Prevalence and validity of ACR/EULAR remission in four European early rheumatoid arthritis cohorts

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Abstract

Objective

In 2011 an ACR/EULAR collaboration developed new remission definitions for RA. In the present study, we evaluated the prevalence and predictive validity of these new ACR/EULAR remission criteria in 4 different European early rheumatoid arthritis cohorts.

Method

Data from a tot al of 722 patients with early RA were analysed. Presence of remission at 6 months, as defined by one of the 4 proposed ACR/EULAR remission definitions was used to predict good functional and radiological outcome between 1 and 2 years of follow-up.

Results

Remission rates at 6 months ranged from 2–17% (Boolean definition) between the four cohorts. The level of HAQ and radiological damage varied between cohorts. Patients in remission at 6 months have an increased likelihood of long-term good outcome in terms of HAQ stability, but not radiographic stability. The performance of the practice definitions of remission was highly similar to the trial definitions. CRP status seems to add little information to the classification of remission in early RA.

Conclusion

In clinical practice, a minority of patients with early RA achieves remission in the first 6 months of treatment. Remission at 6 months is predictive for good HAQ outcome between year 1 and 2 after inclusion, but not radiographic stability.

Key words

rheumatoid arthritis, remission, epidemiology, outcome assessment

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Introduction

Early recognition and intensified treatment of patients with rheumatoid arthritis (RA) has resulted in better radiological and functional outcomes, with remission as an achievable goal. Until recently, remission was defined in a variety of ways, ranging from strict to relaxed definitions, resulting in varying proportions of patients that reached this favourable state (1, 2). To establish homogeneity in striving for remission as the goal of RA treatment, a joint American College for Rheumatology (ACR) and European League Against Rheumatism (EULAR) Task Force presented the 2011 provisional definitions of remission in RA for clinical trials. These definitions, a Boolean definition and an index- based definition (simplified disease activity index, SDAI), were chosen as ACR/EULAR clinical trial definitions, based on the predictive ability and face validity of different combinations of variables collected in clinical trials. For clinical practice, the same 2 definitions were proposed, with the exception of the use of C-reactive protein (CRP) levels (3). Reported remission rates at 12 months range from 18–40% according to the remission definition applied (4), but may indeed be higher in early disease, with increasing ACR/EULAR index-based remission frequencies occurring between 6 and 12 months, reaching levels close to 50% on biologics plus MTX and close to 30% on MTX alone (5).

Several reports have shown the validity of the new criteria in clinical trial settings, but little is known about the validity and predictive ability of the remission definitions in daily practice. An editorial by Jacobsson and Hetland (6) called for validation studies in observational cohorts and especially in early disease. Two previous reports showed that the ACR/EULAR remission definitions developed for trials are similarly valid in observational (early) arthritis cohorts (7, 8); the proposed practice-based definitions were not evaluated. Since data on the performance of the remission definitions in observational early RA is still scarce, the current study aims to 1) assess the prevalence of remission in four different European observational early arthritis cohorts and 2) to validate the remission definitions by evaluating the predictive ability of the new ACR/EULAR remission criteria in this practice-based setting.

Methods

Patients

Data from 4 early arthritis cohorts were analysed (Reade, Amsterdam, The Netherlands (9); University Hospitals Leuven, Leuven, Belgium (10); Radboud University Nijmegen, Nijmegen, The Netherlands (11); and the Medical University of Vienna, Vienna, Austria (12)). Ethical approval for data collection in the original cohort was given in all four centers and all patients gave their written informed consent to participate in the cohort. The main inclusion criteria for each cohort are provided in Table I.

