Prediction of radiographic progression during a treat-to-target strategy by the sequential application of MRI-proven bone marrow edema and power-Doppler grade ≥ 2 articular synovitis in rheumatoid arthritis: retrospective observational study

Ayuko Takatani

Nagasaki University Graduate School of Biomedical Sciences

Mami Tamai (✉ tamaim@nagasaki-u.ac.jp)

<https://orcid.org/0000-0002-2429-7553>

Nozomi Ohki

Nagasaki University Graduate School of Biomedical Sciences

Momoko Okamoto

Nagasaki University Graduate School of Biomedical Sciences

Yushiro Endo

Nagasaki University Graduate School of Biomedical Sciences

Sousuke Tsuji

Nagasaki University Graduate School of Biomedical Sciences

Toshimasa Shimizu

Nagasaki University of Biomedical Sciences

Masataka Umeda

Nagasaki University Graduate School of Biomedical Sciences

Shoichi Fukui

Nagasaki University Graduate School of Biomedical Sciences

Remi Sumiyoshi

Nagasaki University Graduate School of Biomedical Sciences

Ayako Nishino

Nagasaki University Graduate School of Biomedical Sciences

Tomohiro Koga

Nagasaki University Graduate School of Biomedical Sciences

Shin-ya Kawashiri

Nagasaki University Graduate School of Biomedical Sciences

Naoki Iwamoto

Nagasaki University Graduate School of Biomedical Sciences

Takashi Igawa

Nagasaki University Graduate School of Biomedical Sciences

Kunihiro Ichinose

Nagasaki University Graduate School of Biomedical Sciences

Kazuhiko Arima

Nagasaki University Graduate School of Biomedical Sciences

Hideki Nakamura

Nagasaki University Graduate School of Biomedical Sciences

Tomoki Origuchi

Nagasaki University Graduate School of Biomedical Sciences

Masataka Uetani

Nagasaki University Graduate School of Biomedical Sciences

Atsushi Kawakami

Nagasaki University Graduate School of Biomedical Sciences

Research article

Keywords: RA, MRI-proven BME, PD articular synovitis, radiographic progression

Posted Date: April 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-21458/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background : Recently, it is well known the utility of both magnetic resonance imaging (MRI) and ultrasound (US) for rheumatoid arthritis (RA) in clinical practice. To investigate the favorable timing for monitoring of RA by MRI and US for predicting the radiographic progression during a treat-to-target (T2T) strategy.

Methods : Symptomatic wrist and finger joints of 44 active RA patients (median disease duration 8.5 months), recruited in Nagasaki University Hospital from January 2010 to June 2017, were examined by MRI and US at baseline and then at 3-month (US) and 6-month intervals (MRI). The T2T strategy was used through 1 year. MRI was evaluated by RA MRI scoring (RAMRIS) and US by Outcomes Measures in Rheumatology Clinical Trial (OMERACT), respectively. Plain radiographs were assessed by the Genant-modified Sharp score for the symptomatic side. Radiographic progression was defined as an annual increase ≥ 0.75 at 1 year. Factors associated with radiographic progression were analyzed. The optimal use of MRI and US at each timepoint was considered.

Results : Disease activity score (DAS) 28-ESR as well as inflammatory findings of MRI-proven bone marrow edema (BME) and US power-Doppler (PD) signal were reduced during treatment. A logistic regression model revealed that MRI-proven BME at baseline and 6 months and joint counts of PD grade ≥ 2 synovitis at 3 or 6 months are significantly associated with radiographic progression at 1 year.

Conclusions : The combination of MRI and US at each timepoint may help predict radiographic progression in patients with early-stage RA during T2T strategies.

Background

Rheumatoid arthritis (RA) is a chronic inflammatory disease that frequently leads to progressive joint damage [1, 2]. The progression of structural damage in RA can be assessed by radiography and is associated with the development of joint deformity and eventually with disability [3]. With the recent advances in RA treatment, early diagnosis and early intervention are now possible, allowing accurate prognoses for structural damage. Advanced imaging, including magnetic resonance imaging (MRI) and ultrasound (US), has become just as vital for diagnosing, staging, and monitoring disease in patients with RA [4–10].

MRI can be used to quantify synovitis, tenosynovitis, bone marrow edema (BME), and erosion with the use of a validated scoring system, i.e., RA MRI Scoring (RAMRIS) [11]. Several studies have demonstrated that measurements of synovitis and BME have prognostic value and that these values can be used to predict further radiographic changes on radiography [12, 13]. Among MRI findings, BME in particular has been demonstrated to be the strongest predictor of subsequent erosions on radiography [4]. A clinical trial also showed that early changes in the values of synovitis and BME at 12 and 24 weeks are predictive of subsequent radiographic progression at 1 and 2 years, suggesting that changes identified on MRI during treatment indeed have clinical relevance [14].

