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Research Letter

Joint Damage Over Time in Patients With Early Rheumatoid Arthritis Follows Trajectories Related to Distinct Courses of Disease Activity

To the Editor:

The severity of radiographic joint destruction in rheumatoid arthritis (RA) has decreased greatly in the last decades because of improved treatments and treatment strategies.[1] However, joint destruction is still prevalent and strongly correlates with functional disability.[2] This underlines the importance to identify patients at risk for severe radiographic joint destruction.

With great interest we read the study by Platzer et al, who identified, using cluster analyses, 4 distinct trajectories of radiographic progression over a period of 2 years in 1887 patients with active RA included in anti–tumor necrosis factor trials.[3] During a 2-year follow-up, radiographic progression was scored using the Sharp/van der Heijde score (SHS).[4] The trajectories consisted of patients with stable SHS, increasing SHS, or decreasing SHS, or other patients with SHS going both up and down. Increasing SHS was clinically characterized by higher objective inflammatory markers over time (C-reactive protein [CRP], 28-joint swollen joint count [SJC28]) compared to the other clusters; mathematical rules were established to simplify cluster assignment for individual patients.

Since it is of utmost importance to validate findings, we aimed to replicate the trajectories identified by Platzer et al[3] in an independent cohort of patients with early RA (according to the American College of Rheumatology 1987 criteria).[5] Patients were included between 1993 and 2006 in the Leiden Early Arthritis Clinic (EAC), described previously.[6] The initial treatment strategy varied for different inclusion periods: patients included in 1993-1995 were initially treated with nonsteroidal antiinflammatory drugs; patients included in 1996-1998 were initially treated with hydroxychloroquine or sulfasalazine; and patients included in 1999-2006 were promptly treated with methotrexate.[6] Patient consent was obtained, and ethical approval was given by the "Commissie Medische Ethiek" of the Leiden University Medical Centre (B19.008). Patient partners were involved in the design of the EAC cohort.

Radiographic progression was defined as the difference in total SHS of hand and feet radiographs between baseline and 2 years. There were 684 patients studied: the median age was 58 years, 67% were female, and 53% were positive for anticitrullinated peptide antibodies (ACPA). At baseline, median total SHS was 5 (IQR 2-12; Table). The mathematical rules defined by Platzer et al[3] were applied in our RA population. Similarly, as described by Platzer et al,[3] we identified the following: (1) stable cluster including 352 (51.5%) patients; (2) progression cluster including 303 (44.3%) patients with increasing SHS; and (3) other cluster including 29 (4.2%) patients who did not fulfill the mathematical rules of both aforementioned clusters (Figure 1A). No patients improved in SHS over time; thus, a cluster with decreasing SHS was not found.

Patients with increasing SHS (progression cluster) were compared with patients with stable SHS (stable cluster) for clinical characteristics. At diagnosis, patients in the progression cluster were more often ACPA positive (78% vs 30%, $P < 0.001$), had longer symptom duration (median 24 vs 15 weeks, $P < 0.001$) and had slightly higher total SHS (median 6 vs 5, $P = 0.02$) than patients in the stable cluster (Table). Over time, using linear mixed models, patients in the progression cluster had, during total follow-up, higher mean CRP than patients in the stable cluster. SJC28 and Disease Activity Score in 28 joints (DAS28) were higher in the progression cluster, mainly in the first year of follow-up; this difference decreased during the second year of follow-up. Functional disability as measured by Health Assessment Questionnaire (HAQ) was only slightly

Table. Baseline characteristics of patients with early RA falling into different trajectories of radiographic progression.

	Total Study Population, N = 684	Stable SHS (≤ 10), n = 352 (51.5%)	Progression SHS, n = 303 (44.3%)	Other, n = 29 (4.2%)
Age, yrs	58 (46-68)	58 (46-69)	55 (45-66)	72 (64-77)
Female sex	461 (67)	245 (70)	197 (65)	19 (66)
Symptom duration, wks	19 (11-38)	15 (9-31)	24 (13-46)	23 (11-51)
SJC28	6 (3-11)	6 (3-11)	6 (3-10)	8 (4-10)
HAQ	1.0 (0.6-1.5)	1.0 (0.6-1.5)	1.0 (0.5-1.4)	1.6 (0.9-2.3)
DAS28	4.7 (3.9-5.5)	4.6 (3.9-5.6)	4.7 (3.8-5.5)	4.9 (4.4-5.5)
ACPA positive	355 (53)	102 (30)	236 (78)	17 (61)
RF positive	394 (58)	140 (40)	235 (78)	19 (66)
CRP, mg/L	17 (8-39)	15 (6-36)	18 (9-42)	21 (9-56)
Total SHS	5 (2-12)	5 (1-10)	6 (2-11)	23 (19-40)

Data presented as n (%) or median (IQR). ACPA: anticitrullinated protein antibody (positive if > 7 U/mL); CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; HAQ: Health Assessment Questionnaire; RA: rheumatoid arthritis; RF: rheumatoid factor (positive if > 3.5 IU/mL); SHS: Sharp/van der Heijde score; SJC: 28-joint swollen joint count.

