Determining a Magnetic Resonance Imaging Inflammatory Activity Acceptable State Without Subsequent Radiographic Progression in Rheumatoid Arthritis: Results from a Followup MRI Study of 254 Patients in Clinical Remission or Low Disease Activity

Frédérique Gandjbakhch, Espen A. Haavardsholm, Philip G. Conaghan, Bo Ejbjerg, Violaine Foltz, Andrew K. Brown, Uffe Møller Døhn, Marissa Lassere, Jane E. Freeston, Inge Christoffer Olsen, Pernille Bøyesen, Paul Bird, Bruno Fautrel, Merete Lund Hetland, Paul Emery, Pierre Bourgeois, Kim Hørslev-Petersen, Tore K. Kvien, Fiona M. McQueen, and Mikkel Østergaard

ABSTRACT. ***Objective***. To assess the predictive value of magnetic resonance imaging (MRI)-detected subclinical inflammation for subsequent radiographic progression in a longitudinal study of patients with rheumatoid arthritis (RA) in clinical remission or low disease activity (LDA), and to determine cutoffs for an MRI inflammatory activity acceptable state in RA in which radiographic progression rarely occurs.

Methods. Patients with RA in clinical remission [28-joint Disease Activity Score-C-reactive protein (DAS28-CRP) < 2.6, n = 185] or LDA state (2.6 ≤ DAS28-CRP < 3.2, n = 69) with longitudinal MRI and radiographic data were included from 5 cohorts (4 international centers). MRI were assessed according to the Outcome Measures in Rheumatology (OMERACT) RA MRI scoring system (RAMRIS). Statistical analyses included an underlying conditional logistic regression model stratified per cohort, with radiographic progression as dependent variable.

Results. A total of 254 patients were included in the multivariate analyses. At baseline, synovitis was observed in 95% and osteitis in 49% of patients. Radiographic progression was observed in 60 patients (24%). RAMRIS synovitis was the only independent predictive factor in multivariate analysis. ROC analysis identified a cutoff value for baseline RAMRIS synovitis score of 5 (maximum possible score 21). Rheumatoid factor (RF) status yielded a significant interaction with synovitis (p value = 0.044). RF-positive patients with a RAMRIS synovitis score of > 5 vs ≤ 5, had an OR of 4.4 (95% CI 1.72–11.4) for radiographic progression.

Conclusion. High MRI synovitis score predicts radiographic progression in patients in clinical remission/LDA. A cutoff point for determining an MRI inflammatory activity acceptable state based on the RAMRIS synovitis score was established. Incorporating MRI in future remission criteria should be considered. (First Release Dec 15 2013; J Rheumatol 2014;41:398-406; doi:10.3899/jrheum.131088)

Key Indexing Terms:
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From the Department of Rheumatology, Pitie Salpetriere Hospital, APHP, Université Paris 6-UPMC, Paris, France; Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and UK National Institute for Health Research (NIHR) Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK; Department of Rheumatology, Slagelse Hospital, Slagelse, Denmark; Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway; Hull York Medical School, University of York, York, UK; Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup Hospital, Copenhagen, Denmark; and Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; St. George Hospital, University of NSW, Sydney, Australia; King Christian X's Hospital for Rheumatic Diseases, University of Southern Denmark, Odense, Denmark; and Department of Molecular Medicine and Pathology, Faculty of Medicine and Health Sciences, University of Auckland, Auckland, New Zealand.

Dr. Conaghan has been a speaker or on advisory boards for BMS, Janssen, Merck, Pfizer, and Roche.

F. Gandjbakhch, MD, Practicing Rheumatologist, Department of Rheumatology, Pitie Salpetriere Hospital, APHP, Université Paris 6-UPMC; E.A. Haavardsholm, MD, PhD, Postdoctoral Researcher, Department of Rheumatology, Diakonhjemmet Hospital; P.G. Conaghan, MB, BS, PhD, FRACP, FRCP, Professor of Musculoskeletal Medicine, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit; B. Ejbjerg, MD, PhD, Consultant Rheumatologist, Department of Rheumatology, Slagelse Hospital; V. Foltz, MD, Practicing

