EXTENDED REPORT

Radiological damage in patients with rheumatoid arthritis on sustained remission

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Objective: To assess the radiological damage progression in patients with recent rheumatoid arthritis in sustained remission.
Methods: A cohort of 191 patients with active early (<1 year) rheumatoid arthritis was prospectively assessed at baseline, 3 and 5 years by the Disease Activity Score (DAS) and the Sharp–van der Heijde Score (SHS) for radiographic damage. Patients in remission (DAS<1.6) at the 3-year and 5-year time points were compared with patients with a persistently active rheumatoid arthritis by Wilcoxon's signed rank test.
Results: 57 patients died, were lost to follow-up or had incomplete data; 30 (15.7% of those who completed) patients were in remission at 3 and 5 years. The SHS in these two groups was not significantly different at baseline (p = 0.15), but was lower in the remission group at 5 years (p = 0.0047). The median (IQR) radiographic score increased from 0.5 (0–7) at baseline to 2.5 (0–14) after 5 years for the remission group (p = 0.18) and from 2 (0–7) to 13 (3–29) in the group with active rheumatoid arthritis (p<0.001). 5 (16.7%) patients in remission had relevant progression of radiographic damage (ie, progression >4.1 points) and 6 (20%) presented new erosions in a previously unaffected joint between the third and the fifth years.
Conclusion: Patients with early rheumatoid arthritis in sustained remission did not present statistically significant radiographic degradation at the group level; nevertheless, 16.7% of these patients did present degradation. Absence of progression should be part of the remission definition in rheumatoid arthritis.

Rheumatoid arthritis is a chronic disease that affects almost 1% of the population and has an important effect on health, causing pain, fatigue, radiological damage, functional disability, psychological effects and reduced life expectancy.[1] Erosions develop rapidly in 10–26% of patients with rheumatoid arthritis within 3 months of disease onset, and in 75%, it develops within 2 years.[2–4] Clinical remission in early rheumatoid arthritis, obtained in 10–33% of patients in prospective international studies,[2 5–14] is the ultimate aim for doctors treating patients. Several sets of criteria define clinical remission. The preliminary criteria of the American College of Rheumatology (ACR) include six signs and symptoms: duration of morning stiffness not exceeding 15 min, no fatigue, no joint pain by anamnesis, no joint tenderness or pain on motion, no soft tissue swelling in joint or tendon sheaths and erythrocyte sedimentation rate (ESR) <30 mm/h for a woman or <20 mm/h for a man.[15 16] Five or more of the criteria must be fulfilled for at least two consecutive months. Remission may also be defined by using a composite index taking into account joint status, patient global assessment, ESR, and Disease Activity Score (DAS).[17–19] A comparative study showed that 95% of ACR remission visits were also considered as remission by using the DAS with a cut-off value <1.6.[5 20] These two definitions of remission are based on low disease activity and ignore physical function and structural damage.

However, the final goal is to prevent radiological damage and functional disability. The relationship between disease activity and these outcome measures in early rheumatoid arthritis remains a topic of debate.[21–26] In fact, some studies suggest that structural damage can occur independently of arthritis activity.[26–32]

The objective of this study was to assess the radiological damage progression over 5 years in patients with recent rheumatoid arthritis in sustained remission (DAS<1.6).

METHODS

Patients

All consecutive outpatients who were referred from primary care physicians for the purposes of a study of follow-up in early rheumatoid arthritis,[33–36] in four French centres (Montpellier, Paris-Cochin, Toulouse and Tours) and who fulfilled the ACR criteria for rheumatoid arthritis,[37] had a disease duration of <1 year and had not been treated previously with disease-modifying antirheumatic drugs (DMARDs) were included between March 1993 and October 1994. All patients agreed to be enrolled and provided signed informed consent. They were subsequently treated with DMARDs (usually methotrexate, sulfasalazine or a combination of both) that could be modified during the study according to efficacy and tolerance; some patients participated in a randomised, controlled, double-blind 52-week clinical trial of a combination of sulfasalazine and methotrexate compared with a single drug.[38 39] The study was approved by the ethics review board in Montpellier, France.

Clinical and biological assessment

The following evaluation data were collected at baseline: age, sex, disease duration, DAS,[18] Health Assessment Questionnaire (HAQ) score,[40] ESR, C reactive protein (CRP) level, IgA and IgM rheumatoid factor positivity by anti-human Fc IgG ELISA, and anti-cyclic citrullinated protein antibody positivity by ELISA.[34] Human leucocyte antigen (HLA)-DRB1 and HLA-DQB1 genotyping were performed as described previously.[41] Each patient was followed up by the same investigator at 6 months after inclusion, and then at 1, 3 and 5 years.