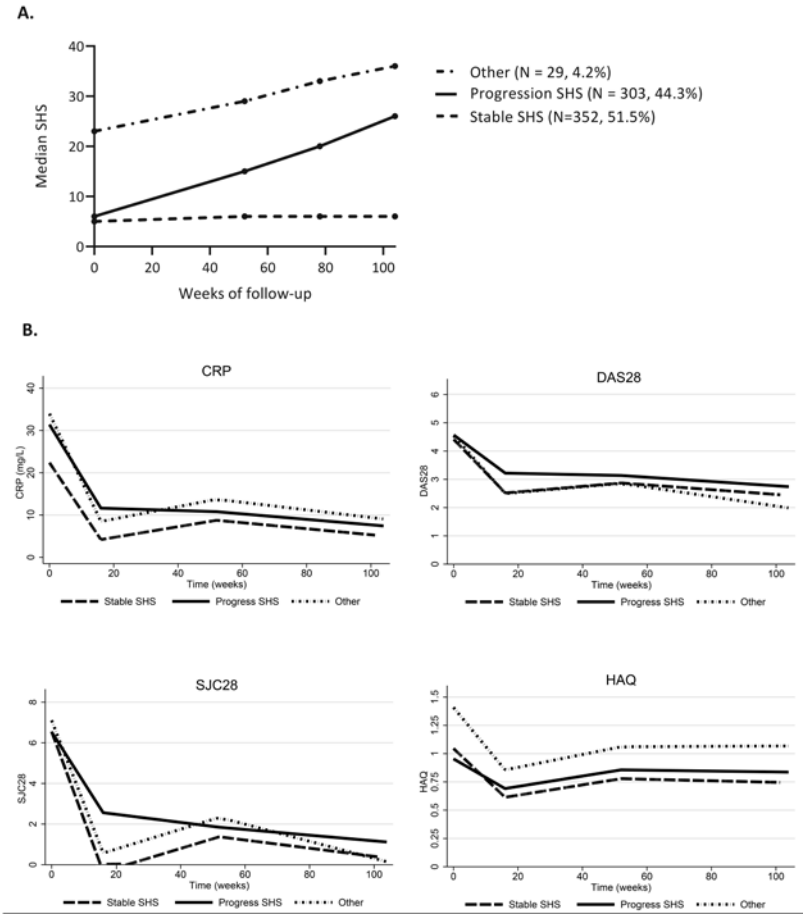

Figure 1. Clusters of radiographic progression during a 2-year follow-up based on SHS (N = 684). (A) Clusters of different trajectories of radiographic progression. Absolute SHS over time. "Progression SHS" is increased SHS over time. "Stable SHS" is ≤ 10 points SHS change over time. Dots represent study visits. (B) Linear mixed models of clinical variables over time per cluster of radiographic progression. *P* values of the difference of mean intercept between stable and progression cluster, respectively, in the first and second year of follow-up: CRP < 0.001, < 0.001; DAS28 < 0.001, 0.25; SJC28 < 0.001, 0.08; HAQ 0.89, 0.58. CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; HAQ: Health Assessment Questionnaire; SHS: Sharp/van der Heijde score; SJC28: 28-joint swollen joint count.

worse in the progression cluster during the entire follow-up period of 2 years (Figure 1B). In the sensitivity analyses, we applied a cut-off value of ≤ 5-point SHS change over time (instead of ≤ 10 points used for the primary analyses) to assign patients to the clusters. When repeating all analyses, results remained similar (Supplementary Figure S1, available with the online version of this article).

Notably, the other patients (n = 29) had remarkably high total SHS at diagnosis (median 23, IQR 19-40) and therefore did not fulfill the mathematical rules of increasing/decreasing SHS by Platzer et al.[3] Looking into more detail, all these patients showed radiographic progression. After assigning these patients to the progression cluster as validation, results shown in Figure 1B did not change (Supplementary Figure S2, available with the online version of this article).

Overall, we determined the presence of clusters of patients with different radiographic trajectories (stable and progressive SHS) in an inception cohort of patients with early RA and our results were partially in line with the mathematical model of Platzer et al.[3] There are 2 important differences in study design. We studied an unselected cohort of consecutive patients with early RA who were treated in an era when initial treatment was often milder than recommended by current guidelines and treat-to-target was infrequent. Platzer et al, in contrast, studied patients selected for a trial on tumor necrosis factor inhibitors.[3] This may explain some differences in baseline characteristics and severity of progression between the populations. Nonetheless, associations of the radiographic courses with (components of) disease activity features and disability were also present in our data from a real-world cohort. Together, these data support the notion that the different radiographic trajectories are clinically relevant.

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DATA SHARING POLICY

Data are available upon reasonable request.

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