Association of Bone Edema with the Progression of Bone Erosions Quantified by Hand Magnetic Resonance Imaging in Patients with Rheumatoid Arthritis in Remission

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ABSTRACT. ***Objective.*** To evaluate the association of synovitis, bone marrow edema (BME), and tenosynovitis in the progression of erosions quantified by hand magnetic resonance imaging (MRI) at 1 year in patients with early rheumatoid arthritis (RA) in remission.

Methods. A total of 56 of 196 patients with early RA in remission at 1 year and with available MRI data at baseline and at 12 months were included. MRI images were assessed according to the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) system. Persistent remission was defined as 28-joint Disease Activity Score-erythrocyte sedimentation rate ≤ 2.6 and/or Simplified Disease Activity Index ≤ 3.3 and/or the new boolean American College of Rheumatology/European League Against Rheumatism remission criteria for a continuous period of at least 6 months. Progression of bone erosions was defined as an increase of 1 or more units in annual RAMRIS score for erosions compared to baseline.

Results. At 1 year, the majority of patients with RA in sustained remission showed some inflammatory activity on MRI (94.6% synovitis, 46.4% BME, and 58.9% tenosynovitis) and 19 of the 56 patients (33.9%) showed MRI progression of bone erosions. A significant difference was observed in MRI BME at 1 year, with higher mean score in patients with progression compared to nonprogression of erosions (4.8 ± 5.6 and 1.4 ± 2.6, p = 0.03).

Conclusion. Subclinical inflammation was identified by MRI in 96.4% of patients with RA in sustained clinical remission. Significantly higher scores of BME after sustained remission were observed in patients with progression of erosions compared to patients with no progression. The persistence of higher scores of BME may explain the progression of bone erosions in patients with persistent clinical remission. (First Release July 1, 2014; J Rheumatol 2014;41:1623–9; doi:10.3899/jrheum.130902)

Key Indexing Terms:
RHEUMATOID ARTHRITIS REMISSION RAMRIS
BONE MARROW EDEMA MAGNETIC RESONANCE

Early diagnosis and prompt initiation of treatment are needed to reduce structural damage and to improve physical function and disability in patients with rheumatoid arthritis (RA). Today, the primary goal of treatment for patients with RA is to achieve clinical remission or low levels of disease activity and to stop progression of structural damage[1]. However, several studies have shown that some patients in clinical remission may develop structural progression on conventional radiography over time[2,3,4]. In those studies, remission was assessed by clinical and biological variables, which may be insufficient to evaluate low-level inflammation in patients in remission. There is evidence that MRI is more sensitive than clinical examination or conventional radiography for detecting inflammation and joint erosions. Studies have demonstrated that most patients in remission or low disease activity state continue to have synovitis and bone marrow edema (BME) detectable by magnetic resonance imaging (MRI)[5,6]. This MRI subclinical inflammation may explain the structural progression on radiography in patients with RA despite clinical remission or low disease activity[7,8].

The aim of our study was to evaluate the association of synovitis, BME, and tenosynovitis with the progression of

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erosions quantified by MRI at 1 year in patients with early RA achieving clinical remission.

MATERIALS AND METHODS

Study design and patients. This is an observational study of a cohort of 196 patients referred to an Early Arthritis Clinic at the Department of Rheumatology of Hospital del Mar (Barcelona, Spain) by primary care physicians and other specialized rheumatologists.

All patients meeting the 1987 American College of Rheumatology (ACR) criteria for RA[9], having a disease duration of < 1 year and having not previously been treated with disease-modifying antirheumatic drugs (DMARD) or tumor necrosis factor antagonist (anti-TNF), were followed with a previously designed protocol.

Patients were treated according to the recommendations of the Spanish Society of Rheumatology (SER) for biologic therapy in RA[10]. According to these recommendations, all patients with active RA should be treated initially with DMARD, especially methotrexate (MTX) or leflunomide (LEF) at appropriate doses, changing to other DMARD, combination therapy, or TNF inhibitors if the therapeutic goal is not achieved [28-joint Disease Activity Score erythrocyte sedimentation rate (DAS28-ESR) ≤ 2.6]. MTX was initiated at a dose of 15 mg a week, in rapid escalation to a dose of 20 or 25 mg if the therapeutic goal was not achieved. LEF was initiated at a dose of 20 mg daily, without a loading dose. When contraindication to these treatments existed, other alternative DMARD (sulfasalazine or antimalarials) were considered initially.

