Structural progression in rheumatoid arthritis remission: can MRI predict it?

Remission has become an achievable goal in rheumatoid arthritis (RA) thanks to a large choice of drug therapies and improvement of treatment strategies. However, the concept of remission is complex, and there are competing definitions based on different sets of clinical criteria. Among RA patients meeting various clinical criteria for remission, radiographic progression is nonetheless frequently observed; evidence suggests that this is associated with subclinical inflammation. Remission criteria should be stringent to ensure that the definition of remission corresponds to the absence of inflammatory activity and risk of radiographic progression. MRI is a validated imaging technique that is more sensitive than clinical examination in detecting subclinical inflammation (e.g., synovitis, osteitis and tenosynovitis) in RA remission. To date, few studies have examined whether MRI can also be used to predict structural progression among RA patients in clinical remission, with conflicting results. Further studies using standardized methods are needed to confirm this predictive capacity and to determine the minimal inflammatory state visible on MRI above which structural progression may occur in RA patients in clinical remission. This could lead to incorporate MRI evaluation in new composite remission criteria. The objective of this review is to evaluate the evidence on the capacity of MRI to predict structural progression in RA patients in remission.

KEYWORDS: MRI ■ radiographic progression ■ remission ■ rheumatoid arthritis

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Definitions of remission in rheumatoid arthritis

Remission is an achievable goal in rheumatoid arthritis (RA). Generally, the concept of remission takes into account three features: absence of inflammatory activity, absence of structural progression and preservation of function [1]. However, various sets of clinical criteria may be used to evaluate these features and there are competing definitions of RA remission (Table 1). The disease activity score (DAS) in 28 joints (DAS28) is the tool most frequently used to define remission, given its ease of use in daily practice [2]. The Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and the new ACR/European League Against Rheumatism criteria for remission are considered to be more stringent [3–5]. The Routine Assessment Of Patient Index Data (RAPID) is another practical questionnaire, mainly used for research purposes [6]. Currently, no definition of remission takes into account disease activity evaluated by imaging methods such as ultrasonography or MRI, despite their high sensitivity in detecting inflammatory activity.

Radiographic structural progression may occur in RA patients in remission

Various studies have demonstrated that radiographic structural progression may nonetheless occur during clinical remission, with estimates ranging from 5 to 33% of patients depending on study and remission criteria used (Table 2). In the SWEFOT trial, 147 patients with low disease activity (LDA) according to DAS28 (DAS28 ≤3.2) were followed-up for 2 years in regular care. While 48% of patients had no radiographic damage at baseline (Van der Heijde-modified Sharp [vHS] = 0), this proportion decreased at 1 year to 26.9%, and 20.2% at 2 years. Despite clinical remission according to DAS28, a change in radiographic scores was found during follow-up: mean (standard deviation) change of the vHS score was 3.96 (7.56) at 1 year and 4.17 (7.28) at 2 years. Similar results were found in RA patients who met SDAI criteria for remission, with a change of the vHS score during follow-up of 3.88 (6.35) at 2 years. Among the 15 patients (15%) who had progression >10 units at 2 years, ten of them were in DAS28 remission [7].

Radiographic structural progression is frequent in RA patients in remission according to DAS criteria, varying from 10 to 33% of the patients. Aletaha *et al.* showed that 31% of 114 patients in remission according to DAS28 had radiographic progression at 1 year [8]. Brown *et al.* observed that 12% of patients in remission according to DAS28 criteria had radiographic progression at 1 year [9]. Similar results were observed in Foltz *et al.*'s study where radiographic progression

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Table 1. Definitions of clinical remission in rheumatoid arthritis.

ACR 81	US FDA	DAS28	DAS44	CDAI	SDAI	ACR/EULAR Boolean	RAPID
Morning stiffness <15mn No fatigue No tender joints No pain with motion No swollen joints/tendons ESR <30 (F), 20 (M) mmH1	ACR 81 remission criteria plus no radiographic progression plus no treatment for at least 6 months	TJC28 SJC28 VAS pat ESR	TJC44 SJC44 VAS pat ESR	TJC28 SJC28 VAS pat VAS phy	TJC28 SJC28 VAS pat VAS phy CRP	TJC ≤1 SJC ≤1 VAS pat ≤1 CRP (mg/dl) ≤1	Questionnaire
Presence of at least five of the six items	–	<2.6	<1.6	≤2.8	≤3.3	All components ≤1	<1

CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease activity score in 28 joints; DAS44: Disease activity score in 44 joints; ESR: Erythrocyte sedimentation rate; EULAR: European League Against Rheumatism; F: Female; M: Male; mmH1: mm at 1 h; RAPID: Routine Assessment Of Patient Index Data; SDAI: Simplified Disease Activity Index; SJC: Swollen joint count; TJC: Tender joint count; VAS pat: Patient visual analog scale; VAS phy: Physician visual analog scale.

at 1 year was shown in nine patients (11%) of 85 patients in remission according to DAS in 44 joints (DAS44) [10].