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Rheumatologist, Department of Rheumatology, Pitie Salpetriere Hospital, APHP, Université Paris 6-UPMC; A.K. Brown, MB, ChB, MRCP, PhD, Hull York Medical School, University of York; U.M. Døhn, MD, PhD, Senior/Registrar, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Copenhagen University Hospital Glostrup; M. Lassere, MBBS(Hons), PhD, Grad Dip Epi, FRACP, FAFPHM, Professor of Medicine, St. George Hospital, University of NSW; J.E. Freeston, MA, MD, MRCP, Senior Lecturer and Honorary Consultant Rheumatologist, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit; I.C. Olsen, PhD, Biostatistician, Department of Rheumatology, Diakonhjemmet Hospital; P. Bøyesen, MD, PhD, Senior Registrar, Department of Rheumatology, Diakonhjemmet Hospital; P. Bird, BMed (Hons), FRACP, PhD, Grad Dip MRI, Senior Lecturer, University of NSW; B. Fautrel, MD, PhD, Associate Professor in Medicine, Department of Rheumatology, Pitie Salpetriere Hospital, APHP, Université Paris 6-UPMC; M.L. Hetland, MD, PhD, DMSc, Consultant and Senior Lecturer in Rheumatology, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup Hospital, and Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen; P. Emery, MA, MD, FRCP, ARC Professor in Rheumatology, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds and NIHR Leeds Musculoskeletal Biomedical Research Unit.

Drs. Gandjbakhch and Haavardsholm contributed equally to this work.

Address correspondence to Dr. Haavardsholm, Diakonhjemmet Hospital, Box 23 Vindern, 0319 Oslo, Norway; E-mail: e.a.haavardsholm@medisin.uio.no

Radiographic progression is an important measure of damage in rheumatoid arthritis (RA), and is related to longterm functional impairment[1,2,3,4]. In patients with active RA, magnetic resonance imaging (MRI)-detected synovitis and osteitis (bone marrow edema) are strong predictors of future radiographic progression[5,6,7,8,9]. According to the recent European League Against Rheumatism and American College of Rheumatology (ACR) guidelines, clinical remission should be the main goal of therapy in RA, with low disease activity (LDA) being an acceptable alternative in more longstanding/established disease[10,11,12,13].

The treatment of RA has advanced considerably over the last decade, especially with the introduction of biologic agents[14] and optimization of treatment strategies[13,15,16,17,18]. However, several studies have shown that radiographic structural progression may still occur despite clinical remission or LDA state[19,20,21,22]. MRI improves the evaluation of disease activity beyond clinical examination[23], and MRI-detected "subclinical inflammation" has been shown to be present in a large proportion of patients in remission or LDA state[24,25,26,27]. MRI findings in such patients have, based on univariate analyses, been reported to be predictive of future radiographic progression[20,25,27]. However, further studies, including multivariate analysis of the independent predictive value of different features, are still needed to clarify the association between MRI inflammatory lesions and radiographic progression in RA remission and LDA state. It is not known whether there is a threshold for MRI inflammation, i.e., an MRI inflammatory activity "acceptable state" that discriminates between patients in remission/LDA state with or without risk of radiographic progression.

The objective of the present longitudinal study of patients in clinical remission or LDA, including clinical, biochemical, MRI, and radiographic assessments, was to determine predictive factors for radiographic structural progression. Further, we aimed to determine cutoffs for a putative MRI inflammatory activity "acceptable state" in RA in which radiographic progression will rarely or never occur.

MATERIALS AND METHODS

The dataset used in this study has been described in detail in a cross-sectional study[27]. A brief outline is given below.

