ACR/EULAR Definitions of Remission Are Associated with Lower Residual Inflammatory Activity Compared with DAS28 Remission on Hand MRI in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine the level of residual inflammation [synovitis, bone marrow edema (BME), tenosynovitis, and total inflammation] quantified by hand magnetic resonance imaging (h-MRI) in patients with rheumatoid arthritis (RA) in remission according to 3 different definitions of clinical remission, and to compare these remission definitions.

Methods. A cross-sectional study. To assess the level of residual MRI inflammation in remission, cutoff levels associated to remission and median scores of MRI residual inflammatory lesions were calculated. Data from an MRI register of patients with RA who have various levels of disease activity were used. These were used for the analyses: synovitis, BME according to the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system, tenosynovitis, total inflammation, and disease activity composite measures recorded at the time of MRI. Receiver-operating characteristic analysis was used to identify the best cutoffs associated with remission for each inflammatory lesion on h-MRI. Median values of each inflammatory lesion for each definition of remission were also calculated.

Results. A total of 388 h-MRI sets of patients with RA with different levels of disease activity, 130 in remission, were included. Cutoff values associated with remission according to the Simplified Disease Activity Index (SDAI) ≤ 3.3 and the Boolean American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) definitions for BME and tenosynovitis (1 and 3, respectively) were lower than BME and tenosynovitis (2 and 5, respectively) for the Disease Activity Score on 28 joints (DAS28) ≤ 2.6. Median scores for synovitis, BME, and total inflammation were also lower for the SDAI and Boolean ACR/EULAR remission criteria compared with DAS28.

Conclusion. Patients with RA in remission according to the SDAI and Boolean ACR/EULAR definitions showed lower levels of MRI-detected residual inflammation compared with DAS28. (First Release July 1 2016; J Rheumatol 2016;43:1631–6; doi:10.3899/jrheum.150849)

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RHEUMATOID ARTHRITIS MAGNETIC RESONANCE IMAGING SCORING

The current primary goals of treatment for patients with rheumatoid arthritis (RA) are to achieve clinical remission or low levels of disease activity, and to reach optimal structural, functional, and quality of life outcomes[1].

Several definitions of remission have been used in clinical practice: modification of the preliminary American Rheumatism Association (ARA) criteria, Disease Activity Score (DAS) and its modification for 28 joints (DAS28), Simplified Disease Activity Index (SDAI), and the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria. The ACR/EULAR provisional definitions of remission (SDAI and Boolean criteria) have demonstrated to be more stringent than the previous criteria[2].

However, some patients in clinical remission assessed by these clinical remission criteria may develop structural joint damage progression on conventional radiography over time[3,4,5].

Advanced imaging techniques such as magnetic resonance

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imaging (MRI) are more sensitive than clinical examination or conventional radiography for detecting synovitis, tenosynovitis, and bone erosions[6,7,8]. In fact, around 95% of patients in clinical remission or low disease activity state (according to DAS28, ACR criteria, or SDAI) continue to have MRI-detected inflammation [synovitis, tenosynovitis, and bone marrow edema (BME)][9,10,11], and this MRI subclinical inflammation may explain the structural progression in some patients with RA despite clinical remission or low disease activity[12,13,14,15].

In our present study, the main objectives were to evaluate the levels of subclinical synovitis, BME, tenosynovitis, and total inflammation quantified by hand MRI (h-MRI), and to compare these values using 3 different definitions of remission.

MATERIALS AND METHODS

Study design. This was a cross-sectional study. To determine the cutoffs associated to remission, we used data from the Centro Radiologia Clínica (CRC)-MRI register of the Hospital del Mar (Barcelona, Spain) of patients with RA (fulfilling the revised 1987 ACR criteria)[16] with different levels of disease activity. Patients from the CRC-MRI register are an appropriate representation of patients with RA [early or established disease and treated with conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and/or biological disease-modifying antirheumatic drugs (bDMARD)]. The study was approved by the local health authorities and the ethics committee. All patients gave written informed consent for the study.

Clinical and laboratory assessment. The following disease and treatment characteristics were recorded: duration of RA, duration of remission, treatment (csDMARD and/or bDMARD), and positivity for rheumatoid factor and/or anticyclic citrullinated peptide antibodies. Clinical and laboratory data were obtained and registered at the same time of MRI acquisition: swollen joint count based on 28 joints (SJC28), tender joint count based on 28 joints (TJC28), visual analog scale (VAS) for pain, patient's VAS global assessment, physician's VAS global assessment, and levels of erythrocyte sedimentation rate (ESR; mm/h) and C-reactive protein (CRP; mg/dl).

