Concise report

Conventional versus ultrasound treat-to-target: No difference in MRI inflammation or MRI joint damage over 2 years in early RA

Ulf Sundin^{1,2}, Anna-Birgitte Aga¹, Øivind Skare¹, Lena B. Nordberg^{1,2}, Till Uhlig^{1,2}, Hilde B. Hammer¹, Désirée van der Heijde^{1,3}, Tore K. Kvien^{1,2}, Siri Lillegraven^{*1}, Espen A. Haavardsholm^{*1,2} and the ARCTIC study group.

**Siri Lillegraven and Espen A. Haavardsholm contributed equally to this study*

¹Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway. ²University of Oslo, Oslo, Norway. ³Department of Rheumatology, Leiden University Medical Centre, Leiden, Netherlands.

Corresponding author

Ulf Sundin, MD

Diakonhjemmet Sykehus, Postboks 23 Vinderen, 0319 Oslo, Norway

Email: uffe.sundin@gmail.com

Telephone: +47 40614198

ORCID ID: <https://orcid.org/0000-0003-1860-6150>

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ABSTRACT

Objective

To investigate whether an ultrasound-guided treat-to-target strategy for early rheumatoid arthritis (RA) would lead to reduced magnetic resonance imaging (MRI) inflammation or less structural damage progression compared to a conventional treat-to-target strategy.

Methods

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 dominant hand was performed at 6 time-points over 2 years and scored according to the OMERACT MRI RA scoring system. 218 patients had baseline and ≥ 1 follow-up MRI and were included in the analysis. Mean MRI score change from baseline to each follow-up and 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%, RR: 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 to a conventional treatment strategy. The findings support that systematic use of ultrasound does not provide benefit in the follow-up of patients with early RA.

Clinical trial registration number: Clinicaltrials.gov ID: NCT01205854

Keywords: Rheumatoid Arthritis, Ultrasonography, Magnetic resonance imaging, Outcome measures, Clinical trials and methods, Diagnostic imaging

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

INTRODUCTION

Clinical remission is the preferred treatment target in modern rheumatoid arthritis (RA) care.[1] In patients who achieve a state of clinical remission, residual subclinical inflammation is frequently detectable by ultrasonography or magnetic resonance imaging (MRI).[2, 3] As such inflammation has been found to be associated with continued structural deterioration of the joints,[4, 5] it has been debated whether treatment also should 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 [9] and the TaSER trial [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 toward 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 to 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

disease activity score (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 disease-modifying anti-rheumatic drug (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 increased methotrexate dose, triple synthetic DMARD and biologic DMARD treatment. In the conventional arm, the decision to adjust therapy was based on level of and change in DAS. In the ultrasound arm, treatment was additionally stepped up if indicated by the ultrasound score (unsatisfactory decrease from the previous visit, defined as <10% change in ultrasound score if $DAS \leq 2.4$, or <20% change in ultrasound score if $DAS > 2.4$), [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 with ultrasound guidance. The study was approved by the regional ethics committee (the Regional Committee for Medical and Health Research Ethics South-East Norway) and 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 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA, DMARD-naivety, time from first patient reported swollen joint less than two 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 intra-rater and inter-rater reliability.[14] Patients in the conventional arm were assessed by ultrasound yearly. Clinical, biochemical data and patient reported outcomes

were recorded at every visit. Radiographs of 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 RA MRI scoring system (RAMRIS) recommendations,[16, 17] with pulse sequences: coronal and axial T1 without contrast enhancement, axial T1 TSE with contrast enhancement and coronal STIR. Images were scored for the RAMRIS features synovitis, tenosynovitis, bone marrow oedema (BME), 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 BME scores, and a combined damage score by normalized summation of the erosion and JSN scores.[18] Reliability of scorings was overall very good when tested in intra-reader and inter-reader comparisons (supplementary table S1). Of the 230 patients from the ARCTIC primary analyses, 218 performed MRI 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 to the full ARCTIC sample (n=230). Results were described as proportions or mean values as appropriate. The mean MRI score change from baseline to each follow-up were estimated and compared between treatment arms using a linear mixed model, adjusted for baseline score, age, gender, centre and anti-citrullinated protein antibody (ACPA) status. 2-year change of 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 for erosive progression were calculated. The analyses of the radiographic vdHSS scores from the main article were repeated for the current subsample. All analyses were undertaken in STATA v.14 (StataCorp, USA).