Like MRI, US has higher sensitivity compared to a clinical examination to detect synovitis [13, 15]. With the use of a grayscale (GS), US visualizes synovial inflammation as hyperplasia, and with power-Doppler (PD) US visualizes synovial inflammation as vascularity; these findings are commonly validated by the Outcomes Measures in Rheumatology Clinical Trial (OMERACT) [16]. We and other investigators have found that articular synovitis at a PD grade ≥ 2 is highly characteristic of rheumatoid synovial inflammation [17, 18]. The OMERACT PDUS score for articular synovitis has shown good sensitivity to change, with post-therapy early responsiveness [10, 19].

However, despite the utility of MRI-demonstrated BME and PD-revealed articular synovitis, the roles of MRI and US monitoring for patients with RA in clinical settings have been controversial. In the IMAGINE-RA study of MRI, the use of MRI for treatment guidance did not improve the rate of disease activity remission or that of radiographic progression compared to a conventional treat-to-target (T2T) strategy [20]. In the TaSER study and the ARCTIC study of ultrasound, compared to clinical evaluations, the use of US for monitoring a cohort of early and active RA patients did not result in a higher frequency of patients in remission [21, 22]. However, these studies applied the MRI and US to all of the patients in the MRI and US arms of the studies, and thus the studies' findings did not address the question of which RA patients would benefit from MRI and/or US in clinical settings. We conducted the present study to attempt to identify the subsets of active RA patients who will benefit by being examined by MRI and US during T2T therapies.

Patients And Methods

Patients

We retrospectively analyzed the cases of the 44 RA patients who were examined both by MRI every 6 months and by US every 3 months for 1 year during treatment by an attempted T2T therapeutic strategy administered by rheumatologists at Nagasaki University Hospital between January 2010 and June 2017. Thirty-one of the 44 patients were incorporated from the Nagasaki Early Arthritis Clinic has been opened in 2001 as part of the Department of Immunology and Rheumatology, Nagasaki University as previously described (6–9). The baseline clinical manifestations and variables included gender, age, disease duration, rheumatoid factor (RF; measured by a latex-enhanced immunonephelometric assay with a cut-off value of 14 IU/mL; Dade Behring, Marburg, Germany), anticyclic citrullinated peptide antibodies (ACPA; measured by an enzyme-linked immunosorbent assay [ELISA] with a cut-off value of 4.5 U/mL; DIASTAT Anti-CCP; Axis-Shield, Dundee, UK), C-reactive protein (CRP; measured by a latex turbidimetric immunosorbent assay; Daiichi Pure Chemicals, Fukuoka, Japan), erythrocyte sedimentation rate (ESR), matrix metalloproteinase 3 (MMP-3; measured by an ELISA with the cut-off values of 59.7 ng/mL for females and 121.0 ng/mL for males; Daiichi Pure Chemicals), tender joint count of 28 joints, swollen joint count of 28 joints, disease activity score 28-ESR (DAS28-ESR), and the treatment information such as the use of disease-modifying antirheumatic drugs (DMARDs), methotrexate (MTX), and biologic (b)DMARDs.

All variables were measured on the same days as described [6–9]. All of the patients were examined every 3 months and treated according to the T2T strategy. Each patient had provided a signed consent form to participate in the study, which was approved by the Institutional Review Board of Nagasaki University Hospital (IRB: 3102866-8, 6020828-2). This was an observational cohort study.

Imaging: MRI, US, radiographs

MRI

Every 6 months, each patient's MRI results of wrist and metacarpophalangeal joints (MCP joints) were acquired using a 1.5T or 3T system (Sigma, GE Medical Systems, Milwaukee, WI, USA) with an extremity coil. Coronal T1-weighted spin echo (TR 450, TE 13) and short-time inversion recovery (STIR; TR 3000, TE 12, T1 160) images were also acquired. The images were evaluated for synovitis, bone marrow edema (BME), and bone erosion with or without an injection of 0.1 mmol/kg of gadolinium-diethylenetriamine (Gd-DTPA; Magnevist, Schering, Germany). The MRI images of the wrist and 1st–5th MCP joints of the most symptomatic side were semi-quantitatively and independently evaluated and scored for synovitis (grade 0–5), BME (grade 0–5), and bone erosion (grade 0–10) by two experienced radiologists (M.U. and N.O.) blinded to patient's clinical status, according to the Rheumatoid Arthritis Magnetic Resonance Imaging score (RAMRIS) as described [27].