Flares during follow-up are frequently reported as a possible explanation for radiographic progression in RA patients in remission. However, flares may not be the only explanation, as radiographic progression has been shown to occur in patients with sustained remission. Molenaar *et al.* observed radiographic progression in 7% of the 187 RA patients in sustained remission according to ACR 81 remission criteria and 6% of the patients in sustained remission according to DAS followed during 2 years [11].

Recent studies have shown that remission is more frequently achieved in early rather than established RA [12–14]. However, both early and established RA patients in remission present with structural progression and there is no evidence, to date, to suggest that its occurrence is influenced by disease duration. Cohen *et al.* found structural progression at 5 years in ten (33%) patients with early RA in remission according to DAS44 criteria [15].

Radiographic progression may be explained by subclinical inflammation during remission

The DAS criteria for remission are not considered stringent and do not confirm the absence of inflammatory activity [3,16]. Aletaha *et al.* showed that joint damage is driven by residual swollen joints in RA remission [8].

In patients in DAS28 remission, radiographic progression was observed more frequently in case of remaining swollen joints: 25 (27%) of the patients with a swollen joint count less than 2 had radiographic progression at 1 year compared with 11 (50%) of patients with a swollen joint count equal or greater than 2. In different studies, no statistically significant difference in the frequency of radiographic progression was observed between patients in LDA state and in remission according to DAS [10,17]. In the SWEFOT trial, 147 patients with LDA according to DAS28 (DAS28 ≤3.2) at 3–4 months after start of methotrexate were followed for 2 years in standard care with clinical and radiographic evaluations. No difference in radiographic progression was seen between patients in DAS28 remission and patients with LDA only at 1 and 2 years follow-up (p = 0.63) [7]. Similar results were found in another cohort of 85 patients with LDA (DAS <2.4) or in remission (DAS <1.6) followed for 1 year: no statistical difference was observed in the frequency of radiographic progression between patients in DAS remission and in DAS-LDA (p = 0.73) [10].

The frequency of radiographic progression may vary according to the criteria used to define remission, with a tendency to observe less radiographic progression among patients meeting the more stringent remission criteria such as SDAI and CDAI, compared with those meeting DAS criteria alone. In a cohort of 535 RA patients over 2 years, Lillegraven *et al.* followed 535 RA patients in remission, according to the new ACR/European League Against Rheumatism criteria, over 2 years and have compared the progression of radiographic joint damage among RA patients in remission according to this criteria compared with remission thresholds for SDAI, CDAI and DAS28 C-reactive protein (CRP) in an observational cohort. They found that radiographic progression occurred in 10% of patients in DAS28 CRP remission, and only 7, 5 and 4% of those in remission according to ACR/European League Against Rheumatism Boolean, SDAI and CDAI criteria, respectively [18].

Clinical criteria must be stringent to ensure that the definition of remission corresponds to the absence of inflammatory activity and risk of radiographic progression. The composite clinical scores currently in use, which evaluate only a limited number of joints and which give weight to subjective measures, such as patient visual analog scale activity, have inherent limitations in detecting inflammatory activity. Objective assessments, such as imaging, are more sensitive than clinical examination and may be useful in detecting subclinical disease activity. Highly sensitive imaging techniques could be used in conjunction with clinical criteria to raise the stringency of remission criteria.

The value of MRI in defining remission

MRI can detect subclinical inflammation

MRI is a validated imaging technique valuable in determining inflammatory activity in RA. Most MRI assessments in RA consist of an examination of the hand and wrist (usually dominant hand) to search for inflammatory features (e.g., synovitis, tenosynovitis, osteitis; i.e., bone marrow edema) and structural damage (erosion). OMERACT definitions of the elementary lesions found in MRI are often used in clinical trials. The Rheumatoid Arthritis MRI Scoring System (RAMRIS), which takes into account synovitis, bone marrow edema and erosion in metacarpophalengeal joints and wrists, has been validated and is reliable and sensitive to change [19].

Various studies have shown that MRI is more sensitive than clinical examination in detecting synovitis among RA patients, including those in remission [20,21]. In a study including 52 erosive biological naive patients starting a combination therapy of adalimumab/methotrexate and followed over 1 year, Dohn *et al.* have demonstrated that, despite a decrease of the MRI scores, remaining MRI synovitis and bone edema could be observed during follow-up. In this study, 38% of the patients were in remission according to DAS28 CRP <2.6 at 1 year [22].

