Concise report

Clinical and ultrasound remission after 6 months of treat-to-target therapy in early rheumatoid arthritis: Associations to future good radiographic and physical outcomes

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ABSTRACT

Objective: To explore associations between remission, based on clinical and ultrasound definitions, and future good radiographic and physical outcome in early rheumatoid arthritis (RA).

Methods: Newly diagnosed RA patients followed a treat-to-target strategy incorporating ultrasound information in the ARCTIC-trial. We defined 6-month remission according to DAS, DAS28-ESR, ACR/EULAR Boolean criteria, SDAI, CDAI and two ultrasound definitions (no power Doppler signal, grey scale score ≤2). Two outcomes were defined; no radiographic progression and good outcome (no radiographic progression + physical function ≥ general population median), both sustained 12-24 months. We calculated the odds ratios (OR) of these outcomes for the remission definitions.

Results: Of 103 patients, 42-82% reached remission at 6 months, dependent on definition. 71% of patients had no radiographic progression and 37% good outcome. An association between 6-month remission and no radiographic progression was observed for ACR/EULAR Boolean remission (44 joints, OR 3.2 CI 1.2 to 8.4), ultrasound power Doppler (OR 3.6 CI 1.3 to 10.0) and grey scale remission (OR 3.2 CI 1.2 to 8.0). All clinical, but not ultrasound remission criteria were associated with achievement of a good outcome.

Conclusions: Our data support ACR/EULAR Boolean remission based on 44 joints as the preferred treatment target in early RA. Absence of ultrasound inflammation was associated with no radiographic progression.

KEYWORDS: Early Rheumatoid Arthritis, Disease Activity, Outcome research, Ultrasonography

INTRODUCTION

Early initiation of disease-modifying anti-rheumatic drug (DMARD) therapy with a defined treatment target within 6 months has become a keystone in the management of patients with rheumatoid arthritis (RA).[1, 2] Prevention of joint damage and disability are now achievable outcomes for a large proportion of newly diagnosed RA patients.[3]

Composite scores such as the Disease Activity Score (DAS), Disease Activity Score in 28 joints (DAS28), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) are used to measure disease activity and guide therapeutic decisions.[1, 4-6] Additionally, the Boolean based American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) remission criterion was developed to optimize radiographic and functional outcomes.[7] The ACR/EULAR task force recommended inclusion of ankles and forefeet in the assessment of remission, although formally not required.[7]

Remission according to composite scores and Boolean based criteria is associated with less radiographic joint damage,[7-9] and remission should be sustained as radiographic progression is a consequence of cumulative inflammation.[10-12] However, not all patients fulfilling clinical remission criteria show absence of radiographic progression, and ongoing subclinical inflammation detected by ultrasonography and magnetic resonance imaging may explain this discrepancy.[13]

The aim of this study was to explore the association between remission at 6 months and two outcomes of importance for evaluation of treatment success, 1) future no radiographic progression and 2) a combined good outcome of no radiographic progression and physical function comparable to the general population. In particular, we wanted to assess how potential ultrasound definitions of remission performed in comparison to clinical definitions.

METHODS

Patients and study design

DMARD-naïve early RA patients fulfilling the 2010 ACR/EULAR criteria were enrolled in the ARCTIC trial, randomising patients to a conventional or ultrasound tight control strategy.[14] Only patients with ultrasound examinations at all visits (ultrasound strategy, N=118) were included in the current analyses to allow for assessment of potential ultrasound definitions of remission. Patients without two radiographs during the second year of the study were excluded (N=15). Patients attended 13 visits in two years with treatment adjustments according to an algorithm targeting clinical remission (DAS<1.6), no swollen joints, and absence of ultrasound power Doppler signal (**Table S1**). Ultrasound examination of 32 joints was performed by trained physicians with semi-quantitative 0-3 scoring of synovitis for grey scale and power Doppler.[14, 15] Patients were started on methotrexate with prednisolone bridging (**Table S1**). Therapy was escalated if the target was not reached, patients with high disease activity and risk factors for progressive joint destruction could start biologics more rapidly (**Table S1**). The study was conducted in compliance with the Declaration of Helsinki.