The protocol and the study were approved by the local health authorities and the ethics committee. Written informed consent was obtained from all patients.

Demographic and clinical assessment. The following demographic and treatment characteristics were recorded at baseline before starting DMARD: age, sex, duration of RA, medical history, previous glucocorticoids and/or nonsteroidal antiinflammatory drugs, and positivity for rheumatoid factor (RF) and anticyclic citrullinated peptide antibody (ACPA) values.

Clinical characteristics were assessed at baseline and at 3, 6, 9, and 12 months, including swollen joint count (SJC 66), 68-joint tender joint count, visual analog scale (VAS) for pain, patient VAS global assessment, physician VAS global assessment, and the score on a Spanish version of the Health Assessment Questionnaire. ESR and C-reactive protein (CRP) levels were also measured at baseline and at each visit. DAS28-ESR, Simplified Disease Activity Index (SDAI), and the new boolean ACR/European League Against Rheumatism (EULAR) remission criteria were calculated at each visit[11,12].

Remission assessment. The clinical remission was defined as a disease state of DAS28-ESR ≤ 2.6 and/or SDAI ≤ 3.3 and/or the new boolean ACR/EULAR remission criteria. Persistent clinical remission was defined as fulfilling this definition for a period of least 6 months without flares or treatment changes before completing 1-year followup. Only patients who fulfilled persistent clinical remission were included in the analysis of MRI in this study.

MRI evaluation. MRI of the dominant wrist and the second to fifth metacarpophalangeal (MCP) joints was obtained at baseline (before treatment) and at 12 months and was performed in a 1.5 Tesla Superconductive system (Signa Echo-speed Excite II; General Electric Medical Systems), equipped with a 4-channel knee coil.

Synovitis, erosion, and BME were defined and scored according to the Outcome Measures in Rheumatology Clinical Trials (OMERACT) Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) recommendations and wrist and finger tenosynovitis were evaluated by a method described by our group[13]. The acquisition of MRI images was performed as described in our previous studies[13,14].

We defined progression of joint erosion as an increase of 1 or more units in annual RAMRIS score for erosions compared to baseline. According to this definition, patients were placed into 2 groups: "progressors" (P) and "nonprogressors" (nP) at 1 year.

Statistical analyses. Baseline and annual observations are reported with descriptive statistics, using mean and SD or median (P_{25}–P_{75}) values depending on variable distribution. Change from baseline to 12 months was analyzed with paired Student's t test for normally distributed data; otherwise Wilcoxon signed-rank test was used. Comparisons between P group and nP group were tested using independent Student t test for normally distributed data and Mann-Whitney U test, respectively.

To assess the reliability of RAMRIS scoring and tenosynovitis, the first 15 pairs (baseline and at 1 year) of MRI were selected. Two experienced readers in RAMRIS scoring and tenosynovitis (JA and MPL) read the images. All sets of images were coded so that readers were unaware of patient identity, clinical data, and chronological order of the films. A second reading was completed after a 2-week interval. The intraclass correlation coefficients (ICC) for intrareader and interreader reliability for a single measure and change were calculated using a 2-way random effect model. Single-measure ICC and average-measure ICC for status and change scores were calculated and were given as medians and ranges. Agreement was considered good if ICC were > 0.60 and very good at > 0.80.

Data evaluation and statistical analysis were performed using SPSS version 18.0 software. P values < 0.05 were considered statistically significant.

RESULTS

Remission rate. At 1 year, of all 196 patients, 56 (28.5%) fulfilled at least 1 definition of remission (96.4% patients fulfilled DAS28-ESR remission, 67.8% SDAI remission, and 58.9% were in remission according the new boolean ACR/EULAR criteria). Thirty-one patients were in remission fulfilling all 3 definitions. All 56 patients also fulfilled the definition of persistent clinical remission (sustained for at least 6 mos).