Patients. Databases from 5 different cohorts were collected from 4 international centers (Table 1). The inclusion criteria for this combined cohort, the Outcome Measures in Rheumatology (OMERACT) Rheumatoid arthritis Acceptable disease activity State (ORAS) cohort were as follows: patients had to fulfill the ACR 1987 criteria[28], be in clinical remission [defined as Disease Activity Score 28 (DAS28-C-reactive protein (CRP) < 2.6] or LDA state (defined as 2.6 ≤ DAS28-CRP < 3.2), and have available MRI data at baseline and radiographic data at baseline and followup. Patients could be treated with synthetic and/or biologic disease-modifying antirheumatic drugs (DMARD). Clinical data [age, sex, disease duration in years, treatment, tender joint count (TJC28), swollen joint count (SJC28), patient visual analog scale (VAS) global assessment, physician VAS global assessment] and laboratory tests [erythrocyte sedimentation rate, CRP, rheumatoid factor (RF), and anticyclic citrullinated peptide (anti-CCP) antibodies at baseline] were collected. DAS28-CRP, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), and proportions of patients in clinical remission and LDA state were calculated for the different composite indices. The previous cross-sectional study including these cohorts described MRI characteristics of the patients with RA in LDA or clinical remission[27]. Seven patients from the Sydney cohort described in the cross-sectional analyses were not included in the current longitudinal analysis, because of different timepoints for followup and the lack of wrist MRI. All patients from the 5 remaining cohorts with available MRI data at baseline and radiographic data at baseline and followup were included in our present study.

MRI acquisition and scoring. An overview of MRI acquisition characteristics in the different cohorts is provided in Table 1. MRI of unilateral wrist and/or metacarpophalangeal (MCP) joints 2–5 were acquired. Synovitis, erosion, and osteitis were defined and scored semiquantitatively according to the OMERACT RAMRIS system[29,30,31,32,33]. By adding scores from the individual joint regions, MRI sum scores for synovitis were calculated [(wrist: 0–9/MCP: 0–12/wrist + MCP: 0–21); osteitis: 0–45/0-24/0–69; and bone erosion: 0–150/0-80/0–230]. The sum score of wrist and MCP were used when available (HURRAH, CIMESTRA, LEEDS, LAFRAME cohorts). In one cohort (ERA, n = 23), only wrist MRI evaluation was available. No adjustment for the scores was made.

Radiographic acquisition and scoring. Timepoints, radiographic scoring systems, and anatomical coverage in the different cohorts are summarized in Table 1. All radiographs were scored using Sharp-derived scoring methods: in 4 studies, the modified Sharp/van der Heijde score (SvdH) was used and in 1 study the Genant modified Sharp score was used[34,35,36,37]. These scoring systems evaluate erosions and joint space narrowing (JSN) separately for hands and feet, and total scores are the sum of erosion and JSN scores. Because the SvdH and the Genant modified Sharp score are comparable in detecting radiographic progression[38] and both demonstrate very good intrarater and interrater reliability[39], no adjustment for the scores was made for the current analysis.

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Table 1. Overview of the individual cohorts.

Center	Cohort Name	No. Patients, n = 294	MRI Equipment	Field Strength, Tesla	Joints	MRI Side	MRI Sequences	Scoring System	Radiographs Timepoints	Radiographs Joints	Radiographs Scoring System
Copenhagen	HURRAH	21	Philips Panorama	0.6	Wrist MCP	Hand with erosion	T1 pre gad without FS (cor, axial); T1 FS post gad (axial); STIR (cor)	RAMRIS	M0 M6	HF	SvdH
Copenhagen	CIMESTRA	84	Esaote C-scan Siemens Impact, Siemens Vision	0.2–1.5	Wrist MCP	Nondominant	T1 pre gad without FS (cor, axial); T1 post gad without FS (cor, axial); STIR (cor)	RAMRIS	M0 M6	HF	SvdH
Leeds	REMISSION	81	Philips Gyroscan	1.5	Wrist MCP	Dominant	T1 and T1 spectral presaturation with inversion recovery post gad (cor, axial)	RAMRIS	M0 M12	HF	Genant
Oslo	ERA	23	General Electric Signa	1.5	Wrist	Dominant	T1 pre gad without FS (cor, axial); T1 post gad without and with FS (cor, axial); STIR (cor); 3D-SPGR	RAMRIS	M0 M6	H	SvdH
Paris	LAFRAME	78	Esaote C-scan	0.2	Wrist MCP	Dominant	3D T1 without FS pre gad (cor, axial); 3D T1 without FS post gad (cor, axial); STIR (cor, axial)	RAMRIS	M0 M12	HF	SvdH

Cor: coronal; gad: gadolinium; FS: fat saturation; MCP: metacarpophalangeal; SE: spin echo; STIR: short-tau inversion recovery; T1: T1-weighted; 3D-SPGR: 3 dimensional spoiled gradient echo; M0: baseline; M6: 6 months; M12: 12 months; HF: hands and feet; H: hands; SvdH: modified Sharp/van der Heijde score; Genant: Genant modified Sharp score; MRI: magnetic resonance imaging.