Definitions of remission

Four clinical composite remission criteria were assessed: DAS, DAS28-erythrocyte sedimentation rate (ESR), CDAI and SDAI. Additionally, we evaluated the ACR/EULAR Boolean criteria, based on 28 and 44 joints, and three alternative definitions of remission: no swollen joints (of 44), no ultrasound power Doppler signal and minimal grey scale synovitis (sumscore ≤2 of 0-96).[14-16]. For secondary analyses, we defined sustained remission as remission at all of the 6, 8, 10 and 12 month visits.

Radiographs and outcomes

Radiographs (12, 16 and 24 months) were scored by two trained readers, blinded for clinical data, in chronological order using the van der Heijde modified Sharp method.[17] We defined no radiographic progression as <1 unit change 12-24 months (average score of the readers). Good outcome was defined as a combination of no radiographic progression and stable physical function assessed by the Patient-Reported Outcome Measurement Information System ≥ the median of the general population between 12-24 months,[18] in line with the good outcome definition used in the development of the ACR/EULAR remission criteria.[7]

Statistical analysis

Baseline characteristics were described as proportions (%), means (SD) and medians [25^{th}, 75^{th} percentile]. Associations between remission status at 6 months and outcomes were assessed using logistic regression, with similar analyses for sustained remission. Additionally, we calculated sensitivities and specificities, positive and negative likelihood ratios. The potential effect modification of biologic therapy on radiographic outcome was assessed by including remission status, biologic treatment and interaction terms in separate logistic regression models for the two main outcomes.

In secondary analyses, we calculated the odds ratios of no radiographic progression according to state of clinical disease activity (remission, low disease activity, moderate/high disease activity) at the 6-month visit, using moderate/high disease activity as reference category.

Missing radiographs were imputed by inter- or extrapolation if a minimum of 2 radiographs were available, whereas missing clinical, laboratory or ultrasound variables at the follow-up visits were imputed by interpolation. Statistical analyses were performed using STATA version 14.

RESULTS

Patient characteristics

Of 103 patients, 74% were female, mean (SD) age was 51.4 (12.9) years, disease duration 6.7 (5.3) months and DAS 3.5 (1.1) (**Table S2)**.

Remission and radiographic progression

ACR/EULAR Boolean remission based on 44 joints was achieved by 42% of patients at the 6-month visit, while 59% were in DAS remission and 49% in SDAI remission (**Table 1**). Mean / median radiographic progression 12-24 months was 0.8 (1.3) / 0.5 [0.0, 1.0], 71% had no progression. Patients in ACR/EULAR Boolean remission (44 joints) had higher odds of no radiographic progression from 12-24 months than patients not in remission, as had patients in ultrasound remission versus not being in ultrasound remission (**Figure 1, Table 1**). Patients in remission according to the composite indices at 6 months, except for CDAI, had a significantly higher odds of no radiographic progression compared to patients with moderate/high disease activity, and this was not significant for patients in low disease activity by any of the definitions (**Table 2**). Adjustment for biologic treatment at the 6-month visit (n=12) did not show any effect on the association between remission and radiographic progression. Results for patient in sustained remission are presented in **Table S3**.

Remission at 6 months and good outcome

A good outcome was achieved by 37%. Being in remission at 6 months according to any established clinical remission criteria predicted a good outcome, while the ultrasound definitions and no swollen joints did not (**Figure 1, Table 1**). Similar results were found for patients in sustained remission **(Table S3).**

Table 1 The performance of various remission criteria at 6 months for identifying patients without radiographic progression 12-24 months and patients with a good combined outcome* 12-24 months. Statistically significant findings are shown in bold. N=103.