US

Ultrasound was performed in both of the patient's hands every 3 months. The most symptomatic hand's wrist and 1st–5th MCPs, proximal interphalangeal joints (PIP joints), and synovitis as grayscale (GS; grade 0–3) and power Doppler scale (PD; grade 0–3) were evaluated semi-quantitatively using OMERACT [28, 29] by trained US experts (S.K. and A.N.) who are certified by the Japan College of Rheumatology. Factors that can affect PD results including room temperature, last use of non-steroidal anti-inflammatory drugs (NSAIDs), and hand position were considered. A systematic multiplanar GS and PD examination of each patient's joints and tendons was performed using an Aplio 500 (Toshiba Medical Systems, Tokyo) or Ascendus system (Hitachi Medical, Tokyo) with high-frequency (18 MHz) linear transducers. The Doppler parameters were adjusted according to the device used; the range of pulse repetition frequency was 800 Hz and the range of velocity was 3.1 cm/sec, with a low wall filter. Interobserver reliability was confirmed in a previous investigation [30].

Plain radiographs

Plain radiographs of both hands were performed every 12 months. The most symptomatic hand was assessed by experienced radiologists (M.U. and N.O.) independently, using the Genant-modified Sharp score (GSS) as described [31]. The main outcome was radiographic progression, defined as a $\Delta\text{GSS} \geq 0.75$ per year according to the ACT-RAY study [32], since only the symptomatic hand was evaluated.

Statistical analysis

We first performed a univariate analysis to identify the variables that are associated with radiographic progression defined as a $\Delta\text{GSS} \geq 0.75$ per year, and we then included all variables at $p \leq 0.2$ in a multiple logistic regression model. Comparisons of characteristics at each timepoint (i.e., at baseline, 3 months, and 6 months) were performed using Student's t-test or the Mann-Whitney U-test for continuous variables or the Pearson chi-square test for nominal variables. Multivariable logistic regression was used to determine which variables were associated with the radiographic progression after 1 year at each timepoint including the baseline, 3 months, and 6 months. All statistical analyses were performed using JMP ver. 13 software (SAS Institute, Cary, NC), and p-values < 0.05 were considered significant.

Results

Table 1 summarizes the baseline demographic data of the 44 patients with RA. The patients' median age was 59 years old, and 86.4% were female ($n=38$). The median disease duration was 8.5 months, RF positivity was observed in 67.4% of the patients, ACPA positivity was seen in 73.4%, and the median GSS was 0.96. All of the patients were categorized as having moderate or high disease activity based on their DAS28 values, which indicated that this patient series was patients with early-stage active RA. Fourteen patients (31.8%) were radiographic progressors (annual increase ≥ 0.75 at 12 months). Serum inflammatory markers (ESR, marginal) and MRI findings were significantly higher in the radiographic progressor group compared to the non-progressor group, whereas the US findings including the PD $\geq$ grade 2 joint counts were not significantly different between these two groups. The DAS28, tender/swollen joint counts, and DMARD choices were also not significantly different between the two groups. For instance, there was no significant difference between these two groups regarding to the use of TNF inhibitor, IL-6 inhibitor, JAK inhibitor, PSL use, respectively (data not shown). Furthermore, there was no significant difference between these two groups regarding to ACPA positivity, RF positivity, either ACPA or RF positivity, both ACPA and RF positivity, respectively (data not shown).

Table 2 provides the results of our comparison of variables at 3 months and 6 months between the radiographic progressor and non-progressor groups. In contrast to the data at baseline, the US inflammatory findings were significantly higher in the radiographic progressor group compared to the non-progressor group at both 3 months and 6 months. The MRI findings of the radiographic progressor group were also significantly higher compared to those of the non-progressor group.

The logistic regression model revealed that the variables that were associated with radiographic progression at 1 year were as follows: (1) the MRI-proven BME score at baseline, (2) the joint count of US PD grade ≥ 2 synovitis at 3 months, (3) the joint count of US PD grade ≥ 2 synovitis at 6 months, and (4) the MRI-proven BME score at 6 months (Table 3). The qualitative analysis demonstrated that the radiographic progressor status was present almost all in the subset of patients with MRI-proven BME at baseline plus US PD grade ≥ 2 synovitis at 3 months, or with MRI-proven BME or US PD grade ≥ 2 synovitis at 6 months (Table 4).

Discussion

This observational study is the first investigation of the importance of the timing of MRI and US examinations of wrist and finger joints in early-stage RA patients during T2T therapeutic strategy, focusing on radiographic progression. It is well known that inflammatory changes detected by MRI and US (especially MRI-proven BME and US-confirmed PD articular synovitis) are subsequent risk factors for radiographic progression [4, 6–9, 14]. However, the notable new evidence revealed herein is that the findings obtained by MRI or US that are associated with further radiographic damage differ at various timepoints during treatment.