Patients with RA according to the 1987 ACR classification criteria at baseline or 1 year who were not using biologicals were included in the current analysis. At baseline and each follow-up visit, patients underwent assessment that included a 28 tender joint count (TJC) and 28 swollen joint count (SJC), patient's assessment of global health on visual analogue scale (range 0–10) (PtGA), patient's assessment of pain and physician's assessment of disease activity (PhGA), erythrocyte sedimentation rate (ESR) and CRP. Functional status was assessed with the Health Assessment Questionnaire (HAQ). Radiographs of the hand and feet were made at baseline and then yearly, and were scored according to the van der Heijde modified total Sharp Score method (mTSS). In Nijmegen, radiographs were scored according to the Ratingen method (13, 14)

Remission definitions

The following 4 ACR/EULAR proposed remission definitions were assessed: first, the Boolean-based clinical trial definition, second, the SDAI ≤3.3, third, the clinical practice Boolean-based definition which omits CRP status and fourth, the Clinical Disease Activity Index (CDAI) ≤2.8 (Table II). For calculation purposes, visual analogue scale scores were recoded where necessary from a 0–100 scale to a 0–10 scale and CRP from mg/l to mg/dl.

Table I. Inclusion criteria of the four early arthritis cohorts.

Cohort	Inclusion criteria	Exclusion criteria	Treatment
Amsterdam	≥2 swollen joints Disease duration ≤2 year No prior DMARD use	Osteoarthritis, gout, SpA, SLE, M Sjögren, infectious arthritis	Based on physician's decision
Leuven	Newly diagnosed RA	Recruitment in industry-sponsored early RA trials	IMT or ICTS, primary based on physician's decision.
Nijmegen	1987 ACR RA Disease duration ≤1 year No prior DMARD use	Diseases other than RA	Based on physician's decision
Vienna	No trauma ≥1 tender and ≥1 swollen joint Morning stiffness >60 min ↑ESR or ↑CRP or RF positivity Symptom duration ≤12 weeks	Any other explanation of synovitis than RA	Based on physician's decision

SpA: spondylarthropathy; SLE: systemic lupus erythematosus; DMARD: disease-modifying anti-rheumatic drug; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; RF: rheumatoid factor; IMT: Initial DMARD monotherapy with MTX or SSZ; ICTS: initial DMARD combination therapy with steroids.

Identical to the way the remission criteria were developed (3), remission was evaluated at 6 months (4 months for the Leuven cohort), well before and thus independent of measurement of the outcome between 12 and 24 months. However, in a clinical practice setting, treatment strategies change depending on the patient's disease activity state and are not fixed like in clinical trials. Patients who did not achieve remission at 6 months could have had further therapeutic changes during the time between month 6 and year 2. Therefore, we performed sensitivity analyses in the Amsterdam cohort with remission at 12 months as well as sustained remission between 6 and 12 months.

Outcome measures

In line with the development of the remission criteria, three definitions of good long-term outcome were defined; first, no progression between year 1 and 2 in the van der Heijde modified Total Sharp Score (ΔmTTS=0); secondly, no increase in HAQ score between year 1 and 2 with HAQ ≤0.5 consistently in the second year after inclusion; and thirdly, no progression in total Sharp score AND no increase in HAQ between year 1 and 2 with HAQ ≤0.5 consistently in the second year.

However, since this is a practice-based setting, with radiographs being scored by one reader only, sensitivity analyses were performed in the Amsterdam cohort, with ΔmTSS≤1 in both outcome definitions.

Table II. ACR/EULAR definitions of remission in rheumatoid arthritis clinical trials.

Boolean based definition:
At any time point, patient must satisfy all of the following:
- Tender Joint Count ≤1*
- Swollen Joint Count ≤1*
- CRP ≤1 mg/dL
- Patient Global Assessment ≤1 (on a 0–10 scale)†

Index based definition:
At any time point, patient must have SDAI ≤3.3§

Boolean based suggestion for clinical practice:
At any time point, patient must satisfy all of the following:
- Tender Joint Count ≤1*
- Swollen Joint Count ≤1*
- Patient Global Assessment ≤1 (on a 0–10 scale)†

Index based suggestion for clinical practice:
At any time point, patient must have CDAI ≤2.8§

*For tender and swollen joint counts, a 28 joint count may miss active joints especially in the feet and ankles and it is preferable to include feet and ankles also when evaluating remission.
†The following wording and response categories should be used for global assessment: Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today? Verbal anchors for the response can range from 'asymptomatic' to 'severe symptoms'.
§SDAI, Simplified Disease Activity Index is defined as the simple sum of the tender joint count (28), swollen joint count (28), patient global assessment (on a 0–10 scale), physician global assessment (on a 0–10 scale) and CRP (mg/dL). CDAI, Clinical Disease Activity Index is the same as the SDAI but minus CRP.