Definition of remission

Remission was defined by a DAS<1.6 at the 3-year follow-up visit, in accordance with Prevoo *et al*.[5] Sustained remission was defined by a DAS<1.6 at the 3-year and 5-year evaluations.

Abbreviations: ACR, American College of Rheumatology; CRP, C reactive protein; DAS, Disease Activity Score; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; MRI, magnetic resonance imaging.

Radiographic assessment

Hand, wrist and foot radiographs were obtained at baseline and at 3 and 5 years. They were evaluated in a blinded manner and in chronological order by two independent observers and scored according to Sharp's method as modified by Sharp–van der Heijde Score (SHS).[42] For each patient, an erosion score, a joint-space narrowing score and a total damage score were noted for the hands and feet. The intraclass, intraobserver and inter-observer coefficients of correlation were calculated on 30 chosen pairs of radiographs of the hands and feet and were always >0.85.[34] No systematic differences were found in any of the scores. We used the mean of the two observers' scores to determine the final radiographic scores for erosions, joint space narrowing and total damage. A new reading and scoring of radiographs by GC was obtained for individual analysis for patients in sustained remission.

To determine a cut-off value for changes in joint space width that would define individual radiological progression of rheumatoid arthritis unrelated to measurement errors (smallest detectable difference), we calculated the mean of the differences between two analyses.[43 44] We selected 30 pairs of radiographs of the hands and feet that were representative of the population studied. The mean (standard deviation (SD)) of the difference between the two analyses performed by the two observers was calculated. Radiological progression, according to the Outcome Measures in Rheumatoid Arthritis Trials Committee recommendations,[44] was then defined by a change in radiological scores greater than the upper boundary of the 95% confidence interval (CI) of the differences—that is, a change of at least 5, 4.9 and 4.1 in the erosions, narrowing and total damage scores, respectively. The radiographic progression was compared between patients with rheumatoid arthritis in sustained remission and patients who did not fulfil the remission criteria, at both 3 and 5 years.

Functional progression

The HAQ score was compared at baseline, 3 years and 5 years in each group. As published previously in patients in remission,[15 24] a value of 0.5 was used to dichotomise the HAQ. A score $\leqslant 0.5$ indicates hardly any difficulties and a score >0.5 indicates minor to major problems in performing activities of daily life.

Statistical methods

Wilcoxon's signed rank test for quantitative variables and χ^2 tests for qualitative variables were used to assess differences between the patient groups and between baseline and 5-year assessment. The significance level was set at 5% (two-sided tests). Analyses were performed using SAS V.8.2.

RESULTS

Demographic, clinical and biological features of the patient cohort

Table 1 shows the baseline characteristics of the patients.

In total, 191 patients (140 women, 51 men) were enrolled in this study, of whom 150 (78.5%) were previously part of a randomised controlled trial.[38 39] The mean (SD) age at diagnosis was 50.5 (14.7) years and the mean (SD) disease duration at inclusion was 3.3 (2.6) months. In all, 154 (80.6%) patients were IgM or IgA rheumatoid factor positive ($\geqslant$20 IU/ml and $\geqslant$7 units/ml, respectively) at baseline and 86 (45%) had at least one rheumatoid arthritis-associated DRB1*04 allele (DRB1*0401, 0404, 0405 or 0408). Six months after inclusion, 178 (93.2%) patients were taking DMARDs: 131 (68.6%) were taking one drug (58 methotrexate, 59 sulfasalazine and 14 other DMARDs) and 47 (24.6%) a combination of methotrexate and sulfasalazine. During the 5-year follow-up, a mean of 1.95 DMARDs (range 1–5) was prescribed (methotrexate to 175 patients, sulfasalazine to 147, intramuscular gold to 41, hydroxychloroquine to 25, D-penicillamine to 14 and ciclosporin to 1). A total of 86 patients received the same DMARD or the same DMARD combination during the 5-year follow-up, and 63 (33%) patients received prednisone treatment (5–15 mg/day) at least once during follow-up.

At 5 years, 26 (13.6) patients were lost to follow-up (6 patients died, 8 refused further follow-up and 12 moved out of the area), and at the 5-year evaluation, 31 (16.2%) had missing data and were excluded from the analysis. The baseline characteristics of these patients did not differ from those of the rest of the cohort.

Remission rate

A total of 48 (35.8%) patients fulfilled the remission criteria at the 3-year follow-up visit, 38 (28.4%) at the 5-year follow-up visit, and 30 (22.4%) at both visits; 78.9% of patients in remission at 3 years were also in remission at 5 years.

These 30 patients in sustained remission (the remission group) were compared with the 104 patients who did not fulfil the remission criteria (DAS<1.6) at both 3 and 5 years.

