






## SHORT REPORT

# Inflammation and biologic therapy in patients with rheumatoid arthritis achieving versus not achieving ACR/EULAR Boolean remission in a treat-to-target study

Nina Paulshus Sundlisæter <sup>1</sup>, Ulf Sundin <sup>1</sup>, Anna-Birgitte Aga,<sup>1</sup> Joseph Sexton,<sup>1</sup> Hilde Berner Hammer <sup>1,2</sup>, Till Uhlig <sup>1,2</sup>, Tore K Kvien <sup>1,2</sup>, Espen A Haavardsholm,<sup>1,2</sup> Siri Lillegraven<sup>1</sup>

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## ABSTRACT

**Objective** To investigate limiting factors of American College of Rheumatology (ACR)/EULAR Boolean remission in rheumatoid arthritis (RA), and compare patients who fulfil the criteria to patients who only partly fulfil the criteria, with respect to imaging inflammation and biologic disease modifying anti-rheumatic drug (DMARD) usage. **Methods** Patients with DMARD-naïve RA were treated according to current recommendations in the ARCTIC trial (Aiming for Remission in rheumatoid arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen). Limiting factors of reaching ACR/EULAR Boolean remission at 2 years were assessed. Imaging inflammation (ultrasound and MRI) in patients in remission was compared with patients failing to fulfil different components of the criteria. The OR of biologic therapy was calculated using logistic regression. **Results** Of 203 patients, 112 (55%) reached ACR/EULAR Boolean remission; 49 (24%) fulfilled three of four criteria. The main limiting factors were patient global assessment (PGA) (59%) and tender joints (22%). Imaging inflammation was not significantly different for patients in remission and patients not fulfilling the criteria due to elevated PGA and/or tender joints, but higher odds of using biologics (OR 3.63, 95% CI 1.73 to 7.61) were observed. **Conclusions** PGA and tender joints were the factors most often limiting achievement of ACR/EULAR Boolean remission. The level of imaging inflammation was not elevated in these patients compared with patients in remission, but the odds of using biologic DMARDs were higher.

## INTRODUCTION

Frequent monitoring of disease activity and treatment tailored towards a defined target is essential in management of patients with rheumatoid arthritis (RA). No single disease activity marker reflects all aspects of the inflammatory process, and composite scores

## Key messages

### What is already known about this subject?

► Remission is the preferred target for treatment of rheumatoid arthritis, with American College of Rheumatology (ACR)/EULAR Boolean remission being one of the most stringent remission definitions. It is debated how to interpret near-remission for ACR/EULAR Boolean criteria, especially when due to increased patient global assessment or tender joint count.

### What does this study add?

► The results show that inflammation measured by ultrasound or MRI was not significantly different between patients with early rheumatoid arthritis missing fulfilment of remission due to patient global assessment and/or tender joints compared to those in full remission after two years of targeted therapy.  
► Compared to patients fulfilling the remission criteria, the use of biologic therapy was significantly higher in patients who had not reached the treatment target.

### How might this impact on clinical practice or further developments?

► Our results support the ongoing work to identify the ideal definition of remission where small adjustments could enable a more individualised treatment target.

have been developed to improve the ability to evaluate the disease course.<sup>1,2</sup>

In 2011, the American College of Rheumatology (ACR) and the EULAR developed remission criteria with the purpose of defining a disease state associated with optimised radiographic and functional outcomes.<sup>3</sup> The Boolean criteria require swollen and tender



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<sup>1</sup>Division of Rheumatology and Research, Diakonhjemmet Hospital, Oslo, Norway

<sup>2</sup>Faculty of Medicine, University of Oslo, Oslo, Norway

### Correspondence to

Dr Nina Paulshus Sundlisæter; ninasundlisater@gmail.com

joints counts, C reactive protein (CRP, mg/dL) and patient global assessment (PGA, 0–10 visual analogue scale (VAS) scale) to be  $\leq 1$ ,<sup>3</sup> making this definition sensitive for isolated elevations in one of the four components. PGA has been shown to be the most frequent limiting factor for reaching ACR/EULAR Boolean remission in established RA.<sup>4,5</sup> However, PGA was found to improve the discriminatory ability of the remission criteria, supporting that the construct might reflect inflammatory activity not caught by the other measures.<sup>3</sup>

Not achieving remission solely due to PGA often presents a challenge in interpretation of the composite scores as non-inflammatory factors (eg, joint damage, fibromyalgia, fatigue and depression) could strongly impact its elevation.<sup>6,7</sup> It has also been discussed if tender joint count potentially overestimates disease activity as it might represent erosive damage and pain sensitisation,<sup>6,8</sup> although in early disease tender joints might be more related to inflammation.<sup>9,10</sup>

The aim of this study was to assess which components of the ACR/EULAR Boolean criteria that most often limit achievement of remission in early RA, and to quantify the extent of imaging inflammation and use of biologic therapy in patients failing to fulfil different combinations of the ACR/EULAR Boolean remission criteria, compared with patients in remission.

