Conventional versus ultrasound treat to target: no difference in magnetic resonance imaging inflammation or joint damage over 2 years in early rheumatoid arthritis

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Concise report

Conventional versus ultrasound treat to target: no difference in magnetic resonance imaging inflammation or joint damage over 2 years in early rheumatoid arthritis

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Abstract

Objective. To investigate whether an ultrasound-guided treat-to-target strategy for early RA would lead to reduced MRI inflammation or less structural damage progression compared with a conventional treat-to-target strategy.

Methods. A total of 230 DMARD-naïve early RA patients were randomized to an ultrasound tight control strategy targeting DAS <1.6, no swollen joints and no power Doppler signal in any joint or a conventional strategy targeting DAS <1.6 and no swollen joints. Patients in both arms were treated according to the same DMARD escalation strategy. MRI of the dominant hand was performed at six time points over 2 years and scored according to the OMERACT RA MRI scoring system. A total of 218 patients had baseline and one or more follow-up MRIs and were included in the analysis. The mean MRI score change from baseline to each follow-up and the 2 year risk for erosive progression were compared between arms.

Results. MRI bone marrow oedema, synovitis and tenosynovitis improved over the first year and was sustained during the second year of follow-up, with no statistically significant differences between the ultrasound and the conventional arms at any time point. The 2 year risk for progression of MRI erosions was similar in both treatment arms: ultrasound arm 39%, conventional arm 33% [relative risk 1.16 (95% CI 0.81, 1.66), $P = 0.40$].

Conclusion. Incorporating ultrasound information in treatment decisions did not lead to reduced MRI inflammation or less structural damage compared with a conventional treatment strategy. The findings support that systematic use of ultrasound does not provide a benefit in the follow-up of patients with early RA.

Trial registration number. Clinicaltrials.gov, http://clinicaltrials.gov, NCT01205854.

Key words: rheumatoid arthritis, ultrasonography, magnetic resonance imaging, outcome measures, clinical trials and methods, diagnostic imaging

CLINICAL SCIENCE

Rheumatology key messages

- Inflammation, assessed by MRI, improved by both clinical and ultrasound-guided treat-to-target strategies in early RA.
- MRI inflammation and joint damage did not differ between clinical and ultrasound-guided treatment strategies.
- The study supports current treatment recommendations, with a defined clinical treatment target in early RA.

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Introduction

Clinical remission is the preferred treatment target in modern RA care [1]. In patients who achieve a state of clinical remission, residual subclinical inflammation is frequently detectable by ultrasonography or MRI [2, 3]. Since inflammation has been found to be associated with continued structural deterioration of the joints [4, 5], it has been debated whether treatment should also target imaging remission [6–8].

Two recent trials have investigated the use of structured ultrasound assessment in a treat-to-target drug escalation strategy in early RA: the ARCTIC trial (NCT02352948) [9] and the TaSER trial (NCT00920478) [10]. Although a beneficial effect of targeting ultrasound remission over clinical remission could not be established in the primary outcome in either of the studies, a trend was observed towards less radiographic erosive damage in the ultrasound arm in both trials. If treatment strategies targeting subclinical inflammation did inhibit structural damage progression, it could possibly have implications on long-term outcomes of function and disability.

MRI is more sensitive than conventional radiography to detect structural lesions, especially in early disease [11–13]. MRI can also visualize and objectively quantify inflammatory lesions. By assessing MRI data from the ARCTIC trial, we aimed to investigate whether management of early RA by a tight control strategy incorporating ultrasound information in treatment decision making would lead to reduced MRI inflammation or less MRI structural damage compared with a conventional tight control strategy.