Cohort specific assumptions or exceptions

To increase the number of cases available for analysis, missing data were substituted where possible. To avoid selection bias and use the existing data optimally, some cohort-specific decisions were made: The Amsterdam and Nijmegen cohort did not register a PhGA and could therefore not calculate the SDAI and CDAI remission definitions. In Nijmegen, missing data on PtGA were substituted by patient general health; if CRP was missing and remission status could therefore not be determined, the ESR remission level was used, using the following assumption: CRP ≤10 ≈ ESR <20. Remission was evaluated at 6 months, except for the Leuven cohort, where it was established at 4 months. In Nijmegen, radiographs were scored according to the Ratingen score instead of the van der Heijde modified Total Sharp Score. It was assumed that these 2 scores were equal in terms of stability over 12 to 24 months. In Vienna, no radiological data were available, so only the second good outcome definition (HAQ) was tested.

Statistical analysis

Due to the large differences in inclusion criteria, inclusion period and treatment between the cohorts, all analyses were performed separately for each cohort, by one researcher (KB). First the prevalence of remission in the study population according to the four definitions was calculated. Next, in line with the development of the remission criteria, likelihood ratios compared the proportion of patients in remission having a good outcome to the proportion of patients not in remission having a good outcome. Chi-square analysis tested the association (predictive validity) of the remission definitions with good outcome. As mentioned above, sensitivity analyses were done in the Amsterdam cohort, to account for differences between trial and clinical practice settings. SPSS v. 17.0 was used for all analyses. The threshold for significance was set at $p<0.05$.

Table III. Baseline demographics and disease characteristics.

Variable	Amsterdam n=468	Leuven n=63	Nijmegen n=120	Vienna n=71
Year of inclusion	1995-2009	2003-2007	1985-2003	2004-2010
Age, year	54 (13)	51 (17)	58 (13)	58 (13)
Female, n (%)	341 (70)	40 (63)	82 (65)	46 (65)
IgM RF positivity, n (%)	259 (56.6)	46 (72)	96 (76)	28 (39)
ACPA positivity, n (%)	262 (60.4)	43 (67)	83 (65)	31 (46)
Symptom duration, months	4.2 (2.5-7.0)	6.2 (3.4-11.1)	n/a	4.8 (2.4-7.1)
DAS-28	5.2 (1.2)	5.4 (1.3)	5.4 (1.4)	4.7 (1.2)
TJC28	6 (3-10)	7 (3-14)	8 (4-15)	4 (2-8)
SJC28	7 (4-11)	7 (4-12)	12 (8-18)	5 (2-8)
PtGA, 0-10	5.3 (3.8-7.2)	5.5 (3.3-7.5)	4.7 (2.3-6.6)	4.8 (3.0-6.2)
PhGA, 0-10	4.0 (2.4-5.7)	4.5 (2.6-5.5)	3.4 (2.4-4.7)	2.6 (1.4-4.2)
CRP, mg/dL	17 (6-42)	18 (8-42)	6 (0-30)	12 (5-29)
ESR, mm/1st hour	29 (16-44)	37 (18-48)	32 (15-54)	25 (14-62)
Pain, 0-10	5.1 (3.2-7.0)	5.1 (3.3-7.0)	4.9 (2.9-6.5)	4.5 (2.2-5.6)
Erosion score	0 (0-0)	0 (0-1)	0 (0-3)*	n/a
% with erosions	23	27	45	n/a
Total Sharp score	0 (0-2)	0 (0-4)	n/a	n/a
% with total Sharp score >0	36	47	n/a	n/a
HAQ, 0-3	1.13 (0.63-1.75)	1.13 (0.5-1.75)	0.64 (0.32-1.23)	0.5 (0-1)

Data are presented as mean (SD) or median (IQR) as appropriate. DAS-28: 28 joint count Disease Activity Score; TJC28: 28 tender joint count; SJC28: 28 swollen joint count; PtGA: patients' global assessment on a 0–10 scale; PhGA: physicians' global assessment on a 0–10 scale; ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein; Pain: VAS pain on a 0–10 scale; HAQ: Health Assessment Questionnaire. *Ratingen score.