Different studies have shown high frequency of inflammatory activity detected by MRI in RA patients in clinical remission. MRI synovitis is present in almost all patients in clinical remission, while MRI bone marrow edema is found in almost a third of the patients. Brown *et al.* observed that synovitis, tenosynovitis and bone marrow edema were observed on MRI of the dominant hand/wrist in 96, 26 and 51.9% of the patients in remission according to DAS28

Table 2. Radiograghic structural progression in rheumatoid arthritis patients in clinical remission.

Study (year)	n	Remission criteria	Disease duration	Treatment	Follow-up (years)	Definition of radiographic progression	Patients with radiographic progression (%)	Ref.
Molenaar *et al.* (2004)	187	ACR remission (n = 97) DAS44 <1.6 (n = 78)	Median: 7 (IQR: 3–12) years	cDMARDs	2	vHS change ≥5 at 2 years	7 6	[11]
Cohen *et al.* (2007)	30	DAS44 <1.6	Mean ± SD: 3.3 ± 2.6 months	cDMARDs	5	vHS change >4.1	33	[15]
Brown *et al.* (2008)	102	Rheumatologist (n = 102) ACR (n = 54) DAS28 (n = 58)		cDMARDs	1	GSS change ≥0.5	19 11 12	[9]
Aletaha *et al.* (2011)	114	DAS28 <2.6	Median: 1 (IQR: 0–18) years	cDMARDs	1	vHS change ≥0.5	31	[8]
Foltz *et al.* (2012)	85	DAS44 <2.4	Mean ± SD: 35 ± 21 months	cDMARDs (96.5%) Biologics (20%)	1	vHS change ≥1	11	[10]
Lillegraven *et al.* (2012)	535	DAS28 <2.6 (n = 106) SDAI <3.3 (n = 37) CDAI <2.8 (n = 26) ACR/EULAR Boolean (n = 30)	Median: 11 (IQR: 4–23) years	cDMARDs (83%) Biologics (38%)	2	vHS change ≥1	30/10† 24/5† 19/4† 20/7†	[18]

†*Values represented as vHS change/≥smallest detectable change.*
CDAI: Clinical Disease Activity Index; cDMARD: Conventional disease-modifying antirheumatic drug; DAS28: Disease activity score in 28 joints; DAS44: Disease activity score in 44 joints; EULAR: European League Against Rheumatism; GSS: Genant-modified Sharp score; IQR: Interquartile range; SD: Standard deviation; SDAI: Simplified Disease Activity Index; vHS: Van der Heidje-modified Sharp score.

and in 96.1, 20.8 and 47.2% of the patients in remission according to ACR criteria [9,23]. Similar results were found by Foltz *et al.*; 85 patients in LDA state (n = 38) or remission (n = 47) according to DAS44 criteria were evaluated by MRI of the hand and wrist according to the RAMRIS system. Synovitis and bone marrow edema were detected in 37 (97.4%) and 13 (34.2%) patients in LDA, and 45 (95.7%) and 14 (29.8%) patients in remission, respectively, without statistical difference between the two groups [10]. A recent international study merging six cohorts from five centers confirmed high frequency of MRI inflammation in patients in clinical remission or LDA state according to DAS28 CRP; MRI synovitis and osteitis – that is, bone marrow edema – were detected in 208 (95%) and 78 (35%) of the 294 patients included in this study [17]. No statistical difference was seen between patients in remission and patients in LDA without remission (synovitis and osteitis present in 96 and 35% of the patients in LDA and in 91 and 36% of the patients in remission, respectively). A tendency towards lower frequencies of MRI osteitis in patients in remission according to SDAI or CDAI compared with DAS28 score was observed.

Can MRI predict structural progression in RA patients in clinical remission?

In active RA, bone marrow edema and synovitis detected on MRI have been shown to be predictive factors for radiographic progression [24]. In the CIMESTRA cohort, including 139 patients with early RA, MRI-bone marrow edema, total vHS score and anti-CCP predicted radiographic progression at 5 years [25]. On the contrary, improvement in MRI bone edema has been found to be associated with protection from structural progression using tight control in early RA [26].

As MRI allows for the detection of subclinical inflammation, studies have begun to examine the predictive value of MRI in predicting structural progression among RA patients in remission (Table 3). Controversal results were found in two studies aiming to evaluate MRI predictive factor of structural progression evaluated on x-rays at 1 year in two cohorts of RA patients in remission. Using a 1.5 T high-field MRI with contrast gadolinium injection, Brown *et al.* showed that MRI synovitis is an independent predictive factor for radiographic progression among RA patients in remission according to a rheumatologist's opinion (OR: 2.98; 95% CI: 1.49–5.97; p = 0.002) [9]. However, in a study using a 0.2 T low-field MRI with gadolinium injection among RA patients in DAS44 remission, Foltz *et al.* found that, none of the OMERACT RAMRIS items (MRI synovitis score, MRI bone marrow edema score and MRI erosion score at baseline) correlated with radiographic progression of hand and feet (vHS score) at 1 year [10].