Materials and methods

Study design

The ARCTIC trial was a 24-month randomized clinical strategy study conducted at 11 centres. Patients were randomized 1:1 to an ultrasound tight control strategy targeting DAS <1.6, no swollen joints and no power Doppler signal in any joint or a conventional tight control strategy targeting DAS <1.6 and no clinically swollen joints. Patients in both arms were treated according to the same DMARD escalation strategy [9]. Starting treatment was methotrexate 15 mg/week increased to 20 mg/week by week 5, with bridging prednisolone. The treatment algorithm further included an increased methotrexate dose, triple synthetic DMARD and biologic DMARD treatment. In the conventional arm, the decision to adjust therapy was based on the level of and change in DAS. In the ultrasound arm, treatment was increased if indicated by the ultrasound score (unsatisfactory decrease from the previous visit, defined as $<10\%$ change in ultrasound score if the DAS was ≤ 2.4 or a $<20\%$ change in the ultrasound score if the DAS was >2.4) [9], thus overruling the clinical assessment. According to the protocol, swollen joints were treated with intra-articular corticosteroids. In the ultrasound arm, joints with power Doppler signal were injected using ultrasound guidance. The study was approved by the Regional Committee for Medical and Health Research Ethics South-East Norway and was performed in compliance with the Helsinki Declaration and guidelines for good clinical practice. All patients provided written informed consent.

Participants

The main inclusion criteria were age 18–75 years, fulfilment of the 2010 ACR/EULAR classification criteria for RA, DMARD naïvety, time from first patient-reported swollen joint less than 2 years and indication for DMARD treatment.

Clinical and radiographic assessments

The study included 13 visits during the 2 year follow-up period [9]. Patients in the ultrasound arm were assessed by ultrasound at every visit, according to a scoring system of 32 joints with high intrarater and interrater reliability [14]. Patients in the conventional arm were assessed by ultrasound yearly. Clinical data, biochemical data and patient-reported outcomes were recorded at every visit. Radiographs of the hands, wrists and feet were obtained regularly for all patients and scored according to the van der Heijde modified Sharp score (vdHSS) after completion of the study [15].

MRI

MRI of the dominant wrist and hand was performed at 0, 3, 6, 12, 16 and 24 months. Acquisitions were done according to the OMERACT Rheumatoid Arthritis MRI Scoring System (RAMRIS) recommendations [16, 17] with pulse sequences: coronal and axial T1 without contrast enhancement, axial T1 turbo spin echo with contrast enhancement and coronal short tau inversion recovery. Images were scored for the RAMRIS features synovitis, tenosynovitis, bone marrow oedema, bone erosions and joint space narrowing (JSN) by one reader blinded for treatment group and clinical data (U. Sundin), in known chronological order. If an anatomical location could not be scored (e.g. technical issues), the missing value was approximated by a linear mixed model using all other available MRI data. A combined inflammation score was computed by normalized summation of the synovitis, tenosynovitis and bone marrow oedema scores and a combined damage score by normalized summation of the erosion and JSN scores [18]. The reliability of scoring was overall very good when tested in intrareader and interreader comparisons (Supplementary Table S1, available at *Rheumatology* online). Of the 230 patients from the ARCTIC primary analyses, 218 had MRI performed at baseline and at least one of the follow-up visits and were included in the current analysis.

Statistics

Baseline characteristics were described for the treatment arms in the subsample ($n = 218$) and compared

with the full ARCTIC sample ($n = 230$). Results were presented as proportions or mean values, as appropriate. The mean MRI score change from baseline to each follow-up was estimated and compared between treatment arms using a linear mixed model, adjusted for baseline score, age, gender, centre and ACPA status. The 2 year change in the erosion, JSN and combined damage scores for each individual patient were investigated by cumulative change plots. The number of patients in each arm with erosive progression during the study period was calculated using the smallest detectable change for MRI erosions as a cut-off (0.61 units) [19]. The 2 year risk and relative risk (RR) for erosive progression were calculated. The analyses of the radiographic vdHSS scores from the main article were repeated for the current subsample, including analysis of the radiographic erosion score of the dominant hand only. All analyses were undertaken in STATA version 14 (StataCorp, College Station, TX, USA).