The DAS28-ESR, SDAI, and Boolean ACR/EULAR remission criteria were calculated from these data.

Definitions of clinical remission. Three different definitions of clinical remission were used in our study: DAS28-ESR ≤ 2.6, SDAI ≤ 3.3, and the Boolean ACR/EULAR remission criteria requiring SJC28 ≤ 1, TJC28 ≤ 1, CRP ≤ 1 (mg/dl), and patient's global assessment ≤ 1 (on a 0–10 cm VAS scale)[17,18].

MRI acquisition and scoring. MRI of the dominant wrist and the second to fifth metacarpophalangeal (MCP) joints were performed in a 1.5 Tesla Superconductive system (Signa Echo-speed Excite II; General Electric Medical Systems) equipped with a 4-channel knee coil.

Imaging sequences were as follows: axial T1-weighted fast spin-echo (FSE) sequences [repetition time 550 m/s, echo time 15 m/s, slice thickness of 3 mm and slice gap of 0.5 mm, matrix 320 × 224, field of view 160 × 160 mm, 4 number of excitations (NEX)], coronal T1-weighted sequences (repetition time 750 m/s, echo time 10 m/s, slice thickness 3 mm and slice gap of 0.5 mm, matrix 256 × 224, field of view 160 × 160 mm, 2 NEX), coronal T2-weighted FSE sequences with fat suppression (repetition time 2500 m/s, echo time 68 m/s, slice thickness 3 mm, matrix 256 × 224, field of view 160 mm, 3 NEX), and axial T2-weighted FSE sequences with fat suppression (repetition time 3000 m/s, echo time 68 m/s, slice thickness of 3 mm and slice gap of 0.5 mm, matrix 256 × 192, field of view 160 × 160 mm, 4 NEX). After intravenous injection of 0.2 ml/kg of Omniscan contrast agent (GE Healthcare), we also performed the following imaging sequences: coronal T1-weighted FSE sequences with fat suppression (repetition time 525 m/s, echo time 10 m/s, slice thickness 3 mm and slice gap of 0.5 mm, matrix 256 × 224, field of view 160 × 160 mm, 2 NEX) and axial T1-weighted sequences with fat suppression (repetition time 675 m/s, echo time 15 m/s, slice thickness 3 mm and slice gap of 0.5 mm, matrix 256 × 192, field of view 160 × 160 mm, 3 NEX).

Synovitis and BME were defined and scored according to the Outcome Measures in Rheumatology Clinical Trials Rheumatoid Arthritis Magnetic Resonance Imaging Scoring (RAMRIS) recommendations in the wrist and MCP joints. Wrist and finger tenosynovitis was defined as above abnormal postgadolinium enhancement around a tendon in T1-weighted sequences with fat suppression in 13 groups of tendons with synovial sheath. The scoring was grade 0 (absence of enhancement), grade 1 (presence of tenosynovitis with incomplete halo), and grade 2 (presence of tenosynovitis with complete halo); the maximum score was 26[19].

All sets of images were read blinded to patient identity, type of treatment, and clinical or laboratory data by 2 experienced readers (rheumatologist MPL and radiologist AS) with high values of intrareader and interreader reliability[20]. The sets were read independently by each reader and the scores were then averaged.

These inflammatory MRI scorings for BME, synovitis, tenosynovitis, and total inflammation were recorded.

All h-MRI with complete data of RAMRIS synovitis, RAMRIS BME, tenosynovitis scoring, total inflammation, and also complete available clinical and laboratory data obtained at the time of h-MRI were included in our analysis.

Statistical analysis. Baseline observations were reported with descriptive statistics, using medians [interquartile ranges (IQR)] or absolute frequencies as appropriate. Comparisons between the 3 disease activity criteria were tested using independent Student t test for normally distributed data and the Mann-Whitney U test otherwise. Receiver-operating characteristic (ROC) analysis was used to identify the best cutoff point(s) of h-MRI. The validation of the cutoffs was based on the disease activity category by the DAS28-ESR, SDAI, or Boolean ACR/EULAR criteria. The value with optimum balance between sensitivity and specificity were selected for each inflammatory lesion (RAMRIS synovitis 0–21, RAMRIS BME 0–69, tenosynovitis 0–26, and the sum of all 3: total inflammation 0–116) and was made on statistical grounds. All analyses were performed using SPSS for Windows version 18.0 (SPSS). P values < 0.05 were considered statistically significant.

RESULTS

We included in our analysis 388 h-MRI sets with RAMRIS synovitis, RAMRIS BME, tenosynovitis scoring, and values of disease activity at the same time. Two hundred sixty-one h-MRI corresponded to 145 patients with early RA and 127 to 51 patients with established disease.