Statistical analyses. Data were analyzed using SAS software, version 9.3. The 5 cohorts were evaluated for radiographic structural progression after 6 months (HURRAH, CIMESTRA, ERA) or 12 months of followup (LEEDS and LAFRAME). No adjustments were performed to account for the length of radiographic followup. In the description of patient characteristics, continuous variables were assessed using mean and SD or median and interquartile range (IQR) as appropriate. Categorical variables were described as percentages. Differences between cohorts were assessed using nonparametric Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables.

Conditional logistic regression analyses (stratified per cohort) were performed to determine predictive factors for radiographic progression. Radiographic progression was defined as a change of total Sharp score between baseline and followup ≥ 1. We examined these baseline variables as possible explanatory variables: age, disease duration, DAS28-CRP, CDAI, SDAI, RAMRIS synovitis, RAMRIS erosion, RAMRIS osteitis, sex, cohort, RF, anti-CCP, synthetic DMARD, biologic DMARD, disease activity (LDA/remission), early RA (> 1 yr duration at inclusion).

The following steps were undertaken to determine predictors of radiographic progression: (1) univariate regression with baseline covariates as stated above; (2) multivariate stepwise (entry level 0.4, exit level 0.05) regression including variables with $p < 0.4$ in the univariate analysis; (3) receiver-operating characteristics (ROC) curve and model fit [Akaike's information criteria (AIC)] analyses to identify the best cutoff point(s) of the selected continuous variables; the optimal cutoff point was chosen according to low AIC and closeness to the (0-1) corner of the ROC curve; (4) analysis with the identified cutoff point(s) in the model; (5) identification of possible interaction (subgroup) effects; several possible effects were included such as disease activity (low/remission), biologic/DMARD treatment, and RF; the cutoff point(s) were re-evaluated with respect to interactions; and (6) final model with interaction effects.

RESULTS

Patient characteristics. Two hundred fifty-four out of the 287 patients with longitudinal data were included in the current analysis (33 patients were excluded because of missing information on followup radiographs). Of the 33 excluded patients, 25 were in clinical remission while 8 were in an LDA state. The patients' characteristics are summarized in Table 2. Comparisons between cohorts show a high degree of heterogeneity across the variables.

MRI findings at baseline. MRI characteristics at baseline have been described and demonstrated that MRI inflammatory activity was observed in the majority of the patients[27]. Of the 254 patients included in this analysis, synovitis was observed in 95% of patients and osteitis in 49%. Median (IQR) RAMRIS synovitis and osteitis scores at baseline were 6 (3–9) and 0 (0–5), respectively.

Predictors of radiographic progression. Sixty patients (24%) had radiographic progression between baseline and followup. Of these 60 patients, 39 (65%) were in remission (DAS28-CRP < 2.6) and 21 (35%) were in LDA without remission (2.6 ≤ DAS28-CRP < 3.2) at baseline, i.e., 21% of

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Table 2. Baseline characteristics of patients. Values are median (interquartile range) for continuous variables and number (%) for categorical variables.