## METHODS

### Patients and study design

Patients with disease modifying anti-rheumatic drug (DMARD)-naïve early RA fulfilling the 2010 ACR/EULAR classification criteria were included in the ARCTIC trial (Aiming for Remission in rheumatoid arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen).<sup>11</sup> Patients were followed by a tight control regime with 13 visits during the 2-year follow-up. Treatment was adjusted according to a predefined algorithm aiming for Disease Activity Score remission and no swollen joints, with an additional target of ultrasound remission in half of the patients. A biologic DMARD could not be prescribed without objective signs of active inflammation.<sup>11</sup> Data were pooled for the current analyses as previous results indicated no differences between the two study groups.<sup>11</sup> The study was conducted in compliance with the Declaration of Helsinki. Patients were not involved in study design, conduct, reporting or dissemination plans.

### Examinations

Clinical examination included swollen joint count (SJC, 0–44) and Ritchie Articular Index.<sup>12</sup> Laboratory tests, the physician's and patient's global assessment on a VAS (0–10), fatigue VAS (0–10) and physical function assessed by the Patient-Reported Outcome Measurement Information System (PROMIS) were evaluated.<sup>13</sup> Remission at the 2-year visit was defined by the ACR/EULAR Boolean remission with SJC  $\leq 1$  of 44, Ritchie

Articular Index  $\leq 1$ , CRP  $\leq 1$  and PGA  $\leq 1$ . At this time point, ultrasound examination of 32 joints and MRI of the dominant hand and wrist were performed in all patients. Ultrasound inflammation was scored as grey scale (GS) synovitis and power Doppler (PD) activity according to a semi-quantitative scale (0–3) by trained physicians using an atlas for reference.<sup>14</sup> The Outcome Measures in Rheumatology Clinical Trials Rheumatoid Arthritis MRI Scoring system was used for scoring of MRI inflammation.<sup>15</sup>

### Statistical analysis

Patients with complete clinical data at the 2-year visit were included. Characteristics at baseline and 2 years were described as proportions and medians (25th, 75th percentile). The proportion of patients fulfilling ACR/EULAR Boolean remission and the proportion fulfilling three out of the four remission criteria were calculated. In the latter cases, the component limiting achievement of remission was identified. We compared patient characteristics and clinical data of patients in complete ACR/EULAR Boolean remission to those who did not achieve remission due to elevated PGA and/or tender joints, and to patients with either SJC or CRP scored above the cut-off without restrictions on tender joints and PGA.  $\chi^2$  test and Wilcoxon rank sum test were used for comparisons as appropriate. MRI scores were compared using median regression, dealing with missing values through multiple imputation. We investigated the odds of biologic treatment at the 2-year visit using logistic regression with patients in remission as the reference group. Sensitivity analyses using ACR/EULAR Boolean remission based on 28 joints were performed.

## RESULTS

Of the 203 patients, 62% were women and the median symptom duration was 5 months at study initiation (table 1). At the 2-year visit, 112 patients (55%) were in ACR/EULAR Boolean remission.

### Limiting factors of ACR/EULAR Boolean remission

ACR/EULAR Boolean remission was not reached by 91/203 (45%) patients, of which 49 failed fulfilment of only one of the four components (figure 1). PGA was the major limiting factor (n=29, 59%), with a median (IQR) PGA of 3.1 (2.0, 4.4) in these patients. Scores were equally distributed between the two treatment groups from the initial randomised trial. The 11 (23%) patients with elevated tender joints had a median Ritchie Articular Index of 2.0 (2.0, 4.0), while in the patients with either swollen joints (n=3, 6%) or CRP (n=6, 12%) as the only limiting factor the median were 2.0 (2.0, 5.0) and 1.5 (1.1, 2.3), respectively. Analyses of ACR/EULAR Boolean remission based on the 28 joint count revealed similar results.