Of the patients in the remission group, 21 (70%) were taking DMARDs at 3 years (methotrexate, 8 patients; sulfasalazine, 3, a combination of methotrexate and sulfasalazine, 7; and other DMARDs, 3), and 17 (56.7%) at 5 years, with 7 changing the DMARD during the 2 years of sustained remission (discontinuation in 4 patients, shift from bitherapy to monotherapy in 2 patients and DMARDs changed because of side effects in 1 patient). In all, 29%, 15% and 13% of patients treated with combination methotrexate/sulfasalazine, monotherapy by methotrexate and by sulfasalazine, respectively, at 3 years were in remission ($p = 0.013$).

Patients in sustained remission ($n = 4$; 13.3%) and those with persistently active disease ($n = 23$; 22%) were taking corticosteroids at baseline ($p = 0.22$). At the third year, the cumulative dose of prednisone and the number of days of treatment by corticosteroids were higher in the non-remission group ($p = 0.001$ and $p = 0.001$, respectively).

The median (interquartile range (IQR)) period between onset of symptoms and first DMARD was 8 (4–14) and 9 (4–14) months in the remission and non-remission groups, respectively ($p = 0.74$). The period between diagnosis and first treatment was 3 (2–6) and 4 (2–7) months, respectively ($p = 0.34$).

At baseline, these two groups had significant differences described previously,[36] with a lower DAS ($p = 0.002$), CRP ($p = 0.02$), rheumatoid factor IgM positivity ($p = 0.02$), HAQ ($p = 0.04$) and a trend for a lower total SHS ($p = 0.15$) in the remission group. Table 2 shows the 5-year results for DAS, HAQ, ESR, CRP and SHS, and indicates a significant improvement for clinical and biological variables in the remission group.

Radiographic progression after 5 years of follow-up

Table 3 shows the radiographic joint damage scores.

The total SHS (median (IQR)) at baseline in the remission and non-remission groups 0.5 (0–7) and 2 (0–7), respectively ($p = 0.15$). At 5 years, they were 2.5 (0–14; no significant change from baseline, $p = 0.18$) and 13 (3–29; significant change, $p<0.001$), respectively in the remission and non-remission groups, with a significant difference between these two groups ($p = 0.005$). The progression of damage at 5 years was higher and significantly different ($p = 0.0014$) for patients with rheumatoid arthritis showing persistent disease activity (Δtotal SHS = 7 (1–19)) compared with those in sustained remission (Δtotal SHS = 1.5 (0–5)).

However, analysis of the radiographs showed that 10 (33%) patients with rheumatoid arthritis in sustained remission at 3

Table 1 Patients' characteristics at baseline*

Baseline variable	Remission group† (n = 30)	Non-remission group (n = 104)	p Value‡
Women, n(%)	21 (70)	81 (77.9)	0.37
Age at RA diagnosis, years	44.3 (13.9)	47.8 (11.8)	0.20
Disease duration, months	6.7	9.2	0.21
HAQ	1.12 (0.69)	1.41 (0.70)	0.04
DAS	3.70 (0.94)	4.24 (0.72)	0.002
ESR, mm/h	32.6 (23.5)	43.5 (29.2)	0.75
CRP, mg/l	19.8 (25.3)	40.7 (49.7)	0.02
RF positivity, n (%)			
IgM RF	13 (46.4)	65 (70)	0.02
IgA RF	17 (60.7)	71 (76.3)	0.10
Anti-CCP antibody, n (%)	12 (48)	45 (53.6)	0.62
HLA-DRB1*04, n (%) §	14 (48.3)	50 (49.5)	0.91
HLA-DRB1*01, n (%)	9 (31.0)	29 (28.7)	0.81
Total SHS¶	4.67 (9.65)	5.41 (7.31)	0.15
Erosion SHS¶	1.33 (2.63)	1.87 (3.54)	0.26
Joint-space narrowing SHS¶	3.33 (7.46)	3.54 (5.5)	0.44

Anti-CCP, anti-cyclic citrullinated protein; CRP, C reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HLA, human leucocyte antigen; RA, rheumatoid arthritis; RF, rheumatoid factor; SHS, Sharp–van der Heijde.
*Except where otherwise indicated, values are the mean (SD). Positive cut-off values were as follows: for IgM RF, ⩾20 IU/ml; for IgA RF, ⩾7 U/ml; for anti-CCP antibodies, ⩾50 U/ml.
†The remission group was defined by patients with RA with DAS<1.6 both at 3 and 5 years.
‡p Values for the comparison of the two groups.
§DRB1*04 includes DRB1*0401, 0404, 0405 and 0408.
¶SHS on radiographic evaluation of the hands and feet.