Results

Of the 218 included patients, 102 were in the conventional arm and 116 in the ultrasound arm. Overall, treatment arms were balanced at baseline, with a mean age of 52.7 and 50.8 years, mean symptom duration of 220 and 207 days, proportion of ACPA-positive patients 83% and 82% and mean DAS of 3.3 and 3.5 in the conventional and ultrasound arms, respectively (Supplementary Table S2, available at *Rheumatology* online). Of the patients in the conventional arm, 52% were female, compared with 72% in the ultrasound arm. Baseline characteristics and radiographic scores of the current subsample ($n = 218$) were similar to those of the ARCTIC primary sample ($n = 230$, data not shown).

Inflammatory MRI features

The mean MRI inflammatory scores were comparable between the treatment arms at baseline, with a RAMRIS synovitis score of 7.0 and 6.3, tenosynovitis score 6.4 and 6.5 and bone marrow oedema 4.3 and 3.7 in the conventional and ultrasound arms, respectively (Supplementary Table S2, available at *Rheumatology* online). All inflammatory variables decreased during the first year and most markedly in the first 3 months. Scores then remained at the same level throughout the second year. There was no statistically significant between-arm difference in the change from baseline for any of the scores at any time point (Fig. 1 and Supplementary Table S3, available at *Rheumatology* online).

Structural joint damage

The baseline mean RAMRIS erosion, JSN and combined MRI damage scores were comparable between arms (Supplementary Table S2, available at *Rheumatology* online). All scores showed a minimal linear increase over time. There were no statistically significant between-arm differences in the change from baseline for any of the scores at any time point. The mean change in the RAMRIS erosion score from baseline to 24 months was 0.63 (95% CI 0.32, 0.94) in the conventional arm and 0.65 (95% CI 0.36, 0.93) in the ultrasound arm, with a difference of 0.02 (95% CI −0.41, 0.44; $P = 0.95$) (Fig. 2A–C, Supplementary Table S3, available at *Rheumatology* online). The change in mean scores for erosions and JSN was driven by a minority of patients with a high progression rate, while a majority of patients showed little or no progression (Fig. 2D–F). In the ultrasound arm, 45 of 116 patients (39%) had MRI erosive progression, compared with 34 of 102 patients (33%) in the conventional arm [RR 1.16 (95% CI 0.81, 1.66), $P = 0.40$].

For the radiographic outcomes, repeated analyses of the vdHSS scores for erosions and JSN on the current subsample showed similar results as for the ARCTIC primary sample, with a borderline-significant difference in the change from baseline to 2 years for the erosion score in favour of the ultrasound arm [difference −0.32 (95% CI −0.67, 0.03), $P = 0.08$).