According to DAS28-ESR, 119 (30.7%) of these h-MRI corresponded to remission. The SDAI and Boolean ACR/EULAR criteria had more stringent definitions of remission: 86 (22.1%) and 82 (21.1%) of these h-MRI corresponded to SDAI ≤ 3.3 and fulfilled the Boolean ACR/EULAR criteria, respectively. Of all 388 h-MRI, 130 (33.5%) fulfilled at least 1 definition of clinical remission (Table 1).

Median (IQR) RAMRIS BME, RAMRIS synovitis, tenosynovitis, and total inflammation on h-MRI were statistically different when comparing h-MRI in clinical remission with h-MRI in active disease state according to the 3 disease activity criteria.

Table 1. Prevalence of h-MRI sets in different states of disease activity. Values are n (%).

Disease Activity State	h-MRI Sets
DAS28-ESR ≤ 2.6	119 (30.7)
DAS28-ESR > 2.6 to ≤ 3.2	55 (14.1)
DAS28-ESR > 3.2 to ≤ 5.1	148 (38.2)
DAS28-ESR > 5.1	66 (17)
SDAI ≤ 3.3	86 (22.1)
SDAI > 3.3 to ≤ 11	92 (23.7)
SDAI > 11 to ≤ 26	150 (38.7)
SDAI > 26	60 (15.5)
Boolean ACR/EULAR criteria	
Yes	82 (21.1)
No	306 (78.9)
Clinical remission	
Yes	130 (33.5)
No	258 (66.5)

h-MRI: hand magnetic resonance imaging; DAS28-ESR: Disease Activity Scores on 28 joints with erythrocyte sedimentation rate; SDAI: Simplified Disease Activity Index; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism.

Prevalence and scoring of MRI inflammatory findings in remission state (h-MRI, n = 130). Despite being in clinical remission, the majority of these 130 h-MRI (95.6%) showed signs of synovitis, BME, and tenosynovitis.

The frequencies of synovitis, BME, and tenosynovitis on h-MRI of patients with RA in remission according to the DAS28-ESR remission definition were 94.1%, 53.8%, and 65.5%, respectively, and some inflammation (total inflammation ≥ 1) was observed in 94.9%. Table 2 illustrates the frequency of h-MRI inflammation activity according to the SDAI and Boolean ACR/EULAR remission criteria. Further, < 5% of the h-MRI corresponded to a complete absence of inflammation (total inflammation = 0). The prevalence of h-MRI with inflammation was not significantly different when the DAS28-ESR, SDAI, or Boolean ACR/EULAR remission criteria were applied.

Median (IQR) RAMRIS score for synovitis was 5 (2–7), for BME was 1 (0–5), for tenosynovitis was 2 (0–5), and for total inflammation was 9 (4–18) on h-MRI in DAS28-ESR remission. While no difference was observed in the median of tenosynovitis with regard to the 3 clinical remission criteria, the median of synovitis, BME, and total inflammation were lower on h-MRI when the SDAI and Boolean ACR/EULAR criteria were used (Table 2).

Cutoff point(s) of the inflammatory MRI lesions using the clinical remission criteria as a gold standard. The ROC curves analysis identified a value of 6 for synovitis and 8 for total inflammation as the best cutoffs points to differentiate between patients with RA in remission or not by all 3 disease activity scores. Cutoffs for BME and tenosynovitis were 2 and 5 for DAS28-ESR ≤ 2.6, respectively. These cutoffs were lower for the SDAI and Boolean ACR/EULAR remission criteria (BME was 1 and tenosynovitis was 3), and no differences in these cutoff points were observed between both the SDAI and the ACR/EULAR remission criteria.

The validity of the inflammatory MRI cutoffs was moderate in all cases with values of sensitivity between 56.5% to 81.0% and specificity between 47.1% to 73.1%. Considering these cutoff points, around 60%–71% of h-MRI were correctly classified (Table 3).

DISCUSSION

Our study evaluated the presence and levels of residual/subclinical inflammation detected by h-MRI in patients with RA classified in remission according to 3 different, widely used clinical remission criteria: DAS28-ESR ≤ 2.6 and the

Table 2. Inflammation findings (prevalence and scoring) on h-MRI in clinical remission: comparison between DAS28-ESR, SDAI, and the Boolean ACR/EULAR criteria. Values are % or median (interquartile range).