First, at the patients' baselines, MRI-proven BME was demonstrated to be more closely associated with radiographic progression compared to US PD grade ≥ 2 articular synovitis. We reported a close association between MRI-proven BME and US PD articular synovitis in a cross-sectional study [23]. In the present longitudinal study however, MRI-proven BME and not US PD grade ≥ 2 articular synovitis was identified as a predictor for radiographic progression. Joint damage, especially bone erosion, is carried out by osteoclasts [24, 25], and the coexistence of MRI-proven BME with osteoclasts by histology has been documents [26]. Therefore, in RA patients, MRI-proven BME may be more directly associated with osteoclastic joint damage compared to PD articular synovitis.

Second, during the first 3 to 6 months of treatment for RA, the involvements of both US PD grade ≥ 2 articular synovitis (at both 3 months and 6 months) and MRI-proven BME (at 6 months) were shown herein to be independent predictors of further radiographic progression at 1 year. We and other investigators have pointed out the importance of PD grade ≥ 2 articular synovitis in the early diagnosis of RA [17, 18] and, like MRI-proven BME, our present findings further support the concept that the continuity of PD grade ≥ 2 articular synovitis is a better hallmark for further radiographic progression.

We also observed that the patients' uses of MTX and bDMARDs during the 1 year of treatment were not significantly different between the radiographic progressor and non-progressor groups. However, it is interesting to note that there is a significant difference between the radiographic progressor and non-progressor groups regarding to MRI-proven BME and US PD grade ≥ 2 articular synovitis at baseline and during the DMARDs treatment. In addition, none of the patients showed an annual GSS increase ≥ 0.75 at 1 year MRI-proven BME being absent at entry. Considering the results obtained by the IMAGINE-RA study, TaSER study and ARCTIC study, regarding the prediction of further radiographic progression, valuable imaging findings by MRI or US are not uniform; rather, they may be different at each timepoint. This suggests that not all patients undergoing a T2T therapeutic strategy should also undergo MRI or US, i.e., serial imaging examinations may not be helpful for monitoring the condition of RA patients without MRI-proven BME at the start of DMARD therapy, whereas such examinations may be valuable for RA patients with MRI-proven BME at the initiation of DMARD therapy.

There are several limitations in the interpretation of the present results. First, this was a small patient series ($n = 44$). For the verification of our findings, a data-driven protocol study of greater numbers of patients is necessary, as is a comparison with at least historical controls. Second, we compared international MRI scores, international US scores, and international radiographic scores; all three of these

international scores focus on wrist and finger joints, whereas the sites examined by MRI, US, and plain radiography were not completely matched with each other. A study with a site-matching approach among MRI, US and plain radiography is necessary to test our present results. In addition, this was an evaluation of only the most symptomatic hand for the comparison of images. It is debatable whether only one hand's findings reflect the inflammation of the entire body and/or other articular sites in RA. Third, since the number of patients was small, we could not identify the patient characteristics for rapid radiographic progression (RRP) or clinically relevant radiographic progression (CRRP); our results are limited to the qualitative analysis of radiographic progression. Since bone erosion is derived from osteoclastic activity whereas joint space narrowing is derived from synovial cell activity, the scores of bone erosion and joint space narrowing are ideally independently assessed, and each association with MRI-proven BME or US PD grade ≥ 2 articular synovitis should be determined in a future clinical study. Fourth, the significance of residual US synovitis during therapy might be different in RA patients treated by conventional synthetic (cs)DMARDs or bDMARDs [3233], but we were not able to separate the patients into csDMARDs-treated and bDMARDs-treated groups. This clinical question must also be addressed in another study. Fifth, there are still room to improve MRI study since we could not add the value of tenosynovitis, and accordingly, there is apparent difference of MRI images obtained by 1.5T and 3T, the latter is superior to the former. Thus, the application of 3T MRI to all the participants may be necessary to confirm the present study.

Conclusions

In conclusion, although several study limitations existed, our analyses demonstrated the favorable timing and findings of MRI-proven BME and PD articular synovitis for the prediction of further radiographic progression during the treatment of RA in clinical practice. Both MRI and US are indispensable modalities, and our present data support the valuable cost-effectiveness of these modalities during the treatment of RA.