Table 2 Five-year activity and radiographic measurements (mean (SD))

5-year variables	Remission group (n = 30)	Non-remission group (n = 104)	p Value*
DAS	0.94 (0.34)	2.49 (0.91)	<0.001
HAQ	0.12 (0.3)	0.72 (0.64)	<0.001
ESR, mm/h	9.4 (6.6)	18.1 (12.9)	0.001
CRP, mg/l	4.6 (3.9)	10.1 (16.9)	0.05
Total SHS	9.0 (13.5)	20.3 (23.2)	0.005
Erosion SHS	2.5 (3.8)	7.4 (9.3)	0.002
Joint-space narrowing SHS	6.6 (11.1)	12.9 (16.5)	0.029

CRP, C reactive protein; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; SHS, Sharp–van der Heidje.
*p Values for the comparison of the two groups.

and 5 years had a significant increase in radiographic damage (smallest detectable difference = 4.1) between baseline and 5 years. This proportion was 57 of 104 (54.8%) for patients with rheumatoid arthritis not in remission. Furthermore, 5 (16.7%) patients in sustained remission had significant radiographic damage progression between the third and the fifth years; three of these patients had no treatment during this period. Erosions were found in 11 (36.7%), 16 (53.3%) and 16 (53.3%) patients in remission at baseline, 3 and 5 years, respectively. However, erosions in a previously unaffected joint developed in 6 patients (20%) between the third and fifth years.

Functional capacity progression after 5 years of follow-up

The mean (SD) HAQ scores at baseline in the remission and non-remission groups were 1.1 (0.7) and 1.4 (0.7), respectively (p = 0.04; table 4). At 3 and 5 years, HAQ scores were 0.2 (0.4) and 0.1 (0.3), respectively, for the remission group (significant variations with baseline, p<0.001); and 0.7 (0.6) at both time points for the non-remission group (significant variation with baseline, p<0.001). There was a significant difference between the two groups at 3 and 5 years (p<0.001). The HAQ score was not significantly different between 3 and 5 years in both groups (p = 0.96 for the remission group and 0.62 for the non-remission group).

A total of 28 (93.3%) patients in sustained remission had a HAQ score ⩽0.5 at 5 years *v* 39 (37.5%) patients with rheumatoid arthritis with persistent disease activity (p<0.001).

DISCUSSION

The main conclusion to be drawn from this study is that sustained clinical remission according to the DAS criteria <1.6 was associated with stability of radiological damage in most patients and a clear improvement of functional capacity over 5 years in cohort of patients with early rheumatoid arthritis. The significant progression at 5 years of the SHS in patients with persistent disease activity confirms that clinical remission is the absolute goal for rheumatoid arthritis treatment to avoid progressive joint destruction, deformities and disability.

Svensson *et al* [45] and Mottonen *et al* [46] found similar results for 23 and 33 remitters, respectively, who had early rheumatoid arthritis treated by DMARDs with a radiographic score not significantly higher after 2 years of follow-up.

Nevertheless, 16.7% (n = 5) of patients in sustained remission had relevant radiographical progression, and 20% (n = 6) developed erosions in a previously unaffected joint between the third and fifth years. A similar result was found by Molenaar *et al*.[26] They assessed the progression of radiological damage over 2 years in 187 patients with rheumatoid arthritis in clinical remission defined with a modification of the ACR criteria by omitting the fatigue criteria.[15 16] Remission persisted in 52% of patients, and the median radiographic score progression over 2 years was null for patients with sustained remission. However, 7% (n = 13) of patients in sustained remission had relevant progression of damage, and 15% (n = 28) developed erosions in a previously unaffected joint. Thus, patients without detectable clinical joint inflammation may continue to experience joint destruction. Makinen *et al*[47] and Jantti *et al*[48] studied the frequency of remission using several sets of criteria, including the ACR criteria (excluding fatigue) and ''radiographic remission'' defined as no worsening of erosion (ie, Larsen Score should not worsen by more than one point), and no new erosion from baseline to 5 years. In all, 19 patients with rheumatoid arthritis fulfilled the ACR criteria for remission, but six were not in radiographic remission. Nevertheless, in this study, the difference in the Larsen Score (one point) was minimum difference usually considered clinically important lower than the minimal clinically important difference usually considered.[49] Sokka *et al*[25] found only one patient without joint tenderness and one without joint swelling with radiographic deterioration (Larsen Score progression >1) on wrist radiographs in a cohort of 58 patients with rheumatoid arthritis.

