rheumatism criterion, and interleukin-6 level. When these variables were combined, year 1 rapid progression made the largest contribution to predicting years 2/3 rapid progression.**

Conclusion. **First-year radiologic progression is the best independent predictor of further rapid progression in early arthritis.**

INTRODUCTION

In early arthritis, the major goal is to identify which patients will develop joint damage (1). Chronic inflammation of the synovial membrane induces bone and cartilage destruction with erosions and joint space narrowing, which are partly related and worsen gradually over time (2,3), predominantly during the first few years of the disease. In rheumatoid arthritis (RA), the rate of progression is highest during the first 2 years and most of the damage occurs within the first 5 years (4,5). The goal of pharmacotherapy is to decrease both disease activity and joint progression. Randomized controlled trials of all the new drugs used in RA, including biologic agents, have been conducted to evaluate the impact on radiographic progression. Although most of these drugs were proven to be effective in diminishing joint damage, persistent progression occurred in some patients despite treatment.

To assess the relevance of a new treatment option in early arthritis, rheumatologists need variables that predict further radiographic progression. All available studies on predicting further radiographic progression have focused on either the erosion status at baseline or damage severity scores at a given point in time (6–8). The potential predictive value of the rate of joint damage progression during

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[1]Gabriel Tobón, MD, PhD: Hospital Morvan, Brittany University, Brest, France; [2]Alain Saraux, MD, PhD, Valerie Devauchelle-Pensec, MD, PhD: Hospital Morvan, Cavale Blanche Hospital, Brittany University, Brest, France; [3]Cedric Lukas, MD, PhD, Bernard Combe, MD, PhD: Lapeyronie Hospital, Montpellier I University, Montpellier, France; [4]Frederique Gandjbakhch, MD: La Pitié Salpétriére Hospital, Paris, France; [5]J. E. Gottenberg, MD, PhD: Strasbourg University Hospital, Strasbourg, France; [6]Xavier Mariette, MD, PhD: Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, INSERM U1012, Le Kremlin Bicêtre, France.

Address correspondence to Valerie Devauchelle-Pensec, MD, PhD, Unit of Rheumatology, Hôpital de la Cavale Blanche, BP 824, F 29609 Brest Cedex, France. E-mail: valerie.devauchelle-pensec@chu-brest.fr.

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Significance & Innovations

- The rate of progression of erosion, narrowing, and total Sharp scores during the first year of arthritis independently predicted further erosion in the next 2 years.
- Progression during the first year is a strong predictor that should be taken into account when treating and monitoring patients with rheumatoid arthritis.

the first few months of the disease has not been investigated. One would expect that a fast rate of progression early in the disease would predict a greater degree of progression later on. However intuitive, this has never been investigated in early arthritis or in RA. During treatment, radiographic progression would be expected to decrease gradually over time, with differences across treatment regimens. The ability to predict rapid radiographic progression would be of considerable help in optimizing the treatment and followup of patients with recent arthritis.

The ESPOIR study is a large, national, multicenter, longitudinal, and prospective cohort of patients with early arthritis <6 months in duration (9) in whom radiographs were obtained annually for several years. The patients were included between December 2002 and March 2005. At inclusion, the patients were disease-modifying antirheumatic drug (DMARD) and steroids naive, except if receiving these drugs for <2 weeks. During followup, the treatments were not randomized but were consistent with international recommendations and standard clinical practice. Thus, within the first 3 years of followup, 59% of the patients received conventional DMARDs, consisting of methotrexate in 68% of patients (n = 313) (10). Only a few of these patients received anti–tumor necrosis factor (anti-TNF) therapy, which was rarely prescribed in 2002–2005 as first-line therapy in France because of national recommendations and was frequently prescribed for independent reasons other than disease activity. Several classic parameters associated with radiographic progression had been recorded in the cohort, such as disease activity, all parameters of the American College of Rheumatology (ACR) 1987 criteria (11) or the new ACR/European League Against Rheumatism (EULAR) criteria (12), radiographic damage at baseline, and several levels of cytokines involved in the inflammatory process.

In the present study, our objective was to identify the parameters predicting further joint damage progression in patients with early arthritis. More specifically, we investigated whether radiographic progression during the first year independently predicted further progression during the next 2 years.

PATIENTS AND METHODS

The present study was approved by the Institutional Review Board of the Montpellier University Hospital. All patients gave written informed consent to the prospective followup study before inclusion.