Abbreviations

ACPA, anticyclic citrullinated peptide antibodies; bDMARDs, biologic DMARDs; BME, bone marrow edema; CRP, C-reactant protein; CRRP, clinically relevant radiographic progression; csDMARDs, conventional synthetic DMARDs; DAS, disease activity score; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; GS, gray scale; GSS, Genant-modified Sharp score; Gd-DTPA, gadolinium-diethylenetriamine; IRB, Institutional Review Board; MCP joint, metacarpophalangeal joint ; MMP-3, matrix metalloproteinase-3; MRI, magnetic resonance imaging; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; OMERACT, Outcomes Measures in Rheumatology Clinical Trial; PIP, proximal interphalangeal joint; PD, power Doppler; RA, rheumatoid arthritis; RAMRIS, RA MRI scoring; RF, rheumatoid factor; RRP, rapid radiographic progression; US, ultrasound; T2T, treat-to-target; 95% C.I., 95% confidential interval;

Declarations

Ethics approval and consent to participate:

This study was approved by the Medical Ethical Committee of the Nagasaki University Hospital, Nagasaki, Japan (Trial registration number: 3102866-8, 6020828-2).

All patients had provided informed consent to participate in the study.

Consent for publication:

All patients had provided informed consent to publish the data.

Availability of data and material:

Please contact author/s for data requests.

Competing interests:

The authors have declared no conflicts of interest with this manuscript.

Funding:

There was no financial funding with this manuscript.

Authors' contributions:

AT, MT, SYK, MU and AK contributed substantially to the conception and design of the study. AT, MT, NO, MO, YE, ST, TS, MU, SF, RS, AN, TK, SYK, NI, TI, KI, HN, TO, MU and AK made substantial contributions to the data acquisition. AT, MT and KA performed the statistical analyses. AT, MT, NO, MO, YE, ST, TS, MU, SF, RS, AN, TK, SYK, NI, TI, KI, HN, TO, MU and AK interpreted the analyzed data. AT, MT, SYK, MU and AK drafted the paper. AT, MT, SYK, KA, MU and AK revised the article for important intellectual content. All authors have read and approved the final manuscript.

Acknowledgements:

None.

References

1. Ostergaard M, Boesen M. Imaging in rheumatoid arthritis: the role of magnetic resonance imaging and computed tomography. *Radiol Med*. 2019.
2. Calabresi E, Petrelli F, Bonifacio AF, Puxeddu I, Alunno A. One year in review 2018: pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol*. 2018; 36:175-184.
3. Aletaha D, Funovits J, Smolen JS. Physical disability in rheumatoid arthritis is associated with cartilage damage rather than bone destruction. *Ann Rheum Dis*. 2011; 70:733-739.
4. Colebatch AN, Edwards CJ, Ostergaard M, van der Heijde D, Balint PV, D'Agostino MA, et al. EULAR recommendations for the use of imaging of the joints in the clinical management of rheumatoid arthritis. *Ann Rheum Dis*. 2013; 72:804-814.
5. Combe B, Landewe R, Daien CI, Hua C, Aletaha D, Alvaro-Gracia JM, et al. 2016 update of the EULAR recommendations for the management of early arthritis. *Ann Rheum Dis*. 2017; 76:948-959.
6. Tamai M, Kawakami A, Uetani M, Takao S, Arima K, Iwamoto N, et al. A prediction rule for disease outcome in patients with undifferentiated arthritis using magnetic resonance imaging of the wrists and finger joints and serologic autoantibodies. *Arthritis Rheum*. 2009; 61:772-778.
7. Tamai M, Kawakami A, Iwamoto N, Kawashiri SY, Fujikawa K, Aramaki T, et al. Comparative study of the detection of joint injury in early-stage rheumatoid arthritis by magnetic resonance imaging of the wrist and finger joints and physical examination. *Arthritis Care Res (Hoboken)*. 2011; 63:436-439.
8. Tamai M, Kita J, Nakashima Y, Suzuki T, Horai Y, Okada A, et al. Combination of MRI-detected bone marrow oedema with 2010 rheumatoid arthritis classification criteria improves the diagnostic probability of early rheumatoid arthritis. *Ann Rheum Dis*. 2014; 73:2219-2220.
9. Nakashima Y, Tamai M, Kita J, Michitsuji T, Shimizu T, Fukui S, et al. Magnetic Resonance Imaging Bone Edema at Enrollment Predicts Rapid Radiographic Progression in Patients with Early RA: Results from the Nagasaki University Early Arthritis Cohort. *J Rheumatol*. 2016; 43:1278-1284.
10. Kawashiri SY, Nishino A, Shimizu T, Umeda M, Fukui S, Nakashima Y, et al. Ultrasound disease activity of bilateral wrist and finger joints at three months reflects the clinical response at six months of patients with rheumatoid arthritis treated with biologic disease-modifying anti-rheumatic drugs. *Mod Rheumatol*. 2017; 27:252-256.
11. Woodworth TG, Morgacheva O, Pimienta OL, Troum OM, Ranganath VK, Furst DE. Examining the validity of the rheumatoid arthritis magnetic resonance imaging score according to the OMERACT filter-a systematic literature review. *Rheumatology (Oxford)*. 2017; 56:1177-1188.
12. Rubin DA. MR and ultrasound of the hands and wrists in rheumatoid arthritis. Part II. Added clinical value. *Skeletal Radiol*. 2019; 48:837-857.
13. Baker JF, Conaghan PG, Gandjbakhch F. Update on magnetic resonance imaging and ultrasound in rheumatoid arthritis. *Clin Exp Rheumatol*. 2018; 36 Suppl 114:16-23.