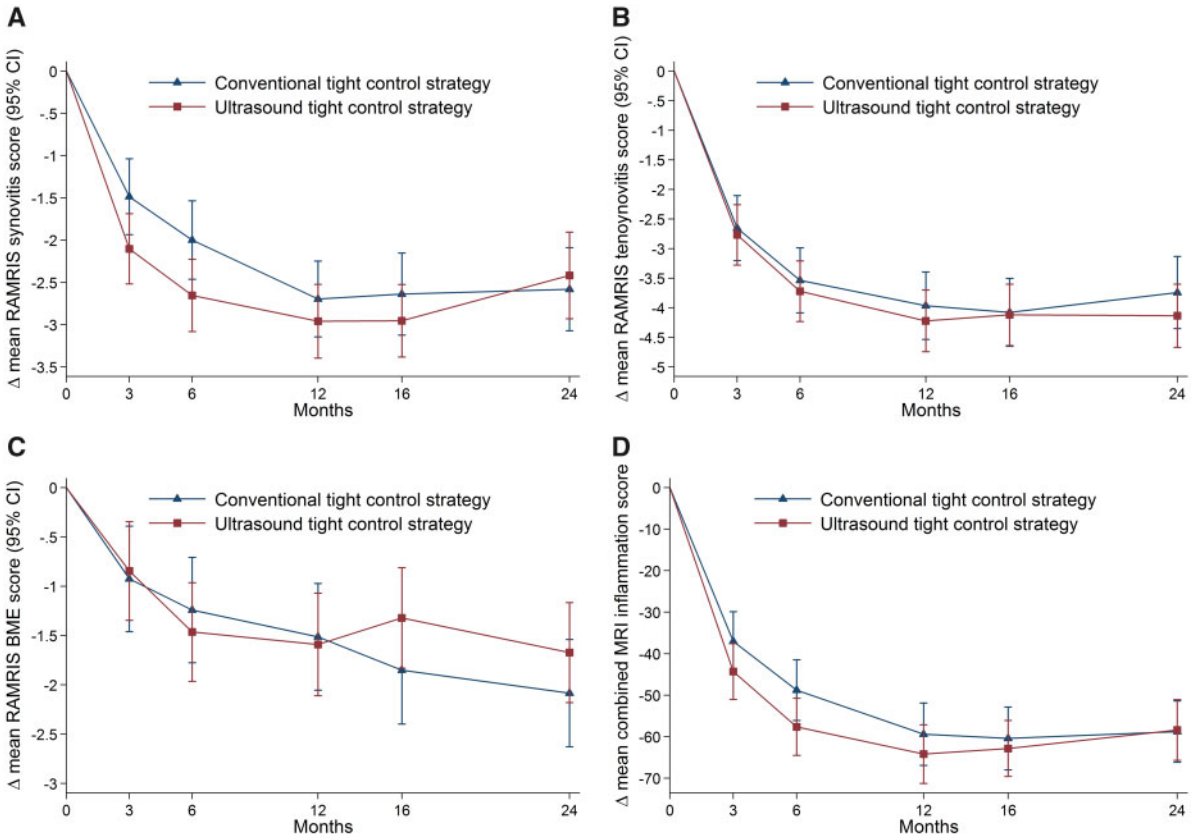
Discussion

In the ARCTIC trial, we did not find that an ultrasound-guided tight control strategy for treatment of early RA led to reduced MRI inflammation or structural damage compared with a conventional tight control strategy.

Despite findings in several previous studies that subclinical inflammation is both frequent and harmful in clinical remission, three large clinical strategy trials—the ARCTIC and TaSER trials (ultrasound targets) and the IMAGINE-RA trial (MRI target; NCT01656278)—have not provided evidence of any significant benefit of targeting imaging remission over clinical remission [9, 10, 20].

The borderline-significant reduction in radiographic erosive progression that was observed in the ARCTIC and TaSER trials suggested that an ultrasound-guided strategy might be of value over a longer time period, but this is not supported by the current results. Our analysis of the ARCTIC MRI data shows no trend towards a difference between the treatment arms in erosive progression or the inflammatory processes that are pathophysiologically upstream to erosive change. A potential source of difference when comparing MRI and radiographic data is that the radiographic score includes both hands and feet, while the MRI assessment includes only the dominant hand. If changes in joint damage occurred predominantly in the feet, these would not be detectable by the MRI examination. However, the trend of a difference in radiographic erosion scores between arms in the ARCTIC trial was present when assessing only the dominant hand. Overall, both the radiographic erosion score and the MRI erosion score show a similar, gradual increase over time, and the group-level trend towards a difference in the radiographic score is small and statistically non-significant. The MRI results, with no trend towards less joint damage progression in the

FIG. 1 Inflammatory MRI features



Mean change from baseline for inflammatory MRI features. Estimates based on a linear mixed effects model adjusted for baseline score, age, gender and ACPA status. Error bars represent 95% CI.

ultrasound arm, support the conclusions of the primary outcomes of the abovementioned trials—that an ultrasound-guided strategy does not lead to improved treatment outcomes. A plausible explanation for this is that participants in these recent trials have received more aggressive and effective treatment than in earlier studies, which might have diminished the importance of subclinical disease activity.

The most important limitation of this study is that a 2 year follow-up time may be too short to detect differences in slow-evolving structural lesions. However, the erosive progression demonstrated here was minimal, making a long-term clinically meaningful difference between the arms unlikely. The strengths of this study include the standardized MRI examination according to established RAMRIS criteria at six time points during the study period in a study representative of a general early RA population.