Cohort	CIMESTRA Copenhagen, n = 84	HURRAH Copenhagen, n = 21	REMISSION Leeds, n = 81	ERA Oslo, n = 23	LAFRAME Paris, n = 78	Total, n = 287	p*
Age, yrs	52 (41–63)	64 (55–71)	57 (46–65)	53 (45–58)	54 (41–60)	55 (43–63)	0.006
Disease duration, yrs	0.7 (0.7–0.83)	5.0 (3.0–11.0)	6.0 (4.0–9.0)	0.7 (0.6–0.9)	2.8 (1.8–3.8)	2.3 (0.8–5.0)	< 0.001
Early RA, < 1 yr	84 (100)	0 (0)	0 (0)	19 (83)	11 (14)	114 (40)	< 0.001
Female	NA	12 (57)	55 (68)	16 (70)	63 (81)	146 (72)	0.111
RF-positive	54 (64)	15 (71)	32 (40)	12 (52)	49 (63)	162 (56)	0.005
Anti-CCP antibodies-positive	52 (62)	NA	NA	NA	48 (62)	100 (54)	0.96
Erosive on radiograph	55 (68)	21 (100)	36 (45)	16 (70)	59 (76)	187 (66)	< 0.001
DMARD	84 (100)	19 (90)	76 (100)	21 (91)	78 (100)	278 (99)	< 0.001
Biologics	0 (0)	21 (100)	5 (6)	0 (0)	16 (21)	42 (15)	< 0.001
Oral corticosteroids	0 (0)	5 (24)	1 (1)	8 (35)	36 (46)	50 (25)	< 0.001
DAS28-CRP	2.1 (1.5–2.8)	2.2 (2.0–2.6)	1.9 (1.5–2.4)	2.3 (1.8–2.6)	2.4 (2.1–2.7)	2.2 (1.8–2.6)	< 0.001
SDAI	1.5 (1.0–2.0)	NA	2.0 (1.0–2.0)	2.0 (1.0–2.0)	NA	3.9 (2.0–6.5)	0.068
CDAI	1.0 (1.0–2.0)	NA	2.0 (1.0–2.0)	2.0 (1.0–2.0)	NA	3.2 (1.5–5.8)	0.002
RAMRIS erosion	1.0 (0–3)	16.0 (10–21)	11.0 (7–21)	9.0 (4–11)	7.5 (6–11)	7.0 (2–12)	< 0.001
RAMRIS synovitis	4.0 (2–6)	13.0 (9–16)	4.0 (2–7)	4.0 (3–5)	6.0 (3–9)	5.0 (3–8)	< 0.001
RAMRIS osteitis	0.0 (0–0)	3.0 (1–8)	5.0 (2–11.5)	2.0 (0–3)	0.0 (0–0)	0.0 (0–4)	< 0.001

* Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables. RA: rheumatoid arthritis; anti-CCP: anticyclic citrullinated peptide antibody; DMARD: disease-modifying antirheumatic drugs; DAS28-CRP: Disease Activity Score 28 joints based on C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging Score; NA: not available; RF: rheumatoid factor.

patients in remission and 31% of patients in LDA progressed. Univariate analysis (Table 3) showed a significant association between radiographic progression and baseline RAMRIS synovitis (p = 0.01), with a trend toward an association between baseline disease activity state and subsequent radiographic progression (LDA vs remission,

Table 3. Search for predictive factors of radiographic progression: univariate analysis.

Explanatory Variables	OR (95% CI)	p
Cohort*		< 0.01**
HURRAH cohort vs REMISSION cohort	0.99 (0.29–3.41)	0.99
CIMESTRA cohort vs REMISSION cohort	0.44 (0.16–1.21)	0.11
ERA cohort vs REMISSION cohort	0.67 (0.17–2.57)	0.55
LAFRAME cohort vs REMISSION cohort	3.39 (1.62–7.12)	< 0.01
Age, per year	1.01 (0.99–1.04)	0.23
Disease duration, per year	0.99 (0.92–1.06)	0.75
Early RA, ≥ 1 yr vs < 1 yr	1.25 (0.35–4.48)	0.36
Female vs male	1.44 (0.66–3.2)	0.36
Rheumatoid factor, positive vs negative	1.38 (0.73–2.61)	0.32
Anti-CCP antibodies, positive vs negative	1.15 (0.51–2.61)	0.73
DMARD, yes vs no*	—	NS***
Biologics, yes vs no	1.55 (0.50–4.78)	0.45
DAS28-CRP, per unit	1.27 (0.70–2.31)	0.43
DAS28-CRP, low activity vs remission	1.69 (0.87–3.31)	0.11
SDAI, per unit	1.01 (0.88–1.12)	0.89
CDAI, per unit	0.96 (0.83–1.12)	0.61
RAMRIS erosion, per unit	1.00 (0.98–1.03)	0.80
RAMRIS synovitis, per unit	1.12 (1.03–1.22)	0.01
RAMRIS osteitis, per unit	1.01 (0.96–1.05)	0.68

* Analyses without cohort stratification. All other analyses with conditional logistic regression stratified by cohort. ** Test of overall cohort effect. *** No OR estimate available because of low separation (almost all patients were taking DMARD). Evaluated using Fisher's exact test. RA: rheumatoid arthritis; anti-CCP: anticyclic citrullinated peptide antibody; DMARD: disease-modifying antirheumatic drugs; DAS28-CRP: Disease Activity Score 28 joints based on C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging Score.