14. Conaghan PG, Emery P, Ostergaard M, Keystone EC, Genovese MC, Hsia EC, et al. Assessment by MRI of inflammation and damage in rheumatoid arthritis patients with methotrexate inadequate response receiving golimumab: results of the GO-FORWARD trial. *Ann Rheum Dis*. 2011; 70:1968-1974.
15. Takase-Minegishi K, Horita N, Kobayashi K, Yoshimi R, Kirino Y, Ohno S, et al. Diagnostic test accuracy of ultrasound for synovitis in rheumatoid arthritis: systematic review and meta-analysis. *Rheumatology (Oxford)*. 2018; 57:49-58.
16. D'Agostino MA, Terslev L, Aegerter P, Backhaus M, Balint P, Bruyn GA, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 1: definition and development of a standardised, consensus-based scoring system. *RMD Open*. 2017; 3:e000428.
17. Kawashiri SY, Suzuki T, Okada A, Yamasaki S, Tamai M, Nakamura H, et al. Musculoskeletal ultrasonography assists the diagnostic performance of the 2010 classification criteria for rheumatoid arthritis. *Mod Rheumatol*. 2013; 23:36-43.
18. Nam JL, Hensor EM, Hunt L, Conaghan PG, Wakefield RJ, Emery P. Ultrasound findings predict progression to inflammatory arthritis in anti-CCP antibody-positive patients without clinical synovitis. *Ann Rheum Dis*. 2016; 75:2060-2067.
19. Naredo E, Collado P, Cruz A, Palop MJ, Cabero F, Richi P, et al. Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. *Arthritis Rheum*. 2007; 57:116-124.
20. Moller-Bisgaard S, Horslev-Petersen K, Ejbjerg B, Hetland ML, Ornbjerg LM, Glinatsi D, et al. Effect of Magnetic Resonance Imaging vs Conventional Treat-to-Target Strategies on Disease Activity Remission and Radiographic Progression in Rheumatoid Arthritis: The IMAGINE-RA Randomized Clinical Trial. *JAMA*. 2019; 321:461-472.
21. Dale J, Stirling A, Zhang R, Purves D, Foley J, Sambrook M, et al. Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. *Ann Rheum Dis*. 2016; 75:1043-1050.
22. Haavardsholm EA, Aga AB, Olsen IC, Lillegraven S, Hammer HB, Uhlig T, et al. Ultrasound in management of rheumatoid arthritis: ARCTIC randomized controlled strategy trial. *BMJ*. 2016; 354:i4205.
23. Kawashiri SY, Suzuki T, Nakashima Y, Horai Y, Okada A, Nishino A, et al. Synovial inflammation assessed by ultrasonography correlates with MRI-proven osteitis in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2014; 53:1452-1456.
24. Schett G. Autoimmunity as a trigger for structural bone damage in rheumatoid arthritis. *Mod Rheumatol*. 2017; 27:193-197.
25. Tanaka S, Tanaka Y, Ishiguro N, Yamanaka H, Takeuchi T. RANKL: A therapeutic target for bone destruction in rheumatoid arthritis. *Mod Rheumatol*. 2018; 28:9-16.
26. Dalbeth N, Smith T, Gray S, Doyle A, Antill P, Lobo M, et al. Cellular characterisation of magnetic resonance imaging bone oedema in rheumatoid arthritis; implications for pathogenesis of erosive disease. *Ann Rheum Dis*. 2009; 68:279-282.