Kirwan[29 30] showed that the link between inflammation and erosion is not clear, and proposed that two pathological processes were at work simultaneously in the joint, one leading to signs and symptoms of inflammation by lymphocytic phenomena and the other leading to direct joint destruction by synovial macrophage cells. Smolen *et al*[31] also indicated that patients without clinical improvement with infliximab and methotrexate showed considerable benefit with regard to the destructive process, suggesting that in such patients these two measures of diseases were dissociated. Furthermore, Garnero *et al*[32] showed that baseline levels of urinary markers of bone

Table 3 Radiographic joint damage in patients with rheumatoid arthritis in clinical remission both at 3 and 5 years as defined by the Disease Activity Score criteria

	Sharp–van der Heijde Score		
Patient group	**Baseline**	**5-year follow-up**	**Change from baseline to 5 years**
Whole cohort (n = 134)			
Mean (SD)	5.23 (7.9)	17.68 (21.9)	12.52 (17.9)
Median (range)	2 (50)	10 (95)	5 (89)
Interquartile range	0–7	1–22	(0–16)
Remission group (n = 30)			
Mean (SD)	4.67 (9.65)	9.03 (13.48)	4.37 (7.48)
Median (range)	0.50 (50)	2.5 (57)	1.5 (32)
Interquartile range	0–7	0–14	0–5
Non-remission group (n = 104)			
Mean (SD)	5.41 (7.31)	20.30 (23.23)	15.01 (19.43)
Median (range)	2 (36)	13 (95)*	7 (89)*
Interquartile range	0–7	3–29	1–19

*p<0.05, versus baseline; p values were determined by Wilcoxon's signed rank test.

were predictive of radiological progression over 4 years in patients with early rheumatoid arthritis, independently of DAS computed on 28 joints and baseline SHS, especially for those without radiological joint damage. Several lines of evidence support the idea that osteoclasts have a role in the erosion of bone in rheumatoid arthritis.[50] Kirwan *et al*[51] suggests that synovitis is more closely related to diffuse cartilage loss than to progression of erosion. Those authors found that the link between synovitis and erosions was abolished by glucocorticoid treatment whereas the link between synovitis and cartilage loss was not, pointing to at least two different mechanisms for these observed radiological features. For McQueen and Robinson[52], bone oedema and synovitis detected by magnetic resonance imaging (MRI) represent two separate pathological processes, which often start together but could later diverge. Bone oedema seen on MRI may represent an intraosseous process that contributes to articular damage via a pathway that is separate from synovial inflammation.[52]

The main differences between Molenaar's study and ours are the cohort characteristics at baseline: their patients were older (mean age 58 years), had a longer disease duration (median 7 years) and did not receive glucocorticoids.[26] In fact, use of low doses of prednisolone taken in addition to traditional treatment in patients with early rheumatoid arthritis has now been shown to substantially reduce radiographic progression[2–4 53–55] and increase the remission rate.[55] Furthermore, the follow-up in our study was longer (5 *v* 2 years) and the definition of remission was different. Moreover, all the patients included in Molenaar's study were in remission and followed up for 2 years, whereas our patients were in remission only at the third-year and fifth-year evaluations.

In our study, 78.9% of patients in remission at 3 years were also in remission at 5 years. This was higher than other studies (52% after 2 years in Molenaar's study and 50% between the second and fifth years in Makinen's study).[26 47] In our cohort, patients with rheumatoid arthritis were considered to be in sustained remission when they had a DAS <1.6 at 3 and 5 years. Furthermore, there were no pronounced therapeutic changes during this period in all patients in sustained remission, which argues against short-term flares. Nevertheless, we cannot rule out the possibility of short-term flares not sufficiently long to warrant change of a DMARD, especially in a period in which not many treatment options were available. In addition, DAS or ACR criteria for remission may not be sufficiently sensitive to rule out some degree of residual inflammation. In fact, patients can be classified by DAS as in remission despite the continued presence of tender and swollen joints, especially when patients have extremely low levels of acute-phase reactants.[56] Synovitis may also be present at a subclinical level and may cause subsequent bone erosion.

Table 4 HAQ scores in patients with rheumatoid arthritis in clinical remission both at 3 and 5 years defined by the DAS criteria

	HAQ			
Patient group	**Baseline**	**3-year follow-up**	**5-year follow-up**	**Change from baseline to 5-years**
Whole cohort (n = 134)				
Mean (SD)	1.34 (0.70)	0.56 (0.61)	0.58 (0.63)	−0.73 (0.73)
Median (range)	1.25 (2.75)	0.37 (2.50)	0.44 (3)	−0.63 (4.11)
Interquartile range	0.75–1.75	0–0.87	0–0.75	−1.14/−0.25
Remission group (n = 30)				
Mean (SD)	1.12 (0.69)	0.17 (0.36)	0.12 (0.30)	−0.97 (0.70)
Median (range)	1 (2.50)	0.00 (1.75)*	0.00 (1.50)*	−0.88 (2.87)
Interquartile range	0.62–1.25	0–0.25	0–0.12	−1.25/−0.5
Non-remission group (n = 104)				
Mean (SD)	1.41 (0.70)	0.68 (0.62)	0.72 (0.64)	−0.65 (0.73)
Median (range)	1.37 (2.75)	0.50 (2.50)*	0.62 (3)*	−0.62 (4.11)
Interquartile range	0.87/1.87	0.12–1	0.25–1	−1/−0.25

Except where otherwise indicated, p values were determined by Wilcoxon's signed rank test.
*p<0.001, versus baseline.