	No radiographic progression						**Good combined outcome***					
	Prevalence of no radiographic progression						Prevalence of good combined outcome					
	Patients in remission n/N (%)	Patients not in remission n/N (%)	Sensitivity	Specificity	LR+ (95% CI)	LR- (95% CI)	Patients in remission n/N (%)	Patients not in remission n/N (%)	Sensitivity	Specificity	LR+ (95% CI)	LR- (95% CI)
Clinical outcomes												
DAS	47/61 (77)	26/42 (62)	0.64	0.53	1.38 (0.91 to 2.10)	0.67 (0.42 to 1.05)	30/61 (49)	8/42 (19)	0.79	0.52	**1.66 (1.22 to 2.24)**	**0.40 (0.21 to 0.78)**
DAS28-ESR	49/64 (77)	24/39 (62)	0.67	0.50	1.34 (0.91 to 1.99)	0.66 (0.40 to 1.07)	31/64 (48)	7/39 (18)	0.82	0.49	**1.61 (1.21 to 2.13)**	**0.37 (0.18 to 0.76)**
SDAI	39/50 (78)	34/53 (64)	0.53	0.63	1.46 (0.87 to 2.44)	0.74 (0.51 to 1.06)	29/50 (58)	9/53 (17)	0.76	0.68	**2.36 (1.59 to 3.50)**	**0.35 (0.19 to 0.63)**
CDAI	36/48 (75)	37/55 (67)	0.49	0.60	1.23 (0.75 to 2.02)	0.84 (0.58 to 1.22)	27/48 (56)	11/55 (20)	0.71	0.68	**2.20 (1.47 to 3.30)**	**0.43 (0.25 to 0.72)**
ACREULAR Boolean (44 joints)	36/43 (84)	37/60 (62)	0.49	0.77	**2.11 (1.06 to 4.21)**	**0.66 (0.49 to 0.89)**	27/43 (63)	11/60 (18)	0.71	0.75	**2.89 (1.80 to 4.62)**	**0.38 (0.23 to 0.64)**
ACREULAR Boolean (28 joints)	36/47 (77)	37/56 (66)	0.49	0.63	1.34 (0.80 to 2.27)	0.80 (0.56 to 1.14)	28/47 (60)	10/56 (18)	0.74	0.71	**2.52 (1.65 to 3.85)**	**0.37 (0.2 to 0.65)**
No swollen joints (44 joints)	50/67 (75)	23/36 (64)	0.69	0.43	1.21 (0.85 to 1.71)	0.73 (0.43 to 1.24)	28/67 (42)	10/36 (28)	0.74	0.40	1.23 (0.93 to 1.62)	0.66 (0.36 to 1.21)
Ultrasound												
Power Doppler=0	64/84 (76)	9/19 (47)	0.88	0.33	**1.32 (1.01 to 1.72)**	**0.37 (0.17 to 0.82)**	32/84 (38)	6/19 (32)	0.84	0.20	1.05 (0.88 to 1.26)	0.79 (0.33 to 1.90)
Grey scale score=<2	39/47 (83)	34/56 (61)	0.53	0.73	**2.00 (1.07 to 3.76)**	**0.64 (0.46 to 0.88)**	20/47 (43)	18/56 (32)	0.53	0.59	1.27 (0.83 to 1.92)	0.81 (0.55 to 1.20)

*Good combined outcome: A combination of no radiographic progression and stable physical function assessed by the Patient-Reported Outcome Measurement Information System (PROMIS) ≥ the median of the general population between 12-24 months.

Table 2: Odds ratios of no radiographic progression 12-24 months according to state of clinical disease activity composite measures at 6 months. Moderate/high disease activity as reference category. Statistically significant findings are shown in bold. N=103.

		No radiographic progression 12-24 months	
	Classification at 6 months, n/N (%)	OR (95% CI)	P-value
DAS			
Moderate/ high disease activity	15/103 (15)	ref	ref
Low disease activity	27/103 (26)	2.71 (0.73 to 10.04)	0.14
Remission	61/103 (59)	**3.84 (1.18 to 12.45)**	**0.03**
DAS28-ESR			
Moderate/ high disease activity	19/103 (18)	ref	ref
Low disease activity	20/103 (19)	3.33 (0.86 to 12.92)	0.08
Remission	64/103 (62)	**3.63 (1.24 to 10.58)**	**0.02**
SDAI			
Moderate/ high disease activity	17/103 (17)	ref	ref
Low disease activity	36/103 (35)	2.02 (0.62 to 6.62)	0.25
Remission	50/103 (49)	**3.15 (0.98 to 10.09)**	**0.05**
CDAI			
Moderate/ high disease activity	17/103 (17)	ref	ref
Low disease activity	38/103 (37)	2.49 (0.75 to 8.22)	0.14
Remission	48/103 (47)	2.67 (0.84 to 8.46)	0.10

DISCUSSION

We found that clinical remission by all established definitions increased the odds of reaching a good combined radiographic and physical outcome in early RA, while achieving ultrasound remission as well as ACR/EULAR Boolean remission was associated with no radiographic progression during the subsequent year. To our knowledge, this is the first study assessing both clinical remission and ultrasound remission with regards to future joint damage and good physical function in patients treated according to current recommendations.[1, 2]