**Table 1** Baseline characteristics. Values are median (IQR) unless otherwise stated

Demographics	n=203
Female, n (%)	125 (61.6)
Age, years	54.1 (42.0, 62.9)
Symptom duration, months	5.4 (2.8, 10.5)
Positive for ACPA, n (%)	165 (81.3)
Positive for RF, n (%)	140 (69.0)
<b>Disease activity</b>	
Disease activity score	3.3 (2.6, 4.1)
Swollen joint count (0–44)	9.0 (4.0, 14.0)
Ritchie Articular Index (0–78)	6.0 (3.0, 12.0)
C reactive protein, mg/dL	0.7 (0.3, 1.8)
Patient's global assessment, VAS (0–10 mm)*	4.9 (2.8, 6.9)
Physician's global assessment, VAS (0–10 mm)*	3.5 (2.3, 5.4)
PROMIS physical function (12.1–62.5)	39.8 (33.3, 45.3)
Fatigue, VAS (0–10 mm)*	3.7 (1.3, 6.3)
Ultrasound grey-scale score (0–96)	19.0 (10.0, 28.0)
Ultrasound power Doppler score (0–96)	7.0 (3.0, 14.0)
MRI RAMRIS synovitis (0–21)	6.0 (4.0, 10.0)
MRI RAMRIS bone marrow oedema (0–75)	1.0 (0.0, 6.0)
MRI RAMRIS tenosynovitis (0–42)	5.0 (2.0, 10.0)

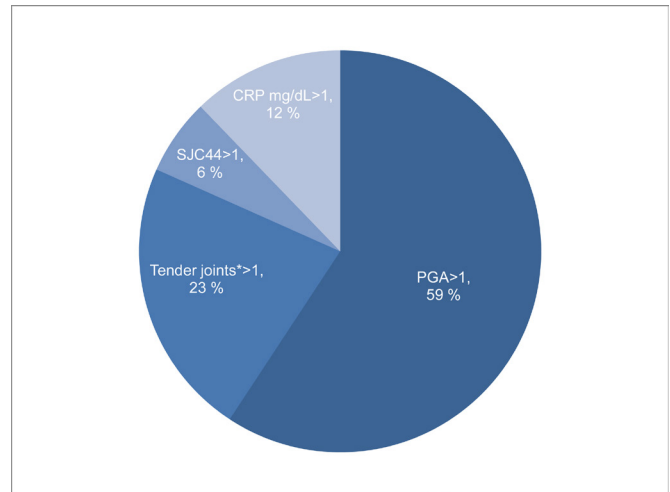
\*These variables were assessed on a VAS 0–100 mm, but converted to the more commonly used VAS 0–10 mm scale. ACPA, anti-cyclic citrullinated peptides; PROMIS, Patient reported Outcome Measurement Information Score Short Form v1.0—Physical Function 20a (reported as T-scores); RAMRIS, Rheumatoid Arthritis MRI Scoring System; RF, rheumatoid factor; VAS, visual analogue scale.

### Characteristics of patients in ACR/EULAR Boolean remission compared with patients not fulfilling the criteria

PGA, tender joints or both of these components were elevated in 61 of the 91 patients not achieving remission. Twenty-nine patients had either SJC >1 or CRP >1 (no restrictions on the PGA and tender joints), while only one patient failed to meet any of the four criteria. Patients missing fulfilment of ACR/EULAR Boolean remission due to PGA and/or tender joints had slightly, but significantly, higher SJC and physician global score compared with those fulfilling remission (table 2). Patients not fulfilling the remission criteria reported more fatigue and impaired physical function compared with those in remission, with the fatigue score especially high in those missing remission due to PGA and/or tender joints (table 2).