Study population. The French Society for Rheumatology initiated a large, national, multicenter, longitudinal, prospective registry known as the ESPOIR cohort of early arthritis and RA (9). Patients were included if they had a clinical diagnosis of definitive or probable RA or of undifferentiated arthritis with a potential for progressing to RA. The inclusion criteria were age between 18 and 70 years, swelling in at least 2 joints for at least 6 weeks, a symptom duration of <6 months, no history of DMARD therapy, and no history of glucocorticoid therapy. Patients were excluded if they had either other clearly defined inflammatory rheumatic or connective tissue diseases or early arthritis with no potential chance to become RA.

The patients were evaluated every 6 months for 2 years, then every year for at least 10 years. Posteroanterior radiographs of the hands and wrists and posteroanterior and oblique radiographs of the feet were to be obtained at inclusion and after 1, 2, and 3 years (13); 535 patients had all radiographs available after 3 years of followup. Among these patients, 35 received TNFα antagonists within the first year; none of these patients experienced rapid progression during the subsequent followup period. Given this strong effect of TNFα antagonist therapy on radiographic progression, we excluded these 35 patients. Therefore, 500 patients were included in the data analysis.

Study design. The baseline assessment included a standardized interview, a general physical examination, laboratory tests (standard blood and urine parameters; enzyme-linked immunosorbent assays [ELISAs] for IgM, IgG, and IgA rheumatoid factors [RFs]; tests for anti–cyclic citrullinated peptide [anti-CCP] and antinuclear antibodies; and HLA–DR typing), and radiographs of the chest, pelvis, hands, and feet in the posteroanterior view and of the feet in the oblique view. Each patient was asked to undergo an evaluation every 6 months by a rheumatologist during the first 2 years and every year thereafter.

ELISA tests. Serum interleukin-1β (IL-1β), IL-1 receptor antagonist (IL-1Ra), IL-2, IL-4, IL-6, IL-10, IL-17, IL-21, monocyte chemotactic protein 1 (MCP-1), TNFα, and interferon-γ (IFNγ) levels were measured using an ELISA test. Serum samples were collected from ESPOIR cohort patients and all samples were stored immediately at −80°C. The laboratory tests were centralized. Serum IL-21 was assessed using an ELISA (Ebioscience) with a detection threshold of 50 pg/ml. Serum concentrations of IL-1β, IL-1Ra, IL-2, IL-4, IL-6, IL-10, IL-17, MCP-1, TNFα, and IFNγ were assayed using a commercially available multiplex bead immunoassay based on the Luminex platform (Fluorokine MAP Multiplex Human Cytokine Panel, R&D Systems), as previously reported (14).

Radiographic evaluation. *Standardized reading.* For each patient, a set of plain radiographs (including posteroanterior radiographs of both hands and wrists and of

both feet) was obtained at the first visit, then 1, 2, and 3 years later in each center following a standardized procedure concerning the technical quality (including joint positioning and exposure). The radiographs were sent to the coordinating center and centrally evaluated.

Interreader correlation coefficients were evaluated for the status score after a training session. Sixty pairs of hand and foot radiographs were read both by GT and a senior reader (VD-P). Intrareader correlation coefficients were assessed after reading all radiographs from 1 center (79 films) performed at 1 year, scored twice with an interval of 1 month by GT.

All sets of radiographs were read by the same observer (GT), who had no information about the patients. The radiographic progression rates from baseline were determined using the modified Sharp/van der Heijde score. The smallest detectable change (SDC), an estimate of the measurement error of simultaneously read films, was computed to define the cutoff level for radiographic progression. Bland-Altman plots were computed using standard methodology (15,16) (see Supplementary Appendix A, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22078/abstract).

Each radiograph was read according to a standardized procedure that included determination of the number of erosions and measurement of joint space narrowing according to the modified Sharp score on the posteroanterior views of the hands and feet (17,18). A sequenced reading was performed (with information on the chronology of the films to improve sensitivity to change). The cumulative scores at the hands and feet were 280 for erosions and 168 for joint space narrowing.

Definition of the rate of progression. The rate of progression was defined as the difference in the modified Sharp scores (erosion score, joint space narrowing score, and total score) at the hands and feet between baseline and a given time point during followup. We computed the rate of progression during the first year (month 12 score minus baseline score) and during the next 2 years (month 36 score minus month 12 score). The definition of rapid progression is not consensual and is based on expert opinion, more frequently on the erosion score than the joint space narrowing score (16). We considered rapid progression as an annual rate of progression >2.5 points for the modified Sharp erosion or narrowing score or >5 points for the modified Sharp total score because the rate of progression >5 points represents 1 joint with severe destruction.