The discrepancy in these results may be explained by the use of different definitions

Table 3. MRI predictive value for structural progression.

Study (year)	n	Remission criteria	Follow-up (year)	Structural progression	Location	Definition of structural progression	Patients with radiographic progression (%)	MRI predictive value	Ref.
Brown *et al.* (2008)	102	Rheumatologist's opinion	1	X-rays	Hands and feet	GSS change ≥0.5	19	MRI synovitis (OR: 2.98; 95% CI: 1.49–5.97; p = 0.002)	[9]
Foltz *et al.* (2012)	85	DAS44 <2.4	1	X-rays	Hands and feet	vHS change ≥1	11	No association between MRI at baseline and structural progression	[10]
Gandjbakhch *et al.* (2011)	85	DAS44 <2.4	1	MRI	Dominant hand	RAMRIS erosion change > SDD	5	MRI osteitis (OR: 1.25; 95% CI: 1.09–1.43; p = 0.0013)	[27]

DAS44: Disease activity score in 44 joints; GSS: Genant-modified Sharp score; OR: Odds ratio; RAMRIS: Rheumatoid Arthritis MRI Scoring System; SDD: Smallest detectable change; vHS: Van der Heidje-modified Sharp score.

of remission and the use of different imaging procedures. In the study performed by Brown *et al.* remission was defined according to the rheumatologist's opinion [9]. In total, 61 (57%) and 59 (55%) of the patients were in remission according to DAS28 and ACR criteria, respectively. In the study performed by Foltz *et al.* all patients were in LDA (n = 38) or in remission (n = 47) according to DAS44 [10]. We can consider that remission according to the rheumatologist's opinion is a less stringent criteria than DAS. The definitions of radiographic progression differed between the two studies and could contribute to the discrepancies of the results. For Brown *et al.*, radiographic progression was defined according to a change of the Genant modified Sharp score ≥0.5, while for Foltz *et al.*, radiographic progression was defined according to a change of the vHS score ≥1. Moreover, MRI capacity for predicting structural progression was observed on individual joints in Brown *et al.*'s study, while Foltz *et al.* examined the MRI capacity for predicting structural progression based on the change of total vHS score at the patient level. The use of different MRI equipment may participate in the discrepancies of the results too.

Both of these studies included large number of patients (102 and 85), and used standardized and blinded evaluation of x-rays and MRI by experienced readers. However, in both studies, MRI evaluation was limited to wrist and MCP of the dominant hand, while radiographic progression was assessed on both hands and feet. MRI evaluation of both hands may be more valuable in predicting radiographic structural progression and further studies are necessary to evaluate this. A lack of power could also explain the discrepancies of the results. In both studies, patients were followed-up for 1 year. Longer follow-up could be useful in order to increase the number of patients with structural progression.

In an observational study of 85 RA patients in LDA state or remission according to DAS44, predictive factors for MRI structural progression at 1 year were evaluated using 0.2 T low-field MRI with gadolinium injection. Structural damage progression was evaluated by using the OMERACT RAMRIS MRI erosion score with MRI evaluation of hand and wrist at baseline and 1 year. In this study, Gandjbakhch *et al.* demonstrated that bone marrow edema appeared as a predictive factor of MRI structural progression, as the odds of structural progression were 25% higher among patients with bone marrow edema visible on MRI (OR: 1.25; 95% CI: 1.09–1.43; p = 0.0013) [27].

Conclusion

Currently, several studies have confirmed that inflammatory activity on MRI is frequent among RA patients in remission. However, only three studies to date have examined whether and how subclinical inflammation visible on MRI can be used to predict structural progression and there is insufficient evidence to assert the value of MRI in predicting structural progression in RA patients in remission as results are controversial.

Future perspective: a new definition of remission taking into account MRI?

Further studies are needed to confirm this predictive potential, as well as to determine the level of subclinical inflammation visible on MRI which could discriminate RA patients with or without risk of structural progression during remission. These data could be used to create new composite criteria taking into account both clinical factors and subclinical inflammation on MRI to define remission.

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Executive summary

- Radiographic structural progression may occur despite clinical remission.
- Inflammatory activity on MRI is frequent among rheumatoid arthritis patients in clinical remission may have a role to explain structural progression.
- Only few studies evaluated the predictive value of MRI for structural progression and results remain controversial.
- Further studies are needed to confirm this predictive potential, as well as to determine the MRI minimal acceptable inflammatory activity state above which structural progression may occur.

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