27. Østergaard M, Peterfy C, Conaghan P, McQueen F, Bird P, Ejbjerg B, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. *J Rheumatol*. 2003; 30:1385-1386.
28. D'Agostino MA, Terslev L, Aegerter P, Backhaus M, Balint P, Bruyn GA, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 1: definition and development of a standardised, consensus-based scoring system. *RMD Open*. 2017; 3: e000428.
29. Terslev L, Naredo E, Aegerter P, Wakefield RJ, Backhaus M, Balint P, et al. Scoring ultrasound synovitis in rheumatoid arthritis: a EULAR-OMERACT ultrasound taskforce-Part 2: reliability and application to multiple joints of a standardised consensus-based scoring system. *RMD Open*. 2017; 3: e000427.
30. Nishino A, Kawashiri SY, Shimizu T, Umeda M, Fukui S, Koga T, et al. Assessment of both articular synovitis and tenosynovitis by ultrasound is useful for evaluations of hand dysfunction in early rheumatoid arthritis patients. *Mod Rheumatol*. 2017; 27:605-608.
31. Genant HK, Peterfy CG, Westhovens R, Becker JC, Aranda R, Vratsanos G, et al. Abatacept inhibits progression of structural damage in rheumatoid arthritis: results from the long-term extension of the AIM trial. *Ann Rheum Dis*. 2008; 67: 1084–9.
32. Dougados M, Kissel K, Conaghan PG, Mola EM, Schett G, Gerli R, et al. Clinical, radiographic and immunogenic effects after 1 year of tocilizumab-based treatment strategies in rheumatoid arthritis: the ACT-RAY study. *Ann Rheum Dis*. 2014; 73:803–809.
33. D'Agostino MA, Terslev L, Wakefield R, Østergaard M, Balint P, Naredo E, et al. Novel algorithms for the pragmatic use of ultrasound in the management of patients with rheumatoid arthritis: from diagnosis to remission. *Ann Rheum Dis* 2016; 75: 1902-8.

Tables

Table1 Demographic data at baseline

	All (N=44)	Δ GSS ≥ 0.75 (n=14)	Δ GSS <0.75 (n=30)	p-value
Age*, y.o.	59.0 (51.5- 65.0)	61.0 (51.5- 70.5)	58.5 (51.0- 64.3)	0.48
Gender, % Female				0.30
Disease duration*, m.	86.4	78.6	90.0	0.84
	8.5 (2.3- 43.5)	10.0 (2.0- 42.0)	7.0 (2.8- 50.0)	
CRP*, mg/dl	0.22 (0.07- 0.62)	0.83 (0.42- 1.95)	0.10 (0.05- 0.36)	<0.001
ESR*, mm/h				0.10
MMP-3*, ng/ml	26 (16- 40)	35.5 (23.8-56)	22 (12- 32)	0.003
	54.9 (34.9- 110.3)	83.9(62.2- 189.0)	43.8(25.3- 77.3)	
Tender joint count 28*	5.0 (2.0- 8.0)	3.5 (2.0- 6.5)	5.5 (1.5- 9.5)	0.33
Swollen joint count 28*				0.85
DAS28-ESR*	5.5 (2.3- 8.0)	5.5 (3.8- 7.3)	5.5 (2.0- 8.3)	0.26
	4.83 (4.00- 5.65)	4.92 (4.24- 5.70)	4.61 (3.43- 5.61)	
US:	5.5 (4- 8)	7 (5-8.8)	5 (4-7.5)	0.33
GS score*		4.5 (2- 7.8)	3 (1.8-6)	0.17
PD score*	4 (2- 6.8)		1 (0.8-3)	0.20
Joint count of PD grade ≥ 2 synovitis*	1.5 (1- 3)	2 (1-3.3)		
MRI:				
Synovitis score*	7.0 (4.0- 10.8)	10.0 (6.0- 11.5)	6.5 (2.0- 9.3)	0.008
BME score*				<0.001
Erosion score*	2.5 (0- 9.8)	14.0 (7.8- 30.3)	1.0 (0- 3.0)	0.008
	4.5 (1.0- 8.8)	10.5 (6.0- 22.0)	3.0 (0- 5.0)	

Previous treatment:		38.6	35.7	40.0	0.79
Any DMARDs, %	MTX,	29.5	28.6	30.0	0.92
%	bDMARDs, %	6.8	7.1	6.7	0.95
Treatment after entry: MTX, %					
bDMARDs, %	bDMARDs within 6				
months, %		90.9	92.9	90.0	0.76
		61.4	78.6	53.3	0.11
		38.6	28.6	43.3	0.35

*median, Q1-Q3; *p*-value, comparison between Δ GSS ≥ 0.75 and Δ GSS < 0.75

BME, bone marrow edema; CRP, C-reactant protein; DAS, disease activity score; DMARD, disease-modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; GS, gray scale; GSS, Genant-modified Sharp score; MMP-3, matrix metalloproteinase-3; MRI, magnetic resonance imaging; MTX, methotrexate; PD, power Doppler; US, ultrasonography;