Statistical analysis. The intra- and interobserver correlation coefficients were computed to evaluate quantitative variables. Quantitative variables were described as the mean ± SD and qualitative variables as the number and percentage. The patient groups were compared using the chi-square test for qualitative variables and the Mann-Whitney U test for quantitative variables. P values less than 0.05 were considered statistically significant.

To determine which variables best separated patients with and without further rapid progression of the erosion, joint space narrowing, or total scores, we performed a univariate analysis to select the variables statistically associated ($P < 0.1$) with rapid progression (sex; Disease Activity Score in 28 joints [DAS28] ≥ 3.2; number of swollen joints; number of tender joints; morning stiffness ≥ 1 hour; arthritis in ≥ 3 joint areas; arthritis of the hand joints; symmetric arthritis; rheumatoid nodules; presence of RF; presence of anti-CCP; ≥ 4 ACR 1987 criteria; joint involvement as defined by the 2010 ACR/EULAR criteria; symptom duration [>6 weeks]; elevated erythrocyte sedimentation rate; elevated C-reactive protein level; ACR/EULAR score ≥ 6; Sharp erosion, narrowing, and total scores at baseline; and levels of the cytokines IL-1Ra, IL-6, IL-10, MCP-1, IL-4, IL-17, IFNγ, TNFα, IL-1β, and IL-2). We selected variables statistically associated with rapid progression; then, for each criterion, sensitivity was plotted against 1 − specificity to obtain the receiver operating characteristic (ROC) curve (19) for each criteria set by varying the cutoff (values lower than the cutoff were considered negative, while other values were considered positive), and the areas under the ROC curves were compared. The sensitivities and specificities were calculated at different cutoff values. The optimal cutoff for a variable was defined as the value nearest to the northwestern-most point of the ROC curve. When 2 similar cutoff values were found, the one with the best sensitivity was chosen. For each criteria set used at baseline, we computed the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) with their 95% confidence intervals to predict the rate of progression during years 2/3. We then included all tests associated with progression in the univariate analysis with $P < 0.1$ in a multiple logistic regression model with backward selection using the likelihood ratio test.

RESULTS

Population. The ESPOIR cohort comprised 813 patients at inclusion (13). Among these patients, after 3 years of followup, the full clinical biologic data and set of radiographs were available for 535 patients. The main reason for excluding patients from the analysis was missing radiographs at baseline (n = 82) and/or at year 1, 2, or 3 (n = 196). We did not find statistical differences between these patients and those who were excluded due to missing data (data not shown). The 35 patients who received TNFα antagonist therapy within the first year were excluded, leaving 500 patients for inclusion into the study, among whom 387 (77%) were women, 45% had RF, and 41% had anti-CCP (Table 1).

Assessment of radiographs. All radiographs were read by the same observer (GT) after a training session and concerning the status score. Intrareader correlation coefficients were 0.97 for the Sharp total score, 0.87 for the Sharp narrowing score, and 0.92 for the Sharp erosion score for GT. Interobserver correlations (GT and VD-P) were 0.93, 0.85, and 0.83 for the Sharp total, the Sharp narrowing, and the Sharp erosion scores, respectively. The calculated SDC for GT was 1, and this was considered the cut point to identify progressors.

Table 1. Baseline features of the patients at inclusion in the ESPOIR cohort (n = 500)*

	Value
Women, no./total (%)	387/500 (77)
Age, mean ± SD years	47 ± 12
Mean ± SD disease duration, days	90 ± 25
Presence of synovitis, no. (%)	405 (81)
Elevated ESR or CRP, no./total (%)	389/423 (92)
IgM-RF, no. (%)	222 (44.4)
Anti-CCP, no. (%)	199 (40)
RF and anti-CCP, no./total (%)	159/498 (32)
Met ACR criteria, no./total (%)	350/492 (71)
DAS28 ≥3.2, no./total (%)	451/489 (92)

* ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; RF = rheumatoid factor; anti-CCP = anti–cyclic citrullinated peptide; ACR = American College of Rheumatology; DAS28 = Disease Activity Score in 28 joints.

Correlation between erosion and joint space narrowing progression during the first year. During the first year, the rates of progression of the erosion and narrowing scores were weakly correlated with each other (r = 0.4). The correlation coefficients between the rate of progression of the erosion and narrowing scores and that of the total score were 0.61 and 0.81, respectively.