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p = 0.11). In the multivariate analysis stratified by cohort, the stepwise selection procedure resulted in RAMRIS synovitis being the only significant independent predictor variable associated with radiographic progression (OR 1.12, 95% CI 1.03–1.22).

Identifying an MRI inflammatory activity acceptable state. Evaluations were done of sensitivity, specificity, positive and negative predictive value, and AIC for different cutoffs (Table 4). These analyses suggested that the best cutoff to discriminate patients with and without risk of radiographic progression was a RAMRIS synovitis score of 5 or 6. The ROC curve for radiographic progression according to RAMRIS synovitis score at baseline in the total population had an area under the curve of 0.64 (95% CI 0.55–0.72 p < 0.01; Figure 1). Possible interactions between RAMRIS synovitis, dichotomized according to cutoffs of 5 and 6, and other variables were investigated. No interaction was found for inflammatory activity at baseline according to DAS28-CRP or disease duration. A significant interaction was found between RAMRIS synovitis with a cutoff at 5 and RF status (p = 0.04). This interaction model gave the best overall model fit according to AIC (see Table 4). ROC curves for RAMRIS synovitis according to RF status are presented in Figure 1, demonstrating better predictive value for RF-positive patients. New multivariate analyses taking into account these new binary variables instead of continuous RAMRIS synovitis score were then performed in the overall population and in the subgroup populations according to RF status (Table 5). A RAMRIS synovitis score > 5 at baseline discriminated well between patients with or without risk of radiographic progression and had a high predictive value for radiographic progression in multivariate analyses with an OR at 4.41 (95% CI 1.72-11.35) for RF-positive patients, stratified by cohort.

Table 4. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for radiographic progression according to different cutoffs of RAMRIS synovitis at baseline. AIC (Akaike's information criteria) for model without and with the interaction with rheumatoid factor (RF) status.

		RAMRIS Synovitis (without RF interaction)				RAMRIS Synovitis (with RF interaction)
Cutoff	Sensitivity	Specificity	PPV	NPV	AIC	AIC
8	0.35	0.80	0.36	0.80	216.9	218.9
7	0.44	0.75	0.36	0.81	214.0	216.1
6	0.56	0.68	0.35	0.83	212.7	213.5
5	0.64	0.60	0.33	0.84	213.2	212.1*
4	0.70	0.54	0.32	0.85	213.6	212.5
3	0.79	0.39	0.29	0.85	215.6	217.0
2	0.86	0.26	0.26	0.85	215.6	218.3

* Final model with lowest AIC (see Table 5 for sensitivity, specificity, and PPV and NPV for this model in both RF-positive and RF-negative patients; with OR adjusted for cohort effect). RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging Score; RF: rheumatoid factor.

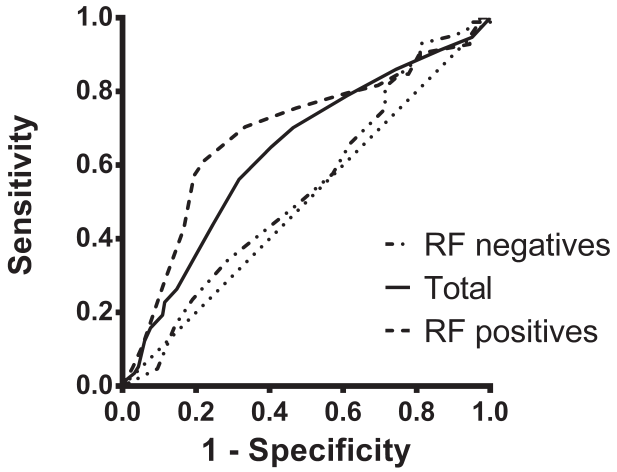


Figure 1. Receiver-operating characteristic curve for Rheumatoid Arthritis Magnetic Resonance Imaging Score synovitis at baseline and prediction of radiographic progression in the total population/rheumatoid factor (RF) negatives/RF positives.