Inflammatory h-MRI	DAS28-ESR ≤ 2.6, n = 119	SDAI ≤ 3.3, n = 86	Boolean ACR/EULAR, n = 82
RAMRIS bone edema, 0–69			
Prevalence	53.8	48.8	48.8
RAMRIS score	1 (0–5)	0 (0–4)	0 (0–5)
RAMRIS synovitis, 0–21			
Prevalence	94.1	95.3	95.1
RAMRIS score	5 (2–7)	4 (2–7)	4 (3–7)
Tenosynovitis, 0–26			
Prevalence	65.5	63.9	65.8
RAMRIS score	2 (0–5)	2 (0–5)	2 (0–5)
Total inflammation, 0–116			
Prevalence	94.9	95.3	95.1
RAMRIS score	9 (4–18)	7 (4–18)	7 (4–17.25)

h-MRI: hand magnetic resonance imaging; DAS28-ESR: Disease Activity Scores on 28 joints with erythrocyte sedimentation rate; SDAI: Simplified Disease Activity Index; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging Scoring.

Table 3. ROC analysis: cutoffs for inflammatory h-MRI lesions for the definition of remission. Comparison between DAS28, SDAI, and the Boolean ACR/EULAR criteria.

Inflammatory h-MRI	ROC Analysis	DAS28 ≤ 2.6, n = 119	SDAI ≤ 3.3, n = 86	Boolean ACR/EULAR Remission Criteria, n = 82
RAMRIS bone edema, 0–69	Cutoff point	2	1	1
	S/Sp, %	62.1/53.8	68.9/51.2	68.9/51.2
	PPV/NPV, %	75.2/38.6	83.2/31.9	83.2/31.9
	AUC (95% CI)	0.60 (0.54–0.66)	0.62 (0.56–0.68)	0.60 (0.53–0.67)
RAMRIS synovitis, 0–21	Cutoff point	6	6	6
	S/Sp, %	58.4/63.9	57.0/67.4	56.5/67.1
	PPV/NPV, %	78.5/40.4	86.0/30.9	86.5/29.3
	AUC (95% CI)	0.64 (0.58–0.70)	0.64 (0.58–0.71)	0.63 (0.57–0.70)
Tenosynovitis, 0–26	Cutoff point	5	3	3
	S/Sp, %	59.1/73.1	73.2/60.5	72.2/58.5
	PPV/NPV, %	81.0/38.6	86.7/39.1	86.7/36.1
	AUC (95% CI)	0.71 (0.65–0.76)	0.69 (0.63–0.75)	0.69 (0.63–0.75)
Total inflammation, 0–116	Cutoff point	8	8	8
	S/Sp, %	81.0/47.1	79.1/51.2	78.8/51.2
	PPV/NPV, %	77.6/52.3	85.1/41.1	85.8/39.3
	AUC (95% CI)	0.69 (0.63–0.74)	0.68 (0.62–0.75)	0.67 (0.60–0.73)

ROC: receiver-operating characteristic; h-MRI: hand magnetic resonance imaging; DAS28: Disease Activity Scores on 28 joints; SDAI: Simplified Disease Activity Index; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging Scoring; S: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve.

ACR/EULAR remission criteria, including SDAI ≤ 3.3 and the Boolean approach.

Our study showed that the presence of MRI-detected joint inflammatory lesions was very high and that there were no differences in prevalence according to these 3 different clinical remission criteria. However, patients in remission defined by the more stringent ACR/EULAR remission criteria, both the SDAI and Boolean approach, showed lower levels of MRI-detected residual joint inflammation compared with the DAS28-ESR.

Clinical remission is currently an achievable goal in a majority of patients with RA. Various definitions of RA remission have been described. Some of them are categorical criteria such as the ARA remission or its modifications and the Boolean ACR/EULAR criteria[17,18]. Other definitions of remission are based on composite disease activity indices such as the DAS and its modification based on 28 joint counts (DAS28), the SDAI, or the Clinical Disease Activity Index (CDAI). Different cutoff points have been proposed to define clinical remission using these composite indices. A cutoff value of ≤ 2.6 for DAS28 and a cutoff point of ≤ 3.3 for SDAI are recommended as measures of remission.

However, definitions of remission according to the DAS28, SDAI, or Boolean ACR/EULAR remission criteria may allow for the presence of tender and/or swelling joints or high levels of ESR and/or CRP; thus, they may not be a true measure of absence of inflammation[21,22,23]. True remission should imply total absence of articular or intra-articular inflammation and biological activity related to RA and no progression of joint damage.