Demographic and clinical data of patients in remission. These 56 patients in remission were predominantly female (76.8%), with a mean ± SD age of 50.1 ± 13.3 years and median disease duration of 3.8 months (1.7–6.3); 58.9% were RF-positive and 57.1% were ACPA-positive at baseline. At entry into the study, 35.7% had radiographic joint damage; however, 91.1% of patients had evidence of MRI erosions.

Treatment of patients in remission at 1 year. At 1 year, 78.6% of the patients had been treated with DMARD alone: MTX (70.5%), LEF (25%), or sulfasalazine (4.5%), and none with combined DMARD. A total of 21.4% of the patients were taking anti-TNF in combination with DMARD therapy or monotherapy (3 patients because of adverse effects and 2 for noncompliance of treatment with DMARD). Regarding the use of other treatments, 41.1% were receiving glucocorticoids at a mean dose of 1.7 ± 2.2 mg/day.

Clinical and MRI variables of patients in remission at 1 year. At 12 months, all patients in clinical remission by DAS28-ESR, SDAI, and/or new boolean ACR/EULAR criteria had a significant decrease in all disease activity variables as measured by joint counts and acute-phase reactants, and in functional capacity.

RAMRIS score for synovitis, BME, and tenosynovitis showed a significant reduction in patients in clinical remission at 1 year. However, even in those patients in clinical remission, persistent synovitis, BME, and tenosynovitis (94.6%, 46.9%, and 58.9% of patients, respectively) were observed in wrist and MCP joints.

In the whole group, the mean RAMRIS score for bone erosions was similar (7.4 ± 10.3 and 7.8 ± 10.5, p = 0.127) at baseline and at 1 year (Table 1). However, at the patient level, progression of bone erosions, defined as an increase of 1 or more units in annual RAMRIS erosion, occurred in 19 of all 56 patients in sustained remission (33.9%).

Comparison of P and nP at baseline. At entry into the study, no difference was observed between P and nP groups of patients in any MRI variable. However, the 19 patients showing progression of bone erosions showed significantly higher values of CRP and a trend to higher mean scores of disease activity according to DAS28-ESR and SDAI values at baseline (Table 2).

Comparison of P and nP at 1 year. The mean values for the DAS28-ESR, SDAI, CRP, and ESR were similar in the 2 groups of patients with sustained remission at 1 year. However, a significant difference was observed in MRI BME, with a higher mean score in P patients compared to nP (4.8 ± 5.6 vs 1.4 ± 2.6, p = 0.03). There was also a tendency toward higher tenosynovitis in the P group at 1 year (Table 2).

We also analyzed other factors that may contribute to progression of bone damage in MRI, such as differences in the treatments (anti-TNF or glucocorticoids), presence of serum RF, and ACPA or remission criteria used between the 2 groups. All patients were treated according to the recommendations of the SER, with similar therapy for both groups. There were no differences in anti-TNF therapies (15.7% in P and 24.3% in the nP group, p = 0.46) and glucocorticoids (42.1% in P and 40.5% % in nP, p = 0.91) between the groups. No differences were found between the percentage of patients positive for RF or ACPA between 2 groups (52.6% RF-positive and 52.6% ACPA-positive in P and 62.2% RF-positive and 59.5% ACPA-positive in nP, all p > 0.05). Finally, there were no significant differences between groups in the percentage of patients in clinical remission according to different criteria applied. The percentages of patients in clinical remission by DAS28-ESR, SDAI, and new boolean ACR/EULAR remission were 94.7%, 78.9%, and 68.4% in the P group and 97.3%, 62.2%, and 48.6% in nP, respectively (p = 0.62, p = 0.20, and p = 0.15).

Reliability of MRI. The intrareader single-measure and average-measure ICC were high for both readers for status score and slightly lower for change, and interreader ICC for status score was high and moderate for change (Table 3).