Conaghan *et al*[57] did not find a mismatch between synovitis detected by MRI and subsequent bone damage, the number of new erosions being proportional to the amount of synovitis in a given joint.

The functional capacity was improved in both the remission and non-remission groups but considerably more so in the remission group. Nevertheless, the HAQ score was lower at baseline in the remission group, and this value was a predictive factor of the 5-year HAQ score and a prognostic factor of remission in early rheumatoid arthritis.[35 36] In previous studies, Welsing *et al*[21] had showed that functional capacity was mainly associated with disease activity in early rheumatoid arthritis, and Molenaar *et al*[24] that functional disability in patients with rheumatoid arthritis in remission was most strongly related to the presence of pain and to a lesser extent to disease activity.

To conclude, our data showed that remission based on the DAS criteria is a clinically relevant goal for management of early rheumatoid arthritis despite the fact that mild radiographic progression may occur in some patients. These data suggest that radiographic damage may be partly independent of clinical joint inflammation, and that regular monitoring of radiographic damage in patients with early rheumatoid arthritis should be mandatory in addition to frequent disease activity measurement, as was recently recommended. Use of MRI and ultrasonography in the follow-up of patients with rheumatoid arthritis in remission for evaluating non-detectable clinical joint inflammation should be studied. Finally, absence of radiographic progression should be part of the remission definition in rheumatoid arthritis even though further studies are needed to decide what degree of radiological progression in patients in clinical remission may have relevance for long-term outcomes.

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Contributors: GC read the *x* rays, coordinated the statistical analysis and drafted the manuscript. BC, MD, AC and PG included and followed up the patients, and shared the design and coordination of the study. BC conceived the study, participated in its design and coordination, and helped to draft the manuscript. LG participated in conceiving the study and coordinating the statistical analysis, and helped to draft the manuscript. JPD participated in the design of the study and supervised the statistical analysis. NR performed the statistical analysis. All authors read and approved the final manuscript.