Radiographic progression during the first year. During the first year, 37 patients (7%) experienced no radiographic progression. In 340 (73%) of the remaining 463 patients, the total Sharp score increased by ≤5 points. The remaining 123 patients (25%) experienced rapid progression, with a total score increase >5 points. Only 10% of these 123 patients had a total score increase >15 points. In 445 patients (89%), the erosion score increased by <2.5 points during the first year. The remaining 55 patients (11%) had a rapid progression of the erosion score. The joint space narrowing score increased by >2.5 points during the first year in 100 patients (20%).

Radiographic progression in the second and third years. *Patients with progression in years 2/3.* Rapid progression in years 2/3 occurred for the total score in 92 patients (18%), the erosion score in 53 patients, and the narrowing score in 146 patients. The erosion, narrowing, and total scores at baseline were significantly higher in the patients who experienced rapid progression in years 2/3 than in the other patients.

Association with classification criteria for RA. All items of the unmodified 1987 ACR criteria set and 2010 ACR/EULAR criteria set (20) were evaluated, except for radiographic changes. Rapid progression in years 2/3 of the erosion, narrowing, and total scores was associated with serologic criteria (autoantibodies) alone or in combination, but not with the clinical criteria (e.g., morning stiffness) in the 1987 ACR or 2010 ACR/EULAR criteria sets (Table 2).

Association with radiologic data. The baseline number of erosions was significantly higher in the subgroup with rapid progression in years 2/3 than in the other patients. The mean ± SD erosion scores at baseline at the hands and feet were 3.5 ± 5.7 in the subgroup with rapid progression in years 2/3 and 1.0 ± 2.8 in the other patients ($P < 0.0001$). Similarly, the total and narrowing scores at the hands and/or feet were significantly higher at baseline in the subgroup with progression in years 2/3. Rapid year 1 progression was significantly associated with rapid progression in years 2/3.

Association with immunologic data. We investigated the associations between rapid progression in years 2/3 and several cytokine levels previously reported to be associated with radiographic damage (Table 3). Baseline cytokine levels were not associated with rapid progression, except for IL-6, which was significantly associated with rapid progression in years 2/3 of the erosion, narrowing, and total scores ($P < 0.0001$).

Predicting rapid progression in the second and third years. Logistic regression analysis was done to identify the best combinations of items for predicting rapid progression in years 2/3. An ROC curve analysis (Figure 1) was used to determine the optimal cutoff for each variable associated with rapid progression in years 2/3, separately and in various combinations. Similar results were found for the erosion, narrowing, and total scores.

Four variables at inclusion were significantly associated with rapid progression of the total score in years 2/3: the erosion score progression during the first year (range −5 to 13), the 2010 ACR/EULAR serologic criterion (RF and/or anti-CCP), IL-6 level, and baseline erosion score at the hands and feet. The baseline erosion score performed less well than the rapid erosion score progression in the first year for predicting further rapid progression. The best combination of these 4 variables was 67% sensitive and 70% specific for predicting rapid progression in years 2/3.

Four variables were significantly associated with rapid progression of the erosion score in years 2/3 (Table 4): the baseline erosion score at the hands and feet (range 0–33) × 1.5, the 2010 ACR/EULAR serologic criterion (RF and/or anti-CCP; 0–3) × 2.1, IL-6 level (range 0–173, mean ± SD 165 ± 21) × 1, and total score increase during the first year × 1.3. Figure 1 shows that the total score progression during the first year was the most specific variable for predicting rapid progression in years 2/3 and shows the value of each variable for predicting rapid progression in years 2/3 (Table 4). Rapid erosion score progression during the first year had 64% sensitivity and was more specific than the Sharp erosion score at baseline (80% versus 71%) in predicting rapid erosion score progression in years 2/3. IL-6 performed less well than all other criteria. The 2010 ACR/EULAR serologic criterion (RF and/or anti-CCP) criterion had good sensitivity but low specificity (63%). The best combination obtained after logistic regression was 80.5% sensitive and 71% specific.

Three variables were significantly associated with rapid narrowing score progression in years 2/3 (Table 4): the rapid total score progression during the first year, the 2010 ACR/EULAR serologic criterion, and IL-6 level. Rapid total score progression during the first year had the best specificity (83%) but lacked sensitivity. The best combination obtained following logistic regression was 68% sensitive