DISCUSSION

Our study showed significantly higher BME values on hand MRI in patients with erosion progression compared to patients without erosion progression at 1 year in a group of 56 patients with early RA after entering sustained clinical remission. However, there were no significant differences in BME at baseline between the groups.

BME has been identified as the strongest baseline single risk factor for progression of bone erosions in longitudinal studies in patients with active RA or even in patients in RA

Table 1. Characteristics of patients with RA in remission. Values are mean ± SD, unless otherwise indicated.

Characteristics, n = 56	Baseline	1 year	p
Clinical variables			
$SJC_{66,}$ median (range)	3.5 (1–6)	0 (0–0)	< 0.001
TJC_{68}, median (range)	2.5 (0–4)	0 (0–0)	< 0.001
DAS28	3.9 ± 1.3	1.9 ± 0.5	< 0.001
SDAI	16.6 ± 12.4	2.6 ± 2.4	< 0.001
HAQ score	0.530 ± 0.520	0.176 ± 0.293	< 0.001
ESR, < 20 mm/h	22.7 ± 16.7	14 ± 11.2	< 0.001
CRP, < 0.8 mg/dl	1.1 ± 1.6	0.3 ± 0.2	< 0.001
VAS pain, 0–100 mm	38.7 ± 20.7	20.8 ± 21	< 0.001
PGA, 0–100 mm	37.6 ± 20.1	17.5 ± 18.4	< 0.001
MRI variables			
RAMRIS synovitis (0–21)	6.1 ± 3.8	4.0 ± 2.4	< 0.001
RAMRIS BME (0–69)	5.9 ± 8.9	2.6 ± 4.2	< 0.001
RAMRIS erosion (0–230)	7.4 ± 10.3	7.8 ± 10.5	0.127
Total RAMRIS (0–320)	19.5 ± 18.8	14.5 ± 15.1	< 0.001
Tenosynovitis (0–26)	6.9 ± 6.4	2.9 ± 4.3	< 0.001

CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints (tender and swollen); ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; MRI: magnetic resonance imaging; RAMRIS: Rheumatoid Arthritis MRI Score; SDAI: Simplified Disease Activity Index; SJC: swollen joint count in 66 joints; TJC: tender joint count in 68 joints; VAS: visual analog scale; PGA: patient global assessment; BME: bone marrow edema.

Table 2. Baseline and annual clinical, laboratory, and MRI characteristics according to MRI evidence of erosion progression at 1 year in patients with RA in remission. Values are mean ± SD, unless otherwise indicated.

Characteristics	Baseline			1 Year		
	Progression, n = 19	No Progression, n = 37	p	Progression, n = 19	No Progression, n = 37	p
Clinical variables						
SJC_{66}, median (range)	3 (1–9)	2 (0–4)	0.25	0 (0–0)	0 (0–0)	0.39
TJC_{68}, median (range)	6 (2–16)	3 (1–5.5)	0.052	0 (0–0)	0 (0–0)	1.0
DAS28	4.5 ± 1.5	3.6 ± 1.1	0.050	1.8 ± 0.5	1.9 ± 0.5	0.65
SDAI	22.2 ± 17.2	13.6 ± 8.0	0.050	3.1 ± 2.7	2.4 ± 2.2	0.42
HAQ score	0.684 ± 0.671	0.451 ± 0.412	0.33	0.200 ± 0.287	0.164 ± 0.300	0.61
ESR, < 20 mm/h	28.3 ± 20.9	19.8 ± 13.6	0.13	11.1 ± 8.0	15.5 ± 12.4	0.16
CRP, < 0.8 mg/dl	2.1 ± 2.2	0.6 ± 0.8	0.01	0.3 ± 0.2	0.3 ± 0.2	0.98
VAS pain, 0–100 mm	43.9 ± 22.0	36.1 ± 19.7	0.28	22.1 ± 18.4	20.1 ± 22.5	0.46
PGA, 0–100 mm	42.1 ± 22.3	35.4 ± 18.6	0.34	20.0 ± 19.6	16.3 ± 17.9	0.55
MRI variables						
RAMRIS synovitis (0–21)	6.3 ± 3.4	5.9 ± 2.9	0.71	4.6 ± 2.0	3.7 ± 2.6	0.11
RAMRIS BME (0–69)	8.3 ± 9.4	3.7 ± 6.1	0.09	4.8 ± 5.6	1.4 ± 2.6	0.03
RAMRIS erosion (0–230)	9.9 ± 13.6	5.1 ± 5.1	0.55	13.5 ± 15.0	4.4 ± 5.0	0.001
Total RAMRIS (0–320)	24.5 ± 20.0	14.9 ± 11.9	0.22	23.0 ± 20.2	10.1 ± 9.3	0.001
Tenosynovitis (0–26)	7.0 ± 5.8	6.8 ± 6.7	0.55	3.4 ± 2.8	2.7 ± 4.9	0.059

CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints (tender and swollen); ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; MRI: magnetic resonance imaging; RAMRIS: Rheumatoid Arthritis MRI Score; SDAI: Simplified Disease Activity Index; SJC: swollen joint count in 66 joints; TJC: tender joint count in 68 joints; VAS: visual analog scale; PGA: patient global assessment; BME: bone marrow edema; RA: rheumatoid arthritis.

remission[5,6]. However, the findings of our study are different and suggest that the persistence of higher levels of BME after entering sustained remission rather than baseline levels may explain progression of bone damage in patients with RA who are in sustained clinical remission.

Our study also found that patients in sustained clinical remission showed certain levels of inflammatory activity on MRI not detectable by clinical assessment.

The concept of remission remains complex and several definitions have been proposed. The ACR/EULAR has developed a provisional definition of remission in RA to unify criteria to define remission and to be more stringent[11,12].

Today, remission occurs frequently in RA and has become a main goal of treatment strategies, but it depends strongly on the definition used; in our study the prevalence was 28.5%, similar to previous studies[15].

Nevertheless, several studies have shown that radiographic structural progression may occur over time in some patients with RA classified as being in clinical remission. Usually, remission is evaluated using clinical and biochemical variables and these measures could be insensitive tools in patients with low levels of disease activity.

There are increasing data to support that MRI is more sensitive than clinical examination for detecting joint inflammation, especially subclinical inflammation; moreover it has shown superior sensitivity compared to conventional radiography for detecting erosions in RA[16,17,18].

Indeed, subclinical inflammation was observed on MRI in most patients in clinical remission in our study (96.4% had synovitis and/or BME and/or tenosynovitis). These results are consistent with Brown, *et al*, who found that 96% and 46.4% of patients in clinical remission according to the DAS28 or ACR criteria, respectively, showed synovitis and BME on MRI[6]. Two studies have demonstrated clearly that MRI inflammation is frequent both in patients in clinical remission and in those with low disease activity state, with synovitis and BME on MRI in 95–96.5% and 31.8–35% of the patients, respectively[5,19].

For that reason, it has been suggested that the imaging findings should be included in new criteria to define "true remission"[20].

Different studies have shown that baseline subchondral BME on MRI is the strongest predictor of radiographic progression even when compared to other clinical and imaging variables[21,22,23,24]. Previous histopathological reports have described a cellular infiltrate involving subchondral bone that correlates with MRI BME in RA. Further, increased numbers of osteoclasts and higher receptor activator of nuclear factor-κB ligand expression have been described in these infiltrates, and these findings support the hypothesis of the relationship between MRI BME and the development of bone erosion over time[25,26,27].

However, there are very few studies evaluating the influence of BME in patients with RA in remission or with low disease activity. Gandjbakhch, *et al* reported the predictive value of baseline BME on MRI in the development and progression of erosions in patients in remission or low disease activity[8].

Table 3. Intrareader and interreader agreement on RAMRIS score and tenosynovitis for status and change (2–way random effect model). Values are mean with 95% CI.