Results

Patients

The 4 cohorts comprised 468 (Amsterdam), 63 (Leuven), 120 (Nijmegen) and 71 (Vienna) patients. Clinical and demographic characteristics of the patients from the four early arthritis cohorts are shown in Table III. Most patients had active disease at baseline, with mean DAS28 between 4.7 and 5.4. Radiographic damage at baseline was minimal in all 4 cohorts. Twelve months after inclusion the percentage of patients receiving DMARD monotherapy was 57% in Amsterdam, 83% in Leuven, 76% in Nijmegen and 49% in Vienna. 15%, 15%, 1% and 1% of patients were treated with initial DMARD combination therapy, and 27%, 80%, 17% and 48% of patients were treated with prednisone within in the first year, respectively.

Outcome measures

Between years 1 and 2, stable damage scores (good radiological outcome) were observed in 40% to 64% of the patients in the individual cohorts. The combination of no HAQ progression and consistent HAQ ≤0.5 (good functional outcome) was found in 22–74%. Finally, a combination of good radiological and good functional outcome was found in 11–20%. Median HAQ and mTSS scores at 1 and 2 years, of patients in remission compared to patients not in remission at 6 months, are presented in Table IV.

Prevalence of remission

The rates of remission 6 months after inclusion showed considerable variation between the cohorts: depending on the definition used, it ranged between 2% (Nijmegen Boolean) and 28% (Vienna CDAI). Mean (SD) DAS28 at 6 months was 2.4 (1.2), 2.8 (1.1), 4.4 (1.5) and 2.8 (1.2), respectively. Fifty-seven percent (Amsterdam), 54% (Leuven), 11% (Nijmegen) and 44% (Vienna) of patients reached DAS28<2.6 at 6 months. Remission rates were slightly higher when CRP was omitted from the definition (Boolean *vs*. Boolean minus CRP and SDAI *vs*. CDAI) but the differences were not statistically significant. In Amsterdam, Nijmegen, and Vienna remission rates increased over time, whereas it decreased in Leuven (Table IV); In the Amsterdam cohort, remission rates at 12 months were slightly higher than at 6 months, with 9% in Boolean remission and 11% in Boolean remission without CRP. However, sustained remission was present in only 3% and 4% of patients, respectively.

Predictive ability

In Amsterdam, patients in remission at 6 months by the two Boolean definitions had an increased likelihood of stable HAQ scores in the subsequent year after inclusion. However, despite significantly different radiographic progression between patient in and not in remission, the likelihood of radiographic stability was not increased ($p=0.339$ and $p=0.456$). When the good outcome definition was the combination of the two separate outcomes, likelihood was increased again (Table V).

In Vienna, all patients in remission at 6 months by the two Boolean definitions had good long-term outcome in terms of HAQ outcome. The same applies to the two Nijmegen patients in remission (Table V). Although likelihood ratios could thus not be calculated, logistic regression analysis in these two cohorts demonstrates that patients in remission at 6 months have a higher probability of having good long-term outcome compared to patients not in remission ($p<0.05$). In Leuven, only patients in

Table IV. Median (IQR) HAQ and Sharp score at 6 months in patients in remission and patients not in remission.