Table 2. Baseline parameters associated with rapid progression in years 2/3*

	Rapid progression of erosions (>2.5 points) in years 2/3			Rapid progression of narrowing (>2.5 points) in years 2/3			Rapid progression of total score (>5 points) in years 2/3		
	Yes (n = 53)	No (n = 447)	*P*	Yes (n = 146)	No (n = 354)	*P*	Yes (n = 92)	No (n = 408)	*P*
Female sex	38/53 (72)	349/447 (78)	0.3	116/146 (79)	271/354 (76)	0.5	71/92 (77)	316/408 (77)	1
ACR criteria									
1. Morning stiffness ≥1 hour	46/53 (87)	392/447 (88)	0.83	128/146 (87)	310/354 (87)	0.55	80/92 (87)	358/408 (88)	0.8
2. Arthritis in ≥3 joint areas	45/53 (85)	360/447 (93.5)	0.58	124/146 (85)	281/354 (79)	0.09	79/92 (86)	326/408 (80)	0.23
3. Arthritis of hand joints	53/53 (100)	418/447 (93)	0.06	142/146 (97)	329/354 (93)	0.06	90/92 (98)	381/408 (93)	0.13
4. Symmetric arthritis	44/53 (83)	349/447 (78)	0.48	113/146 (77)	280/354 (79)	0.7	74/92 (80)	319/408 (78)	0.6
5. Rheumatoid nodules	1/53 (2)	11/447 (2)	1	4/146 (3)	8/354 (3)	0.7	4/92 (5)	8/408 (2)	0.24
6. RF	38/53 (72)	184/447 (41)	0.0001†	85/146 (58)	137/354 (39)	0.0001†	60/92 (65)	162/408 (40)	0.0001†
≥4 ACR 1987 criteria	47/53 (89)	336/447 (75)	0.3	119/146 (81)	264/354 (74)	0.1	79/92 (86)	304/408 (74)	0.02
ACR/EULAR criteria									
Joint involvement	31/35 (88)	360/396 (91)	0.69	97/108 (90)	294/320 (92)	0.7	56/63 (89)	335/365 (92)	0.3
Symptom duration (>6 weeks)	32/36 (89)	370/394 (94)	0.28	104/109 (95)	298/321 (93)	0.5	45/64 (70)	160/366 (44)	0.0001†
Elevated ESR or CRP	36/36 (100)	353/387 (45)	0.09	105/108 (95)	284/315 (90)	0.02†	62/63 (98)	327/360 (91)	0.04†
RF or anti-CCP	29/36 (80)	176/394 (45)	0.0001†	69/109 (63)	136/321 (42)	0.0001†	45/64 (70)	164/366 (44)	0.0001†
anti-CCP	35/52 (67)	164/446 (37)	0.0001†	76/145 (53)	123/353 (35)	0.0001†	57/91 (63)	142/407 (35)	0.0001†
ACR/EULAR score ≥6	28/35 (80)	252/387 (65)	0.09	81/108 (75)	199/314 (63)	0.03†	49/63 (77.7)	231/359 (64)	0.04†
Radiologic data									
Rapid progression of erosions in year 1	25/53 (47)	30/447 (7)	0.0001†	34/146 (23)	21/354 (6)	0.001†	28/92 (30)	27/408 (6)	0.001†
Rapid progression of narrowing in year 1	30/53 (57)	144/447 (32)	0.0001†	69/146 (47)	105/354 (29)	0.001†	47/92 (51)	127/408 (31)	0.001†
Rapid progression of the total score in year 1	34/53 (64)	78/447 (17)	0.0001†	63/146 (43)	59/354 (16)	0.001†	49/92 (53)	103/408 (25)	0.001†
Sharp erosion score, mean ± SD	5.6 ± 7.6	1 ± 2.4	0.0001†	2.7 ± 5	1 ± 2.8	0.07	3.5 ± 5.7	1 ± 2.8	0.0001†
Sharp narrowing score, mean ± SD	5 ± 6	2.4 ± 3	0.003†	3.8 ± 4.5	2.3 ± 3	0.005†	4.5 ± 5.1	2.4 ± 3.3	0.003†
Sharp total score, mean ± SD	10.6 ± 10.7	4.3 ± 5.6	0.0001†	6.4 ± 7	3.2 ± 5	0.2	7.8 ± 8	3.3 ± 4.9	0.0001†

* Values are the no./total (percentage) unless otherwise indicated. ACR = American College of Rheumatology; RF = rheumatoid factor; EULAR = European League Against Rheumatism; ESR = erythrocyte sedimentation rate; CRP = serum C-reactive protein level; anti-CCP = anti–cyclic citrullinated peptide.
† Significant.