### Imaging inflammation and use of biologic therapy

Inflammation measured by ultrasound or MRI was not significantly different for patients not fulfilling remission due to PGA and/or tender joints compared with patients



**Figure 1** Limiting factors of ACR/EULAR Boolean remission. Percentages of patients fulfilling three out of the four remission criteria at 2 years (n=49). ACR, American College of Rheumatology; CRP, C reactive protein; PGA, patient global assessment on a visual analogue scale (0–10 cm); SJC44, swollen joint count (0–44). \*Assessed by Ritchie Articular Index 0–78. The approach used to handle this variable when calculating ACR/EULAR Boolean remission was outlined in the statistical analysis plan for the ARCTIC trial (Aiming for Remission in rheumatoid arthritis: a randomised trial examining the benefit of ultrasound in a Clinical Tight Control regimen).<sup>11</sup>

in remission. In patients not fulfilling the remission criteria with either CRP or swollen joints scored above the cut-off, there was higher median ultrasound GS and PD scores compared with patients in remission (table 2), while no significant difference was observed for the MRI scores. In the group fulfilling the ACR/EULAR Boolean remission criteria, 14% were on biologic therapy. In comparison, 38% received biologic therapy in the group with elevated PGA and/or tender joints and 35% in the group with either CRP or swollen joints scored above the cut-off. This corresponds to an OR (95% CI) of 3.63 (1.73 to 7.61) for using biologic therapy in those missing remission due to PGA and/or tender joints and 3.16 (1.24 to 8.01) in those with CRP or SJC elevation (table 2).

### DISCUSSION

PGA and tender joints were the components most often limiting achievement of ACR/EULAR Boolean remission in patients with early RA treated according to current recommendations, while few patients had swollen joints or elevated CRP. In patients who failed to meet these more subjective components of the criteria, the level of imaging inflammation measured by ultrasound and MRI was not elevated compared with patients in full remission, but the use of biologic therapy was higher.

The findings support that patient reported outcomes might limit fulfilment of ACR/EULAR remission in some patients without active inflammation assessed by inflammatory markers, swollen joints and imaging.<sup>7 16 17</sup>

**Table 2** Characteristics of patients in ACR/EULAR Boolean remission at 2 years compared with patients missing fulfilment of remission due to PGA and/or tender joints, and patients with either swollen joints or CRP above cut-off\*

	ACR/EULAR Boolean remission (ref), n=112	44SJC $\leq$ 1 & CRP $\leq$ 1 +PGA >1 and/or tender joints >1, n=61	P value for comparison to reference group	44SJC >1 or CRP >1 (no restrictions on tender joints and PGA), n=29	P value for comparison to reference group
Age, years	53.6 (41.1, 63.4)	53.3 (43, 61.2)	0.77	59.4 (51.9, 64.6)	0.08
Female, n (%)	65 (58.0)	44 (72.1)	0.07	16 (55.2)	0.78
Positive for ACPA, n (%)	88 (78.6)	53 (86.9)	0.18	23.0 (79.3)	0.93
Positive for RF, n (%)	74 (66.1)	43 (70.5)	0.55	22 (75.9)	0.31
Swollen joint count (0–44)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	<0.001	2.0 (0.0, 4.0)	<0.001
Ritchie Articular Index (0–78)	0.0 (0.0, 0.0)	2.0 (0.0, 3.0)	<0.001	2.0 (0.0, 5.0)	<0.001
C reactive protein, mg/dL	0.2 (0.1, 0.4)	0.3 (0.1, 0.4)	0.50	0.6 (0.4, 1.3)	<0.001
Patient's global assessment, VAS (0–10)†	0.3 (0.1, 0.5)	2.7 (1.6, 4.2)	<0.001	2.2 (0.9, 5.0)	<0.001
Physician's global assessment, VAS (0–10)†	0.2 (0.1, 0.8)	0.8 (0.4, 1.2)	<0.001	1.8 (0.5, 3.0)	<0.001
PROMIS physical function (12.1–62.5)	62.5 (50.0, 62.5)	45.3 (40.2, 50.0)	<0.001	44.2 (38.9, 51.2)	<0.001
Fatigue, VAS (0–10)†	0.4 (0.1, 1.2)	3.4 (1.7, 5.0)	<0.001	1.0 (0.7, 5.5)	<0.001
Ultrasound power Doppler score (0–96)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.75	0.0 (0.0, 4.0)	<0.001
Ultrasound Grey Scale score (0–96)	3.0 (1.0, 5.5)	3.0 (0.0, 6.0)	0.69	6.0 (4.0, 11.0)	<0.001
MRI RAMRIS synovitis (0–21)	4.0 (2.0, 5.6)	4.0 (1.9, 5.0)	1.00	4.1 (2.0, 6.6)	0.92
MRI RAMRIS bone marrow oedema (0–75)	1.0 (0.0, 2.7)	1.0 (0.0, 2.4)	1.00	2.0 (0.0, 3.0)	0.09
MRI RAMRIS tenosynovitis (0–42)	1.0 (0.0, 2.6)	1.0 (0.0, 2.0)	1.00	2.0 (0.0, 5.9)	0.14
Biologic treatment, n (%)	16 (14.3)	23 (37.7)	<0.001	10 (34.5)	0.012
Any intra-articular injections, n (%)‡	87 (77.7)	54 (88.5)	0.08	25 (86.2)	0.31
Total prednisolone dose (mg)‡§	607.5 (455.0, 825.0)	605.0 (435.0, 890.0)	0.85	735.0 (445.0, 1887.5)	0.11
Any NSAID use, n (%)‡	54 (48.2)	28 (45.9)	0.77	15 (51.7)	0.74
Patients with adverse events, n (%)‡	82 (73.2)	58 (95.1)	<0.001	25 (86.2)	0.15
Patients with serious adverse events, n (%)‡	5 (4.5)	1 (1.6)	0.33	2 (6.9)	0.59