MRI Variables	ICC	Measure	Baseline	1 Year	Change
RAMRIS synovitis	ICC intrareader	Reader 1			
		SmICC	0.96 (0.87–0.99)	0.91 (0.60–0.98)	0.76 (0.61–0.97)
		AvmICC	0.98 (0.93–0.99)	0.95 (0.75–0.99)	0.79 (0.63–0.99)
		Reader 2			
		SmICC	0.99 (0.96–0.99)	0.96 (0.81–0.99)	0.85 (0.77–0.99)
		AvmICC	0.99 (0.98–0.99)	0.98 (0.89–0.99)	0.90 (0.84–0.99)
	ICC interreader	SmICC	0.96 (0.86–0.98)	0.94 (0.75–0.98)	0.90 (0.65–0.96)
		AvmICC	0.98 (0.92–0.99)	0.97 (0.85–0.99)	0.87 (0.68–0.95)
RAMRIS BME	ICC intrareader	Reader 1			
		SmICC	0.98 (0.92–0.99)	0.72 (0.60–0.94)	0.71 (0.42–0.98)
		AvmICC	0.99 (0.96–0.99)	0.84 (0.63–0.97)	0.75 (0.46–0.99)
		Reader 2			
		SmICC	0.99 (0.97–0.99)	0.80 (0.27–0.96)	0.78 (0.46–0.95)
		AvmICC	0.99 (0.98–0.99)	0.88 (0.43–0.98)	0.87 (0.51–0.97)
	ICC interreader	SmICC	0.98 (0.95–0.99)	0.99 (0.96–0.99)	0.83 (0.61–0.96)
		AvmICC	0.99 (0.97–0.99)	0.99 (0.98–0.99)	0.86 (0.69–0.99)
RAMRIS erosion	ICC intrareader	Reader 1			
		SmICC	0.99 (0.96–0.99)	0.76 (0.32–0.95)	0.72 (0.52–0.96)
		AvmICC	0.99 (0.98–0.99)	0.86 (0.42–0.97)	0.83 (0.61–0.98)
		Reader 2			
		SmICC	0.98 (0.94–0.99)	0.89 (0.54–0.98)	0.76 (0.60–0.91)
		AvmICC	0.99 (0.97–0.99)	0.94 (0.70–0.99)	0.82 (0.71–0.98)
	ICC interreader	SmICC	0.96 (0.86–0.98)	0.93 (0.69–0.98)	0.69 (0.40–0.86)
		AvmICC	0.98 (0.92–0.99)	0.96 (0.82–0.99)	0.71 (0.46–0.92)
Total RAMRIS	ICC intrareader	Reader 1			
		SmICC	0.99 (0.96–0.99)	0.88 (0.50–0.97)	0.74 (0.32–0.91)
		AvmICC	0.99 (0.98–0.99)	0.93 (0.67–0.98)	0.76 (0.38–0.93)
		Reader 2			
		SmICC	0.97 (0.91–0.99)	0.96 (0.83–0.99)	0.68 (0.40–0.96)
		AvmICC	0.98 (0.95–0.99)	0.98 (0.90–0.99)	0.70 (0.52–0.99)
	ICC interreader	SmICC	0.95 (0.84–0.98)	0.98 (0.92–0.99)	0.91 (0.77–0.96)
		AvmICC	0.97 (0.91–0.99)	0.99 (0.96–0.99)	0.94 (0.81–0.98)
Tenosynovitis	ICC intrareader	Reader 1			
		SmICC	0.98 (0.96–0.99)	0.96 (0.81–0.99)	0.87 (0.60–0.98)
		AvmICC	0.99 (0.98–0.99)	0.98 (0.89–0.99)	0.91 (0.62–0.99)
		Reader 2			
		SmICC	0.98 (0.95–0.99)	0.97 (0.86–0.99)	0.84 (0.56–0.91)
		AvmICC	0.99 (0.97–0.99)	0.98 (0.92–0.99)	0.88 (0.60–0.96)
	ICC interreader	SmICC	0.98 (0.94–0.98)	0.99 (0.94–0.99)	0.92 (0.74–0.98)
		AvmICC	0.99 (0.97–0.99)	0.99 (0.97–0.99)	0.94 (0.82–0.99)

SmICC: single-measure intraclass correlation coefficients; AvmICC: average measure intraclass correlation coefficients; MRI: magnetic resonance imaging; RAMRIS: Rheumatoid Arthritis MRI Score; BME: bone marrow edema.