DISCUSSION

This large international multicenter study confirms that progression of joint damage occurs in a significant proportion of patients with RA in clinical remission or LDA state. The OMERACT RAMRIS synovitis score was identified as a significant independent predictor of this progression, and we have identified a cutoff point for an MRI inflammatory activity acceptable state in RA clinical remission and LDA state, below which radiographic erosive progression rarely occurs.

Modern imaging techniques [ultrasonography (US) and MRI] have proven to be more sensitive than clinical examination for detection of synovitis in RA[23,40,41], and several previous studies have shown that MRI inflammation (termed "subclinical") is frequent both in patients in clinical remission and in LDA state[20,24,25]. In our present study including 254 patients, MRI synovitis and osteitis were frequent and observed in wrist and/or MCP joints in 95% and 49% of the patients, respectively. Previous studies have

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Table 5. Predictive value of RAMRIS synovitis for radiographic progression above the best cutoffs at baseline.

	Entire Population	RF-positive Patients	RF-negative Patients
RAMRIS synovitis > 5	OR 2.42 (1.24–4.72)* Sensitivity: 0.64 Specificity: 0.60 PPV: 0.33 NPV: 0.84	OR 4.41 (1.72–11.35)* Sensitivity: 0.78 Specificity: 0.61 PPV: 0.42 NPV: 0.88	OR 1.09 (0.40–2.80)* Sensitivity: 0.43 Specificity: 0.58 PPV: 0.20 NPV: 0.80
RAMRIS synovitis > 6	OR 2.55 (1.29–5.05)* Sensitivity: 0.56 Specificity: 0.68 PPV: 0.35 NPV: 0.83	OR 3.90 (1.56–9.76)* Sensitivity: 0.67 Specificity: 0.70 PPV: 0.45 NPV: 0.85	OR 1.39 (0.49–3.91)* Sensitivity: 0.38 Specificity: 0.66 PPV: 0.22 NPV: 0.81

* Adjusted for cohort effect. RAMRIS: Rheumatoid Arthritis Magnetic Resonance Imaging Score; RF: rheumatoid factor; PPV: positive predictive value; NPV: negative predictive value.

suggested that this subclinical inflammation detected by MRI and US may be a prognostic marker for further radiographic progression or flare of disease activity[20,25,26,41,42,43,44]. For patients with active RA disease, osteitis seems to be the most important predictor of radiographic progression.

In an inception cohort of 84 patients with early RA, osteitis was an independent predictor of structural progression on conventional radiography and MRI[5]. In the randomized controlled CIMESTRA trial of 130 patients with RA, baseline osteitis score of MCP and wrist joints was the strongest independent predictor of radiographic progression in hands, wrists, and forefeet after 2 years[7]. The 5-year followup of these patients confirmed a longterm predictive ability of osteitis[6]. However, several studies have also found MRI synovitis to be of predictive value. Conaghan, *et al* showed a relationship between MRI synovitis and the development of subsequent MRI erosive damage[9]. Bøyesen, *et al*[8] found that both baseline and 1-year cumulative measures of MRI synovitis and osteitis independently predicted 3-year radiographic progression. In our present study, osteitis was less frequent than synovitis, and in the longitudinal analyses only synovitis was an independent predictor of radiographic progression. Our results suggest that MRI synovitis may be more important than osteitis for patients in clinical remission or LDA, but further studies are needed to clarify this.

In our present study, 24% of the 254 patients displayed radiographic progression during a followup period of 6–12 months. This radiographic progression occurred in patients both in remission (21% of patients) and LDA (31% of patients). Radiographic joint damage is one of the main consequences of RA and is associated with impaired physical function[1,2,3,4]. Thus, if a patient with RA achieves clinical remission but has ongoing joint damage, the situation will not be satisfactory. The importance of radiographic progression is also illustrated by the process of the development of the 2011 ACR/European League Against Rheumatism (EULAR) remission criteria, where candidate criteria were tested for their ability to predict good radiographic and functional outcomes[45,46]. A study comparing several remission criteria, including the 2011 ACR/EULAR criteria, in established RA found similar results[22]. Thus, our results are consistent with previous findings in other cohorts of patients in clinical remission or LDA, where radiographic progression is found in 10% to 30% of patients with RA[20,21,25,47,48].