REFERENCES

1 **Silman AJ**, Hochberg MC. Epidemiology of the rheumatic diseases. In: New York: Oxford University Press, 1993.
2 **Harrison B**, Symmons D. Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a rewiew of the literature. II. Outcome at three years. *Rheumatology* 2000;**39**:939–49.
3 **Machold KP**, Stamm TA, Eberl GJ, Nell VK, Dunky A. Very recent onset arthritis: clinical, laboratory, and radiological findings during the first year of disease. *J Rheumatol* 2002;**29**:2278–87.
4 **van der Heijde DM**. Joint erosions and patients with early rheumatoid arthritis. *Br J Rheumatol*, 1995;**34** Suppl 2, 74–8.
5 **Prevoo ML**, van Gestel AM, van T Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatism Association preliminary remission criteria in relation to the disease activity score. *Br J Rheumatol* 1996;**35**:1101–5.
6 **Mottonen T**, Paimela L, Ahonen J, Helve T, Hannonen P, Leirisalo-Repo M. Outcome in patients with early rheumatoid arthritis treated according to the ''sawtooth'' strategy. *Arthritis Rheum* 1996;**39**:996–1005.
7 **Sokka T**, Hannonen P. Utility of disease modifying antirheumatic drugs in ''sawtooth'' strategy. A prospective study of early rheumatoid arthritis patients up to 15 years. *Ann Rheum Dis* 1999;**58**:618–22.
8 **Young A**, Dixey J, Cox N, Davies P, Devlin J, Emery P, *et al*. How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS). *Rheumatology* 2000;**39**:603–11.
9 **Lindqvist E**, Saxne T, Geborek P, Eberhardt K. Ten year outcome in a cohort of patients with early rheumatoid arthritis: health status, disease process, and damage. *Ann Rheum Dis* 2002;**61**:1055–9.
10 **Visser H**, le Cessie S, Vos K, Breedveld FC, Hazes JM. How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. *Arthritis Rheum* 2002;**46**:357–65.
11 **Schumacher HR Jr**, Habre W, Meador R, Hsia EC. Predictive factors in early arthritis: long-term follow-up. *Semin Arthritis Rheum* 2004;**33**:264–72.
12 **Tengstrand B**, Ahlmen M, Hafstrom I. The influence of sex on rheumatoid arthritis: a prospective study of onset and outcome after 2 years. *J Rheumatol* 2004;**31**:214–22.
13 **Teir J**, Gray J, Pendlebury A, Grennan DM. Outcome of patients with early rheumatoid arthritis over a two year period. Ann Rheum Dis, 1999;**58**:323.
14 **Eberhardt K**, Fex E. Clinical course and remission rate in patients with early rheumatoid arthritis: relationship to outcome after 5 years. *Br J Rheumatol* 1998;**37**:1324–9.
15 **Pinals RS**, Masi AT, Larsen RA. Preliminary criteria for clinical remission in rheumatoid arthritis. *Arthritis Rheum* 1981;**24**:1308–15.
16 **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.
17 **van der Heijde DM**, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, *et al*. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. *Ann Rheum Dis* 1990;**49**:916–20.
18 **van der Heijde DM**, van 't Hof M, van Riel PL, van de Putte LB. Development of a disease activity score based on judgment in clinical practice by rheumatologists. *J Rheumatol* 1993;**20**:579–81.
19 **van Gestel AM**, Prevoo ML, van 't Hof MA, van Rijswijk MH, van de Putte LB, van Riel PL. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum* 1996;**39**:34–40.
20 **van Gestel AM**, Anderson JJ, van Riel PL, Boers M, Haagsma CJ, Rich B, *et al*. ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology. *J Rheumatol* 1999;**26**:705–11.
21 **Welsing PM**, van Gestel AM, Swinkels HL, Lambertus AL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. *Arthritis Rheum*, 2001;*44*, 2009–17.
22 **Wolfe F**, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. *Arthritis Rheum* 1998;**41**:1571–82.
23 **Sokka T**, Kankainen A, Hannonen P. Scores for functional disability in patients with rheumatoid arthritis are correlated at higher levels with pain scores than with radiographic scores. *Arthritis Rheum* 2000;**43**:386–9.
24 **Molenaar ET**, Voskuyl AE, Dijkmans BA. Functional disability in relation to radiological damage and disease activity in patients with rheumatoid arthritis in remission. *J Rheumatol* 2002;**29**:267–70.
25 **Sokka T**, Kautiainen H, Mottonen T, Hannonen P. Erosions develop rarely in joints without clinically detectable inflammation in patients with early rheumatoid arthritis. *J Rheumatol* 2003;**30**:2580–4.
26 **Molenaar ET**, Voskuyl AE, Dinant HJ, Bezemer PD, Boers M Dijkmans BA. Progression of radiologic damage in patients with rheumatoid arthritis in clinical remission. *Arthritis Rheum* 2004;**50**:36–42.
27 **Mulherin D**, Fitzgerald O, Bresnihan B. Synovial tissue macrophage populations and articular damage in rheumatoid arthritis. *Arthritis Rheum* 1996;**39**:115–24.
28 **Mulherin D**, Fitzgerald O, Bresnihan B. Clinical improvement and radiological deterioration in rheumatoid arthritis: evidence that the pathogenesis of synovial inflammation and articular erosion may differ. *Br J Rheumatol* 1996;**35**:1263–8.
29 **Kirwan JR**. The relationship between synovitis and erosions in rheumatoid arthritis. *Br J Rheumatol* 1997;**36**:225–8.
30 **Kirwan JR**. The synovium in rheumatoid arthritis: evidence for (at least) two pathologies. *Arthritis Rheum* 2004;**50**:1–4.
31 **Smolen JS**, Han C, Bala M, Maini RN, Kalden JR, van der Heijde D, *et al*. Evidence of radiographic benefit of treatment with infliximab plus methotrexate in rheumatoid arthritis patients who had no clinical improvement: a detailed subanalysis of data from the anti-tumor necrosis factor trial in rheumatoid arthritis with concomitant therapy study. *Arthritis Rheum* 2005;**52**:1020–30.
32 **Garnero P**, Landewe R, Boers M, Verhoeven A, van der Linden S, Christgau S, *et al*. Association of baseline levels of markers of bone and cartilage degradation with long-term progression of joint damage in patients with early rheumatoid arthritis: the COBRA study. *Arthritis Rheum* 2002;**46**:2847–56.
33 **Combe B**, Dougados M, Goupille P, Cantagrel A, Eliaou JF, Sibilia J, *et al*. Prognostic factors for radiographic damage in early rheumatoid arthritis. *Arthritis Rheum* 2001;**44**:1736–43.