RESULTS

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

Inflammatory MRI features

Mean levels of MRI inflammatory scores were comparable between the treatment arms at baseline, with RAMRIS synovitis score 7.0 and 6.3, tenosynovitis score 6.4 and 6.5, and BME 4.3 and 3.7 in the conventional and ultrasound arms respectively (**supplementary table S2**). 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 change from baseline for any of the scores at any time-point (**figure 1, supplementary table S3**).

Structural joint damage

Baseline mean level of RAMRIS erosions, JSN and combined MRI damage score were comparable between arms (**supplementary table S2**). All scores showed a minimal linear

increase over time. There were no statistically significant between-arm differences in change from baseline for any of the scores at any time-point. Mean change in RAMRIS erosion score from baseline to 24 months were 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, difference 0.02 (95% CI -0.41; 0.44), *p*-value 0.95 (**figure 2 A-C, supplementary table S3**). The change in mean scores for erosions and JSN were driven by a minority of patients with a high progression rate, while a majority of patients showed little or no progression (**figure 2 D-F**). In the ultrasound arm, 45 of 116 patients (39%) had MRI erosive progression, compared to 34 of 102 patients (33%) in the conventional arm, RR: 1.16 (95% CI 0.81; 1.66), *p*-value=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 change from baseline to 2 years for the erosion score in favour of the ultrasound arm (difference: -0.32 (95% CI -0.67 to 0.03, *p*-value=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 to 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) – have not provided evidence of any significant benefit of targeting imaging remission over clinical remission.[9, 10, 20] The borderline-significant reduction in radiographic progression rate that was observed in the ARCTIC and TaSER trials suggested that an ultrasound guided strategy might be of value on a longer perspective, but this is not supported by the current results.

Our analysis of the ARCTIC MRI data shows no difference between the treatment arms in erosive progression or the inflammatory processes that are pathophysiologically upstream to erosive change. The MRI results thus 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 into strategic treatment decisions and targeting therapy towards ultrasound remission do 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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The ARCTIC study group: Hallvard Fremstad, Ålesund Hospital, Ålesund, Norway; Tor Magne Madland, Haukeland University Hospital, Bergen, Norway; Åse Stavland Lexberg, Drammen Hospital, Drammen, Norway; Hilde Haukeland, Martina Hansens Hospital AS, Sandvika, Norway; Erik Rødevand, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway; Christian Høili, Hospital Østfold HF, Moss, Norway; Hilde Stray, Haugesund Rheumatism Hospital AS, Haugesund, Norway; Anne Noraas Bendvold, The Rheumatology Clinic Dovland/Bendvold, Kristiansand, Norway; Dag Magnar Soldal, Hospital Sørlandet Hospital HF, Kristiansand, Norway and Gunnstein Bakland, University Hospital of North Norway, Tromsø, Norway.

COMPETING INTERESTS

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ETHICAL APPROVAL

The study was approved by an independent ethics committee (the Regional Committee for Medical and Health Research Ethics South-East; reference number 2010/744).

DATA SHARING

The authors commit to making the relevant anonymized patient level data and study protocol available on reasonable request. Requests should be directed to the corresponding author, uffe.sundin@gmail.com.

FIGURES

Figure 1 A-D: 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.

Figure 2 A-C: 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. JSN=joint space narrowing. RAMRIS=OMERACT RA MRI Score.