Table 3. Association between baseline cytokine levels and rapid progression in years 2/3*

	RP of the erosion score			RP of the narrowing score			RP of the total score		
	Yes	No	*P*	Yes	No	*P*	Yes	No	*P*
Level of cytokine									
IL-1Ra	1,240 ± 830	1,370 ± 1,330	0.99	1,423 ± 1,532	1,224 ± 942	0.3	1,297 ± 766	1,212 ± 1,215	0.88
IL-6	20 ± 26	10 ± 18	0.0001†	22 ± 23	13.7 ± 19	0.0001†	24.4 ± 24	14 ± 19	0.0001†
IL-10	0.09 ± 0.4	1 ± 15	0.633	0.16 ± 0.5	1.1 ± 15.4	0.07	0.14 ± 0.4	1.05 ± 14	0.3
MCP-1	201 ± 84	231 ± 170	0.57	228 ± 168	218 ± 126	0.88	201 ± 81.5	226 ± 149	0.408
IL-4	0.12 ± 0.5	0.7 ± 9.8	0.67	0.13 ± 0.7	0.8 ± 9.3	0.8	0.08 ± 0.4	0.07 ± 8.7	0.1
IL-17	0.08 ± 0.4	0.4 ± 3.5	0.22	0.3 ± 1.2	0.4 ± 3.4	0.8	0.13 ± 0.5	0.4 ± 3.2	0.38
IFNγ	0.1 ± 0.4	0.2 ± 0.8	0.66	0.2 ± 0.7	0.12 ± 0.7	0.26	0.1 ± 0.4	0.14 ± 0.7	0.75
TNFα	1.7 ± 1.4	3 ± 8	0.08	2.3 ± 2.2	2.9 ± 7.5	0.7	2.07 ± 1.7	2.83 ± 7.1	0.48
IL-1β	0.3 ± 2.2	0.5 ± 2.6	0.36	0.2 ± 1.5	0.2 ± 2.5	0.9	0.22 ± 1.3	0.19 ± 2.3	0.95
IL-2	0.7 ± 1.7	1.2 ± 6.5	0.25	0.7 ± 2.2	0.9 ± 6	0.5	0.5 ± 1.3	0.96 ± 5.7	0.3

* Values are the mean ± SD. RP = rapid progression; IL-1Ra = interleukin-1 receptor antagonist; MCP-1 = monocyte chemotactic protein 1; IFNγ = interferon-γ; TNFα = tumor necrosis factor α.
† Significant.

and 54% specific for predicting rapid narrowing score progression in years 2/3.

DISCUSSION

To assess the relevance of a treatment option in early arthritis, rheumatologists need variables that predict further radiographic progression. However, all of the available studies on predicting further radiographic progression have focused either on the erosion status at baseline or on damage severity scores at a given point in time. The potential predictive value of the rate of joint damage progression during the first few months of the disease has never been investigated in early arthritis or RA. Conceiv-