However, in our study we found higher values of BME in patients with progression of erosions at 1 year compared to patients without progression after sustained remission.

The prevalence of MRI progression of erosions was higher in our study compared to other studies, probably owing to the definition of progression of bone erosions on MRI[8,28]. Gandjbakhch, *et al*, evaluated the progression of bone erosions as the mean change in RAMRIS erosion score higher than the smallest detectable difference (SDD) at 1 year[8]. In contrast, our definition was less strict and we considered progression of bone erosion as an increase of 1 or more units in annual RAMRIS score for erosions compared to baseline. In fact, some studies have shown that the values of SDC (smallest detectable change) or SDD obtained in imaging series could be insensitive for defining relevant progression, because the progression scores of erosions are usually lower than the cutoff values of SDD or SDC[29,30].

All patients in our study were in remission at 1 year and achieved remission during the first year of treatment with sustained remission for at least 6 months. Therefore they were not in remission at baseline and that could also explain the global higher rate of erosion progression found at 1 year.

In our study, the patients in the P group showed statistically higher levels of CRP at baseline and a trend to higher mean scores of disease activity according to DAS28-ESR and SDAI values at baseline when compared to nP patients. The association between these baseline measures of disease activity and radiographic progression over time in early RA has been reported in several studies[31,32]. This association could partially account for the higher erosion progression in our group of progressors. However, in our study, patients achieving remission did so very early after initial treatment, and CRP, DAS28-ESR, and SDAI values analyzed at a single point in time (baseline visit only) are not representative of global disease activity over time. Aletaha, *et al* showed that in patients with RA who are near remission without joint swelling, the average progression in joint damage was similar in patients with high or low CRP values at baseline[33], similarly to our study (median of SJC at 1 yr was 0).

Moreover, there were no statistical differences in MRI variables between both groups at baseline, but we did find significantly higher values for BME at 1 year in the P group compared to nP, and this strongly suggests an association between persistence of BME and progression of erosions.

Many studies have shown a relationship between different factors of progression of joint damage over time such as duration of RA, as well as RF/ACPA positivity or treatments. We did not find significant differences between the 2 groups in the duration of disease or in the percentage of patients with RF or ACPA. Several studies in patients with early RA suggested that low-dose glucocorticoids (alone or combined with DMARD) decrease the progression of structural damage[34,35,36,37]. At the end of our study, around 40% of P and nP were taking low-dose glucocorticoids; there was no statistical difference between these groups. Moreover, patients with progression of bone erosions did not differ from those without progression in terms of type of initial DMARD treatment or use of DMARD or anti-TNF therapy at 1 year.

One study has shown that the patients who achieved a state of remission according the new ACR/EULAR remission had a lower progression of radiological damage at 2 years when compared to DAS28 remission[4]. In contrast to these findings, we found no significant differences in the percentage of patients in remission by DAS28, SDAI, or boolean ACR/EULAR criteria between patients with or without progression of erosions by MRI at 1 year.

Finally, onset of remission (3 or 6 months after initiation of treatment) could also influence progression of erosions. However, the low number of patients reaching remission at 3 months (only 7 of 56) precluded analysis.

Our study has some limitations. The limited number of patients analyzed could account for some of the differences from the results found in other studies related to progression of erosions. Also, in our observational study, patients had active disease at baseline and achieved persistent remission during followup. This might diminish discriminatory power to some degree.

Despite these limitations, our findings showed a significant association of persistence of high values of BME in patients with progressive erosions after sustained remission. This strongly suggests that subclinical inflammation, detected as persistence of BME on MRI, and especially the height of BME score, may explain the structural progression reported in patients with RA in clinical remission. Further longitudinal studies are needed to determine the critical cutoff of BME for the development of erosions or erosion progression in RA. These results also suggest important implications for monitoring BME, to achieve true remission and to facilitate therapy decisions.

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