EULAR recommends achievement of remission within 6 months in early RA.[1, 2] In our study, a good combined outcome was predicted by remission according to any assessed clinical composite score. In addition to the two ultrasound remission definitions, only ACR/EULAR Boolean remission at six months, with assessment of 44 joints, predicted no radiographic progression when comparing patients in remission to all patients not in remission. These findings support ACR/EULAR Boolean remission as the preferred definition of remission in early RA,[1] but also underline previous publications recommending inclusion of the feet when assessing remission.[7, 19] When assessing

categories of disease activity, low disease activity at 6 months was less associated with no radiographic progression than achievement of remission by this point. This adds validity to the choice of remission as the preferred treatment target in early RA.[1, 2]

Good physical function is important to patients. We found that being in ultrasound remission did not capture the functional aspects of the disease as well as the clinical criteria. Thus, our data support clinical definitions of remission when aiming for a good combined outcome, although the data suggest limited specificity and sensitivity for all remission definitions. This is in line with the recent findings that targeting ultrasound remission is not superior to targeting clinical remission or low disease activity.[14, 20] However, the importance of being in ultrasound remission on other patient related outcomes, such as pain, needs to be further explored. In some cases, components of the clinical disease activity measures might be influenced by non-RA-related factors,[2] and in such settings ultrasonography might be suitable to help guide treatment decisions to prevent radiographic progression.

A limitation of our study is the overall low radiographic progression, which makes it difficult to study the association between remission and future joint damage. Thus, the absence of significant associations between sustained clinical remission and radiographic progression may be attributed to the low overall radiographic progression. This has also been proposed as a possible explanation in the COBRA-light trial which demonstrated that remission was associated with a good functional outcome, but not predictive of absent radiographic progression.[21] The low rate of radiographic progression reflects RA management when applying modern treatment strategies. As the results presented in this report are based on secondary or exploratory analyses, the possibility of lack of power cannot be excluded. Another limitation is the use of 44 joint count that might not be feasible in clinical practice. The results are strengthened by the broad inclusion criteria compared to industry-sponsored pharmaceutical trials, capturing a broad range of early RA patients, and the opportunity to

assess ultrasound remission. However, the generalizability of the findings to other clinical settings, with different treat-to-target strategies, and to other populations such as established RA, is unknown.

In conclusion, absence of ultrasound inflammation was associated with no subsequent radiographic progression, while being in ACR/EULAR Boolean remission after six months of targeted therapy increases both the odds of no radiographic progression and a good outcome. Our results support current recommendations stating that ACR/EULAR remission including assessment of the feet should be the preferred treatment target in early RA, and that low disease activity is a less preferred target.

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Contributors All authors were involved in drafting the article 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. Conception and design of the study: ABA, ICO, HBH, TU, DvdH, TKK, SL and EAH. Acquisition of data: ABA, HBH, TU and EAH. Analysis and interpretation of data: NPS, ABA, ICO, HBH, TU, DvdH, TK, SL and EAH.

Competing interest: ICO has received consultancy honorarium from Pfizer; ABA has sat on advisory boards for UCB, AbbVie, and Pfizer and received honorariums for development of educational material for UCB; HBH has received honorariums as a speaker from AbbVie, Bristol-Myers Squibb, Roche, UCB Pharma, Novartis and Pfizer; TU has received honorariums as a speaker from AbbVie, Bristol-Myers Squibb, Lilly, Roche, Novartis, UCB Pharma, and Pfizer; DvdH has received consultancy honorariums from AbbVie, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Celgene, Daiichi, Eli Lilly, Galapagos, Merck, Novartis, Pfizer, Roche, Sanofi Aventis, Janssen, and UCB and is owner of Imaging Rheumatology; TKK has received fees for speaking and/or consulting from AbbVie, Biogen, BMS, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Epirus, Hospira, Merck-Serono, MSD, Mundipharma, Novartis, Oktal, Orion Pharma, Hospira/Pfizer, Roche, Sandoz and UCB; EAH has received research funding from Pfizer, UCB, Roche, MSD, and AbbVie for the submitted work, honorariums as a speaker from Pfizer, UCB, Roche, and AbbVie, and honorariums for development of educational material from Pfizer and has sat on advisory boards for Pfizer, Eli Lilly, Celgene.

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Patient consent Obtained.

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).