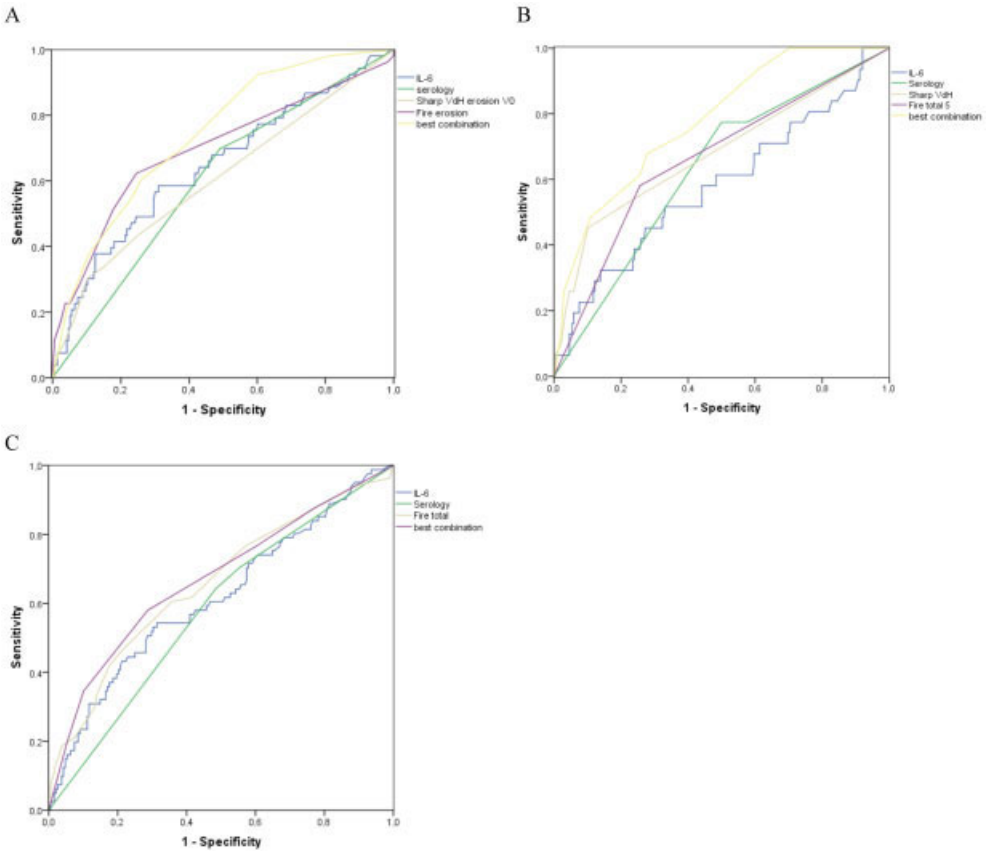

Figure 1. Receiver operating characteristic curves for each variable and best combination of variables identified by logistic regression for predicting rapid progression of the total (**A**), erosion (**B**), and narrowing (**C**) scores in the second and third years. IL-6 = interleukin-6; Sharp VdH = Sharp score as modified by van der Heidje.

Table 4. Diagnostic value of the items selected by logistic regression, alone or in combination, for predicting rapid progression in years 2/3*

Item (range)	OR	Cutoff	Sensitivity	Specificity	PPV	NPV
Rapid erosion score progression, years 2/3 (Sharp erosion score >2.5 points)						
IL-6 (0–173)	1.5	9	25/53 (47)	311/442 (70)	25/156 (16)	311/339 (92)
Serologic criterion (0–3)	6	2.5	29/36 (80)	249/394 (63)	29/174 (17)	249/256 (97)
Sharp erosion score at inclusion (0–33)	4	0.5	36/53 (68)	317/447 (71)	36/166 (22)	317/334 (95)
Rapid total score progression in year 1 (−5 to 13)	4	2.5	34/53 (64)	358/447 (80)	34/123 (26)	358/377 (95)
Best combination		5	29/36 (81)	277/389 (71)	29/141 (21)	277/284 (98)
Rapid narrowing score progression, years 2/3 (Sharp joint space narrowing score >2.5 points)						
IL-6 (0–173)	2	9	67/143 (47)	263/352 (75)	67/156 (43)	263/339 (77)
Serologic criterion (0–3)	2	2.5	61/109 (56)	208/321 (65)	61/174 (35)	208/256 (81)
Rapid total score progression in year 1 (−6 to 30)	3	5	63/146 (43)	295/354 (83)	63/122 (52)	295/378 (78)
Best combination		3	71/106 (67)	176/319 (55)	71/214 (33)	176/211 (84)
Rapid total score progression, years 2/3 (Sharp total score >5 points)						
IL-6 (0–173)	1.5	8.8	49/90 (54)	298/405 (73)	49/156 (31.5)	298/339 (88)
Serologic criterion (0–3)	6	2.5	43/64 (67)	235/366 (64)	43/174 (25)	235/256 (92)
Sharp erosion score at inclusion (0–33)	3	0.5	50/92 (54)	292/408 (71)	50/166 (30)	392/334 (87)
Rapid erosion score progression in year 1 (−5 to 13)	5	2.5	59/92 (64)	334/408 (82)	59/133 (44)	334/337 (91)
Best combination		5	40/62 (65)	262/363 (72)	40/141 (28)	262/284 (92)

* Values are the no./total (percentage) unless otherwise indicated. OR = odds ratio; PPV = positive predictive value; NPV = negative predictive value; IL-6 = interleukin-6.

ably, the rate of progression may be a stronger predictor of further damage than the joint damage score at a given point in time. In this study, we demonstrated that rapid progression during the first months of early arthritis is the best independent predictor of further rapid progression in comparison with classic parameters.

We considered a progression of >5 points/year in the total Sharp score as rapid progression with strong pertinence in clinical practice. However, data from studies in the literature are divergent. These are subjective data based on the SDC and expert opinion (16), used also in matrix risk models (21). Some authors considered an improvement of >5 points/year in the total Sharp score as only progression and not rapid progression (22).