Table 2A. CRP, ESR, MMP-3, DAS28, US findings at 3 months

	All (N=44)	Δ GSS ≥ 0.75 (n=14)	Δ GSS < 0.75 (n=30)	<i>p</i> -value
CRP*, mg/dl	0.07 (0.04-0.22)	0.30 (0.15-0.60)	0.05 (0.03-0.10)	<0.0001
ESR*, mm/h	16 (10-29)	29 (15-32)	14.5 (9.8-22.5)	0.068
MMP-3*, ng/ml	43.7 (34.7-55.9)	68.6 (46.1-165.7)	39.6 (29.3-48.2)	<0.0001
DAS28-ESR*	2.92 (2.09-4.04)	3.64 (2.78-4.60)	2.41 (1.86-3.37)	0.020
US:	4 (2.5-6.5)	5 (4-8.5)	4 (2-6)	0.028
GS score*	2 (0-3)	3 (2-4)	1 (0-3)	0.0083
PD score*	1 (0-1)	1 (1-1.5)	0 (0-1)	0.0070
Joint count of PD grade ≥ 2 synovitis*				

Table 2B. CRP, ESR, MMP-3, DAS28, US and MRI findings at 6 months

	All (N=44)	Δ GSS ≥ 0.75 (n=14)	Δ GSS < 0.75 (n=30)	<i>p</i> -value
CRP*, mg/dl	0.09 (0.03-0.30)	0.36 (0.12-0.62)	0.04 (0.02-0.12)	0.0012
ESR*, mm/h	18.5 (9.25-28)	27.5 (15.5-39)	15 (8-25)	0.014
MMP-3*, ng/ml	40.1 (29.5-62.7)	56.8 (45.7-121.3)	36.6 (28.1-52.7)	0.0055
DAS28-ESR*	2.64 (1.99-4.00)	4.38 (3.15-5.27)	2.48 (1.90-3.23)	0.0009
US:	3 (2-5)	5.5 (3-8.75)	2 (1-4.25)	< 0.001
GS score*	1 (0-2.75)	3 (1-7.5)	0 (0-1)	< 0.0001
PD score*	0 (0-1)	1 (0-2.25)	0 (0-0)	< 0.0001
Joint count of PD grade ≥ 2 synovitis*				
MRI:	5 (2-8.5)	8 (5.3-12.5)	4 (0-7)	0.0028
Synovitis score*	0 (0-6)	6 (4.3-16.8)	0 (0-0.5)	< 0.0001
BME score*	4 (1-10.5)	14.5 (5.5-24.5)	2 (0-5)	0.0046
Erosion score*				

*median, Q1-Q3; *p*-value, comparison between Δ GSS ≥ 0.75 and Δ GSS < 0.75

BME, bone marrow edema; CRP, C-reactant protein; DAS, disease activity score; ESR, erythrocyte sedimentation rate; GS, gray scale; GSS, Genant-modified Sharp score; MMP-3, matrix metalloproteinase-3; MRI, magnetic resonance imaging; PD, power Doppler; US, ultrasound;

Table 3. Multivariate analysis at baseline, 3 and 6 months for Δ GSS ≥ 0.75

A. At baseline

	Unit	Odds ratio	95% C.I.	<i>p</i> -value
MRI-proven BME score	1	1.68	1.26 – 2.89	< 0.0001

R²=0.66, AIC=23.35

B. At 3 months

	Unit	Odds ratio	95% C.I.	<i>p</i> -value
DAS28-ESR	1	1.54	0.80 – 2.98	0.19
Joint count of PD grade $\geq$ 2 synovitis	1	2.49	1.09 – 7.70	0.027

$R^2=0.18$, AIC=46.76

C. At 6 months

	Unit	Odds ratio	95% C.I.	<i>p</i> -value
MRI-proven BME score	1	1.42	1.09 - 1.96	0.0056
Joint count of PD grade $\geq$ 2 synovitis	1	6.44	1.13 – 65.6	0.029

$R^2=0.46$, AIC=32.28

BME, bone marrow edema; C.I., confidential interval; DAS, disease activity score; ESR, erythrocyte sedimentation rate; GSS, Genant-modified Sharp score; MRI, magnetic resonance imaging; PD, power Doppler; US, ultrasound

Table 4. Comparison for radiographic progression by the presence of MRI-proven BME and PD grade $\geq$ 2 synovitis

MRI BME:				
(at baseline, 6 months)	(1, 1) or (1, 0)	(1, 0)	(0, 0)	(0, 0)
USPD $\geq$ 2 synovitis:				
(at 3 months, 6 months)	(1, 1) or (1, 0) or (0, 1)	(0, 0)	(1, 1) or (1, 0) or (0,1)	(1, 1)
	(n=21)	(n=12)	(n=4)	(n=7)
Δ GSS $\geq$ 0.75	13	1	0	0
Δ GSS <0.75	8	11	4	7

Number in parentheses, 1: positive, 0: negative;

p -value 0.0058 (Pearson chi-square test)

BME, bone marrow edema; GSS, Genant-modified Sharp score; MRI, magnetic resonance imaging; PD, power Doppler; US, ultrasonography;