Imaging techniques such as MRI and ultrasonography have demonstrated to be more sensitive than clinical examination for detecting joint inflammation[24,25,26]. Krabben, *et al* compared MRI and clinical joint examination at the patient level, and showed that a high proportion of joints with MRI-detected inflammation had no signs of inflammation on clinical examination (the prevalence of some MRI inflammation in clinically non-swollen joints was 27% in MCP joints, 66% in the wrist, and 13% in metatarsophalangeal joints)[25].

Previous studies using MRI assessment in cohorts of patients with RA in clinical remission or low disease activity have revealed subclinical inflammation on h-MRI in most patients, with a prevalence around 95% regardless of the remission criteria used. To our knowledge, Brown, *et al*'s[10] study was the first to demonstrate a high prevalence of synovitis and BME on h-MRI (96% and 46.4%, respectively) in patients with RA in remission using the ARA and/or DAS28 criteria. Since then, new studies have clearly demonstrated that residual/subclinical MRI inflammation is frequent in patients in both clinical remission and low disease activity state (by DAS, SDAI, or DAS28-CRP)[9,10,11,12]. In our study, we observed a similar high prevalence of residual inflammation on h-MRI in patients with RA in clinical remission as in these previous studies even when more stringent remission criteria such as the Boolean ACR/EULAR were applied, thus confirming and extending these observations. Total absence of residual inflammation was found in only less than 5% of patients in remission.

While the prevalence (presence/frequency) of residual/subclinical MRI inflammatory lesions in patients with RA in remission is high and similar regardless of the remission

criteria used, no studies have examined the levels of this MRI-detected residual inflammation comparing different remission criteria. The level of residual clinical activity in patients with RA in remission is partially dependent on the definition of remission used. The SDAI and Boolean ACR/EULAR criteria are considered the more stringent measures of clinical remission compared with DAS28-ESR[26,27,28,29]. Therefore, h-MRI scores for inflammatory lesions should be lower when applying these more stringent criteria.

Gandjbakhch, *et al* reported a tendency for lower frequencies of BME in wrist and/or MCP joints according to the SDAI or CDAI criteria compared with the DAS28-CRP criteria in a cohort of 188 patients with RA fulfilling different clinical remission criteria, whereas no difference in frequencies of synovitis was observed[9]. To our knowledge, no other studies have compared the frequency or median levels (IQR) of inflammation on h-MRI according to the clinical remission criteria used.

In our study, the prevalence of h-MRI presenting BME in at least 1 joint and the medians (IQR) for RAMRIS synovitis, RAMRIS BME, and total inflammation were lower on h-MRI in clinical remission defined by the SDAI and Boolean ACR/EULAR criteria compared with h-MRI in DAS28-ESR remission; however, no statistical significance could be analyzed because of the overlap of the h-MRI scores among these 3 clinical remission criteria. Our study also showed that the best cutoff values associated to remission for BME and tenosynovitis were lower using the SDAI and Boolean ACR/EULAR criteria compared with the DAS28 remission criteria.

Our study has some limitations. Our MRI protocol includes 2-dimensional FSE pulse sequences rather than 3-D gradient echo sequences, and slices of 3-mm thickness and a gap of 0.5 mm are included in coronal and axial sequences. This MRI protocol has been used in all our previous studies, but for studies with patients in remission with lower levels of inflammatory scores, this protocol might need to be adjusted to assure assessment reliability. Because ours is a retrospective study, we could not change these variables, but the same protocol was used for acquisition of all sets of MRI and the technician was always the same.

Our study supports the idea that the ACR/EULAR remission criteria are more stringent than the DAS28 remission criteria, allowing for less MRI-detected residual active joint inflammation. Our data also suggest that MRI could be useful to accurately measure levels of residual joint inflammation and may contribute to defining more stringent remission criteria to avoid progression of joint damage seen in a proportion of patients with RA in clinical remission defined by the DAS28 or ACR/EULAR remission criteria[3,4,5]. This should be evaluated in longitudinal studies.

Indeed, 1 longitudinal study demonstrated that baseline RAMRIS synovitis was a strong predictor of subsequent radiographic progression in patients in clinical remission or low disease activity. The study also identified a cutoff value for RAMRIS synovitis of 5, which was associated with a very low risk of radiographic joint damage progression[30]. However, the study presented some limitations because of the use of different cohorts with different designs and using different MRI units and readers.

Our study showed that the more stringent SDAI and Boolean ACR/EULAR remission criteria are associated with lower levels of residual joint inflammation on h-MRI in patients with RA in remission compared with the DAS28 criteria. The concept of imaging remission could be useful to define more stringent and accurate RA remission criteria, but it is still unclear. More data are needed before including modern imaging techniques such as MRI in the definition of remission in addition to clinical criteria.

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