Conventional radiography is still regarded as the reference standard for assessing joint damage and adjusting treatment in RA. Radiographic scores include erosions and joint space narrowing. Erosions are the most typical abnormalities and are strongly associated with the diagnosis and prognosis of RA (18,23,24). In our cohort of early arthritis, joint space narrowing occurred frequently during the first few years, indicating that this abnormality should be taken into account in addition to erosions. However, changes in joint space narrowing may be related to the subjective nature of the qualitative joint evaluation (25–27) and to differences in patient position between radiographic acquisitions (28). However, we previously studied the quality of radiographs in the ESPOIR cohort (following a standardized procedure concerning technical quality, including joint positioning and exposure) (13) and demonstrated that both exposure and joint positioning criteria were considered to be of good quality by the readers.

Several points in these results must be debated. In the ESPOIR cohort of early arthritis, at inclusion, patients had an active disease with a mean ± SD swollen joint count of 7.19 ± 5.37 and mean ± SD DAS28 score of 5.11 ± 1.31. A total of 578 patients (71%) at inclusion fulfilled the ACR criteria for RA and 22% had erosions on hand and/or feet radiographs (9). These data can be compared to several other cohorts of early arthritis (23,29–31), where erosive disease was present in 7–32% of the patients at inclusion and was directly related to inclusion and exclusion criteria. In the ESPOIR cohort, patients were eligible for inclusion if they had a definitive or probable clinical diagnosis of RA or a diagnosis of undifferentiated arthritis with a potential for progressing to RA; consequently, these patients were at high risk of developing RA and this probably explained the high level of radiographic progression. Therefore, for all cohorts of early arthritis, it is obviously difficult to generalize results and the inclusion criteria must be carefully checked. Moreover, our analysis excluded patients receiving anti-TNF therapy (7%) during the first year of followup. This represents only a few patients that were treated outside of the national recommendation in 2002. In more recent cohorts, such results could be analyzed in order to generalize the reported predictive values of rapid progression during the first year. Radiographic progression occurred during the first year of the ESPOIR cohort, but the scores usually increased by <5 points per year. Importantly, the total score indicated rapid progression during the first year in 24.6% of patients after exclusion of the patients treated with TNFα antagonists. This is in accordance with cohorts of early arthritis with a high risk of developing RA (32), but also consistent with the treatment available (anti-TNF therapy was not recommended in the first line).

One of the main objectives for the treatment of RA is to improve or maintain the quality of life of patients. Long-

term functioning, participation in social roles, and life satisfaction might consequently have become relevant goals. There has been growing interest in the assessment of RA from the perspective of the patient, which has led to the development of new indices to evaluate the impact of treatments, such as the Rheumatoid Arthritis Impact of Disease score (33). However, it is well known that quality of life is impaired mainly because of joint abnormalities (34) and that joint space narrowing is related to impairment of physical function and work disability (35). The ability to predict rapid progression could impact quality of life.

We also explored if RA activity during the first year could predict rapid radiographic progression in year 2/3. However, in this cohort, 416 (80%) of 514 patients had a good response, considered as a DAS28 improvement of >0.6 between inclusion and 1 year. Neither DAS28 at inclusion nor DAS28 change at 1 year were associated with rapid progression. A previous study also did not demonstrate a close relationship between DAS28 and radiographic progression (36).

The development of bone erosions is mediated by proinflammatory cytokines via the activation of osteoclasts (37,38), chondrocytes, or the cartilage matrix and matrix metalloproteinases (39–41). We evaluated the serum levels of several cytokines, IL-1Ra, and MCP-1. Only the IL-6 level correlated with the progression of erosions (42); however, it had low predictive values. It has been demonstrated previously in the same cohort that IL-6 was already associated with radiographic progression at 1 year (14).

The aim of this study was to identify predictors of rapid progression at years 2/3. Patients with rapid progression in years 2/3 had significantly higher baseline Sharp scores at the hands and/or feet. Rapid progression in years 2/3 was significantly associated with the presence of RF or anti-CCP (alone or in combination), rapid progression during the first year, presence of erosions at baseline, and IL-6 level. The best combination of variables for predicting rapid progression in years 2/3 based on the erosion, narrowing, or total score had a very good NPV and a moderate PPV. In other words, most of the patients (83–97%) without the best combination of variables did not experience rapid progression in years 2/3, and patients with this combination had a 21–33% risk of experiencing rapid progression in years 2/3. Logistic regression demonstrated that year 1 rapid progression independently predicted further rapid progression. Our results constitute the first evidence that the rate of progression during the first year is an important parameter for predicting radiographic progression.

In conclusion, the rate of progression of erosion, narrowing, and total Sharp scores during the first year of arthritis independently predicted further erosion in the next 2 years. Progression during the first year is a strong predictor that should be taken account when treating and monitoring patients with RA.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Devauchelle-Pensec had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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