Values are median (IQR) unless otherwise stated.

\*One patient who failed to meet all of the four ACR/EULAR Boolean remission criteria is not included in these comparisons.

†These variables were assessed on a VAS 0–100 mm, but converted to the more commonly used VAS 0–10 mm scale.

‡Over 24 months.

§Cumulative dose per patient.

ACPA, anti-cyclic citrullinated peptides; ACR, American College of Rheumatology; CRP, C reactive protein; NSAID, Non-steroidal anti-inflammatory drug; PGA, patient global assessment; PROMIS, Patient reported Outcome Measurement Information Score Short Form v1.0—Physical Function 20a (reported as T-scores); RAMRIS, Rheumatoid Arthritis MRI Scoring System; RF, rheumatoid factor; SJC, swollen joint count; VAS, visual analogue scale.

A recent study has proposed a modified threshold (cut-off of  $\leq 2$ ) for PGA in the ACR/EULAR Boolean criteria,<sup>18</sup> and a meta-analysis shows that a Boolean-based remission definition excluding the PGA yielded similar prediction of future good radiographic outcome as the original definition.<sup>19</sup> The latter study proposed that this alternative remission definition might prevent unnecessary and potential harmful therapy escalations. In our study,

significantly more patients who had not achieved remission were using biologic therapy compared with those in remission. When treating RA to target, further escalation of DMARDs is most likely inappropriate in the patients without signs of active inflammation. Communication of realistic goals for the disease modifying intervention is important early in the disease course, as is identification

of non-pharmaceutical interventions necessary for the individual patient.<sup>5,20</sup>

The number of patients in near-remission was low, with especially few patients failing fulfilment of remission due to elevated CRP or SJC. We could therefore not perform comparative analyses assessing patients failing one of the four components separately. The lack of a formal tender joint count is a limitation, while the opportunity to compare inflammation assessed by imaging between patients in remission and close to remission strengthens the study. Due to the stringent treatment algorithm, our dataset was not suitable for exploring disease activity at biologic DMARD introduction.

In conclusion, PGA and tender joints most frequently limited achievement of ACR/EULAR Boolean remission in this early RA treat-to-target study with high remission rates. The level of inflammation assessed by imaging was not elevated in patients failing to fulfil these more subjective components compared with patients in full ACR/EULAR Boolean remission, but the use of biologic DMARDs was significantly higher. Further research is still needed to define more individualised targets suited to guide treatment.

**Twitter** Ulf Sundin @UlfSundin

**Contributors** All authors were involved in drafting the manuscript or revising it critically for important intellectual content and approved the final manuscript to be submitted and agreed to be accountable for all aspects of the work. A-BA, HBH, TU, TKK, EAH and SL contributed to conception and design of the ARCTIC study. A-BA, HBH, TU and EAH contributed to acquisition of data. NPS, US, A-BA, JS, HBH, TU, TKK, EAH and SL contributed to analysis and interpretation of data.

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#### ORCID iDs

Nina Paulshus Sundlisæter <http://orcid.org/0000-0002-1295-0172>  
 Ulf Sundin <http://orcid.org/0000-0003-1860-6150>  
 Hilde Berner Hammer <http://orcid.org/0000-0001-7317-8991>  
 Till Uhlig <http://orcid.org/0000-0002-6881-9552>  
 Tore K Kvien <http://orcid.org/0000-0002-8441-3093>

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