In 2010 an international task force published recommendations to achieve optimal therapeutic outcomes, providing guidance on how to "treat to target"[12]. Within these recommendations it was stated that "a state of clinical remission" is the primary target for treatment of RA. The EULAR recommendations from 2010 state that "treatment should be aimed at reaching a target of remission or low disease activity as soon as possible"[13], while the more recently published ACR recommendations refer to the ACR/EULAR definition of remission[11,45,46], as well as to alternative index-based measures. There are no references to how modern imaging techniques should be used to determine whether a patient is in remission in these recommendations. However, the EULAR/ACR collaborative recommendations on how to report disease activity in clinical trials include a research agenda highlighting the potential role of imaging modalities in the definition of remission and the role of MRI and US in measuring synovitis[49]. The concept of "imaging remission", i.e., clinical remission without inflammatory activity assessed by imaging methods, seems to be an attractive target to reduce the risk of joint damage and subsequent reduced physical functioning.

The aim of the current study was to evaluate the predictive value of MRI for radiographic progression in patients in clinical LDA and remission, and to determine an MRI-acceptable inflammatory disease activity state, where structural progression will not occur. Our results suggest that RAMRIS synovitis is associated with radiographic progression in patients in remission or LDA. A significant interaction was found between RAMRIS synovitis and RF status, with a stronger association between RAMRIS

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synovitis and radiographic progression in RF-positive patients, while no significant association was found for RF-negative patients. The identification of a MRI-acceptable inflammatory disease activity state was performed using ROC curves and evaluation of sensitivity and specificity. A cutoff point of RAMRIS synovitis at 5 appeared to be the more appropriate to define this MRI-acceptable inflammatory disease activity state with a sensitivity of 0.78 and also a high negative predictive value of 0.88 with regard to the risk of radiographic progression. Based on the interaction between RF status and RAMRIS synovitis in our present study, MRI evaluation seems to be especially valuable for RF-positive patients. Our model implies that RF-positive patients in clinical remission or LDA could benefit from an MRI scan for risk stratification, and that those patients with RAMRIS synovitis of 6 or more units should be closely monitored and may be candidates for a possible step-up of antirheumatic therapy, whereas RF-positive patients with a score ≤ 5 may be candidates for less rigorous followup and possible step-down of therapy.

Some limitations of our present study should be considered. MRI and radiographic readers were different in the different cohorts, and the followup period varied between 6 and 12 months. The number of joints assessed by radiography and/or MRI differed slightly between the cohorts, and the radiographic scoring was performed with 2 different, albeit comparable/similar, Sharp-derived scoring methods. It is encouraging that despite these limitations, which would be expected to lower the power to detect a relationship between baseline and followup outcomes, we found a statistically significant and clinically meaningful association of MRI findings with subsequent radiographic damage. To assure the reliability of the data and because of the heterogeneity between the cohorts, all analyses were adjusted for cohort effect. Our result implies that MRI synovitis predicts radiographic progression in RF-positive patients with RA in remission or LDA. This international collaboration is to our knowledge the largest study aiming to assess the value of MRI to predict radiographic progression in a longitudinal followup of patients with RA in remission or LDA. All MRI were assessed using the RAMRIS in all cohorts, and both the MRI evaluation and radiographic readings were performed by experienced readers.

Our study shows that MRI inflammatory activity is frequent in patients in remission or LDA, and that the RAMRIS synovitis score is an independent predictor of radiographic progression in RF-positive patients. An acceptable MRI inflammatory activity state could be determined to identify a subgroup in which radiographic progression would rarely occur, to adjust treatment and frequency of followup. Further studies are necessary to confirm the value of performing MRI on patients in remission. This could be investigated in strategy trials in which patients in remission were randomized to MRI followup or not, and in the MRI-followup arm, patients would receive treatment modification in case of "unacceptable" MRI findings, with clinical and radiographic primary endpoints. This would potentially lead to the proposal of new definitions of remission in RA taking into account MRI findings.

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