34 **Meyer O**, Labarre C, Dougados M, Goupille P, Cantagrel A, Dubois A, *et al.* Anticitrullinated protein/peptide antibody assays in early rheumatoid arthritis for predicting five year radiographic damage. *Ann Rheum Dis* 2003;**62**:120–6.
35 **Combe B**, Cantagrel A, Goupille P, Bozonnat MC, Sibilia J, Eliaou JF, *et al.* Predictive factors of 5-year health assessment questionnaire disability in early rheumatoid arthritis. *J Rheumatol* 2003;**30**:2344–9.
36 **Gossec L**, Dougados M, Goupille P, Cantagrel A, Sibilia J, Meyer O, *et al.* Prognostic factors for remission in early rheumatoid arthritis: a multiparameter prospective study. *Ann Rheum Dis* 2004;**63**:675–80.
37 **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.
38 **Maillefert JF**, Combe B, Goupille P, Cantagrel A, Dougados M. Long term structural effects of combination therapy in patients with early rheumatoid arthritis: five year follow up of a prospective double blind controlled study. *Ann Rheum Dis* 2003;**62**:764–6.
39 **Dougados M**, Combe B, Cantagrel A, Goupille P, Olive P, Schattenkirchner M, *et al.* Combination therapy in early rheumatoid arthritis: a randomised, controlled, double blind 52 week clinical trial of sulphasalazine and methotrexate compared with the single components. *Ann Rheum Dis* 1999;**58**:220–5.
40 **Fries JF**, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;**23**:137–45.
41 **Combe B**, Eliaou JF, Daures JP, Meyer O, Clot J, Sany J. Prognostic factors in rheumatoid arthritis: comparative study of two subsets of patients according to severity of articular damage. *Br J Rheumatol* 1995;**34**:529–34.
42 **van der Heijde D**, van Riel P, Nuver-Zwart HH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989;**1**:1036–8.
43 **Bland JM**, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;**1**:307–10.
44 **Lassere M**, Boers M, van der Heijde D, Boonen A, Edmonds J, Saudan A, *et al.* Smallest detectable difference in radiological progression. *J Rheumatol* 1999;**26**:731–9.
45 **Svensson B**, Schaufelberger C, Teleman A, Theander J. Remission and response to early treatment of RA assessed by the Disease Activity Score. BARFOT study group. Better Anti-rheumatic Farmacotherapy. *Rheumatology* 2000;**39**:1031–6.
46 **Mottonen T**, Hannonen P, Korpela M, Nissila M, Kautiainen H, Ilonen J, *et al.* Delay to institution of therapy and induction of remission using single-drug or combination-disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. *Arthritis Rheum* 2002;**46**:894–8.
47 **Makinen H**, Kautiainen H, Hannonen P, Sokka T. Frequency of remissions in early rheumatoid arthritis defined by 3 sets of criteria. a 5-year followup study. *J Rheumatol* 2005;**32**:796–800.
48 **Jantti J**, Kaarela K, Kautiainen H, Isomaki H, Aho K. Radiographic remission in seropositive rheumatoid arthritis. A 20-year follow-up study. *Clin Exp Rheumatol* 2001;**19**:573–6.
49 **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.
50 **Gravallese EM**, Goldring SR. Cellular mechanisms and the role of cytokines in bone erosions in rheumatoid arthritis. *Arthritis Rheum* 2000;**43**:2143–51.
51 **Kirwan J**, Byron M, Watt I. The relationship between soft tissue swelling, joint space narrowing and erosive damage in hand X-rays of patients with rheumatoid arthritis. *Rheumatology* 2001;**40**:297–301.
52 **McQueen F**, Robinson E. Bone edema and synovial inflammation: comment on the editorial by Kirwan. *Arthritis Rheum* 2004;**50**:3734–5.
53 **Kirwan JR**. Systemic low-dose glucocorticoid treatment in rheumatoid arthritis. *Rheum Dis Clin North Am* 2001;**27**:389–403.
54 **Fex E**, Jonsson K, Johnson U, Eberhardt KB. Development of radiographic damage during the first 5-6 yr of rheumatoid arthritis. A prospective follow-up study of a Swedish cohort. *Br J Rheumatol* 1996;**35**:1106–15.
55 **Svensson B**, Boonen A, Albertsson K, van der Heijde D, Keller C, Hafstrom I. Low-dose prednisolone in addition to the initial disease-modifying antirheumatic drug in patients with early active rheumatoid arthritis reduces joint destruction and increases the remission rate: A two-year randomized trial. *Arthritis Rheum* 2005;**52**:3360–70.
56 **Sesin CA**, Bingham CO. Remission in rheumatoid arthritis: wishful thinking or clinical reality? *Semin Arthritis Rheum* 2005;**35**:185–96.
57 **Conaghan PG**, O'Connor P, McGonagle D, Astin P, Wakefield RJ, Gibbon WW, *et al.* Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:64–71.

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