References

1. Smolen JS, Landewe R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Annals of the rheumatic diseases. 2017;76:960-77.
2. Smolen JS, Breedveld FC, Burmester GR, et al. Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Annals of the rheumatic diseases. 2016;75:3-15.
3. Morel J, Combe B. How to predict prognosis in early rheumatoid arthritis. Best practice & research Clinical rheumatology. 2005;19:137-46.
4. Aletaha D, Smolen JS. The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) to monitor patients in standard clinical care. Best practice & research Clinical rheumatology. 2007;21:663-75.
5. van der Heijde DM, van 't Hof M, van Riel PL, et al. Development of a disease activity score based on judgment in clinical practice by rheumatologists. The Journal of rheumatology. 1993;20:579-81.
6. Prevoo ML, van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis and rheumatism. 1995;38:44-8.
7. Felson DT, Smolen JS, Wells G, et al. American College of Rheumatology/European League against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Annals of the rheumatic diseases. 2011;70:404-13.
8. Klarenbeek NB, Koevoets R, van der Heijde DM, et al. Association with joint damage and physical functioning of nine composite indices and the 2011 ACR/EULAR remission criteria in rheumatoid arthritis. Annals of the rheumatic diseases. 2011;70:1815-21.
9. Lillegraven S, Prince FH, Shadick NA, et al. Remission and radiographic outcome in rheumatoid arthritis: application of the 2011 ACR/EULAR remission criteria in an observational cohort. Annals of the rheumatic diseases. 2012;71:681-6.
10. van Leeuwen MA, van der Heijde DM, van Rijswijk MH, et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. A comparison of radiologic damage, physical disability, joint counts, and acute phase reactants. The Journal of rheumatology. 1994;21:425-9.
11. Boyesen P, Haavardsholm EA, Ostergaard M, et al. MRI in early rheumatoid arthritis: synovitis and bone marrow oedema are independent predictors of subsequent radiographic progression. Annals of the rheumatic diseases. 2011;70:428-33.
12. Naredo E, Collado P, Cruz A, et al. Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. Arthritis and rheumatism. 2007;57:116-24.
13. Haavardsholm EA, Lie E, Lillegraven S. Should modern imaging be part of remission criteria in rheumatoid arthritis? Best practice & research Clinical rheumatology. 2012;26:767-85.
14. Haavardsholm EA, Aga AB, Olsen IC, et al. Ultrasound in management of rheumatoid arthritis: ARCTIC randomised controlled strategy trial. BMJ (Clinical research ed). 2016;354:i4205.
15. Hammer HB, Bolton-King P, Bakkeheim V, et al. Examination of intra and interrater reliability with a new ultrasonographic reference atlas for scoring of synovitis in patients with rheumatoid arthritis. Annals of the rheumatic diseases. 2011;70:1995-8.
16. Padovano I, Costantino F, Breban M, et al. Prevalence of ultrasound synovial inflammatory findings in healthy subjects. Annals of the rheumatic diseases. 2016;75:1819-23.
17. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. The Journal of rheumatology. 2000;27:261-3.
18. Hays RD, Spritzer KL, Fries JF, et al. Responsiveness and minimally important difference for the patient-reported outcomes measurement information system (PROMIS) 20-item physical

functioning short form in a prospective observational study of rheumatoid arthritis. Annals of the rheumatic diseases. 2015;74:104-7.
19. Landewe R, van der Heijde D, van der Linden S, et al. Twenty-eight-joint counts invalidate the DAS28 remission definition owing to the omission of the lower extremity joints: a comparison with the original DAS remission. Annals of the rheumatic diseases. 2006;65:637-41.
20. Dale J, Stirling A, Zhang R, et al. Targeting ultrasound remission in early rheumatoid arthritis: the results of the TaSER study, a randomised clinical trial. Annals of the rheumatic diseases. 2016;75:1043-50.
21. Konijn NPC, van Tuyl LHD, Boers M, et al. Do Short and Sustained Periods of American College of Rheumatology/European League Against Rheumatism Remission Predict Functional and Radiographic Outcome in Early Rheumatoid Arthritis Patients With Low Overall Damage Progression? Arthritis care & research. 2017;69:989-96.

FIGURE LEGEND

Figure 1: The association between remission at 6 months and no radiographic progression (blue bars) and good combined outcome (orange bars, no radiographic progression + physical function ≥ median in the general population), both 12-24 months.