In conclusion, we could not find any difference between an ultrasound-guided treat-to-target strategy and a conventional clinically guided treat-to-target strategy in the MRI outcomes for inflammatory activity and structural damage. This supports the previous conclusions from the ARCTIC trial, that adding ultrasound information to strategic treatment decisions and targeting therapy towards ultrasound remission does not lead to improved outcomes and may cause overtreatment, with potentially adverse effects for patients, as well as inefficient use of health resources. Our findings support the current treatment recommendations for early RA.

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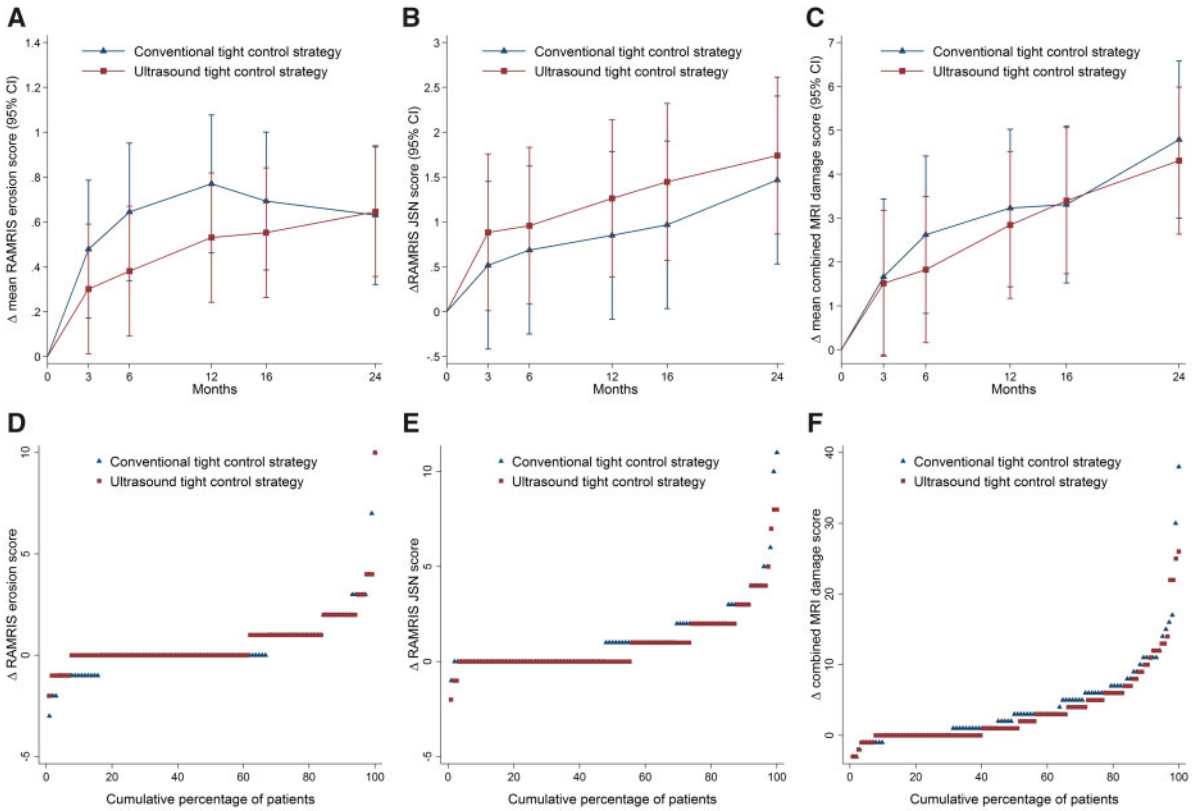
Fig. 2 Structural damage MRI features



Mean change from baseline for MRI structural damage scores. Estimates based on a linear mixed effects model adjusted for baseline score, age, gender and ACPA status. Error bars represent 95% CI. D-F: cumulative 2 year change for all patients.

anonymized patient-level data and study protocol available upon reasonable request. Requests should be directed to the corresponding author.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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