Amsterdam		In remission	Not in remission	*p*-value*
Boolean		n=32	n=436	
HAQ	1 year	0.00 (0.00-0.25)	0.63 (0.13-1.13)	<0.001
HAQ	2 year	0.13 (0.00-0.25)	0.63 (0.00-1.13)	<0.001
mTSS	1 year	0 (0-2)	1 (0-5)	0.002
mTSS	2 year	0 (0-2)	2 (0-9)	0.002
Boolean minus CRP		n=36	n=432	
HAQ	1 year	0.06 (0-0.38)	0.63 (0.13-1.13)	<0.001
HAQ	2 year	0.13 (0-0.72)	0.63 (0.00-1.13)	0.001
mTSS	1 year	0 (0-2)	1 (0-5)	0.006
mTSS	2 year	0 (0-3)	2 (0-9)	0.005
Leuven		In remission	Not in remission	*p*-value*
Boolean		n=9	n=54	
HAQ	1 year	0.00 (0.00-0.13)	0.50 (0.00-1.13)	0.016
HAQ	2 year	0.38 (0.000-1.13)	0.44 (0.00-1.13)	0.794
mTSS	1 year	2 (0-4)	1 (0-7)	0.902
mTSS	2 year	2 (0-5)	2 (0-8)	0.548
Boolean minus CRP		n=10	n=53	
HAQ	1 year	0.00 (0.00-0.31)	0.50 (0.00-1.13)	0.027
HAQ	2 year	0.32 (0.00-0.88)	0.50 (0.00-1.25)	0.519
mTSS	1 year	2 (0-6)	1 (0-7)	0.556
mTSS	2 year	3 (0-7)	2 (0-8)	0.901
SDAI/CDAI		n=12	n=47	
HAQ	1 year	0.00 (0.00-0.00)	0.500 (0.00-1.13)	0.002
HAQ	2 year	0.31 (0.00-0.59)	0.63 (0.00-1.25)	0.320
mTSS	1 year	1 (0-3)	1 (0-7)	0.860
mTSS	2 year	2 (0-5)	2 (0-8)	0.527
CDAI		n=13	n=46	
HAQ	1 year	0.00 (0.00-0.13)	0.50 (0.00-1.13)	0.003
HAQ	2 year	0.25 (0.00-0.56)	0.50 (0.03-1.44)	0.187
mTSS	1 year	1 (0-4)	5 (0-16)	0.789
mTSS	2 year	2 (1-5)	5 (0-16)	0.845
Nijmegen		In remission	Not in remission	*p*-value*
Boolean/Boolean minus CRP		n=2	n=118	
HAQ	1 year	0.00; 0.45#	0.40 (0.18-0.77)	0.314
HAQ	2 year	0.00; 0.05#	0.54 (0.15-0.96)	0.014
Total Ratingen score	1 year	0; 1#	4 (0-10)	0.280
Total Ratingen score	2 year	0; 1#	6 (0-16)	0.191
Vienna		In remission	Not in remission	*p*-value*
Boolean		n=12	n=59	
HAQ	1 year	0.00 (0.00-0.09)	0.38 (0.00-0.75)	0.001
HAQ	2 year	0.00 (0.00-0.00)	0.38 (0.00-0.63)	<0.001
Boolean minus CRP		n=13	n=58	
HAQ	1 year	0.00 (0.00-0.19)	0.38 (0.00-0.78)	0.002
HAQ	2 year	0.00 (0.00-0.00)	0.38 (0.00-0.66)	<0.001
SDAI		n=19	n=51	
HAQ	1 year	0.00 (0.00-0.25)	0.38 (0.00-0.88)	0.004
HAQ	2 year	0.00 (0.00-0.13)	0.38 (0.00-0.75)	0.001
CDAI		n=20	n=50	
HAQ	1 year	0.00 (0.00-0.34)	0.38 (0.00-0.75)	0.017
HAQ	2 year	0.00 (0.00-0.13)	0.38 (0.00-0.75)	0.003

mTSS: van der Heijde modified Total Sharp Score; *Mann-Whitney U-test; #real HAQ/mTSS values of the two patients in remission.

CDAI remission have a good long-term outcome in terms of HAQ outcome; when the two separate outcomes were combined, the likelihood of good long-term outcome was increased for patients in SDAI and CDAI remission (at 4 months). The sensitivity analyses in the Amsterdam cohort showed highly similar predictive ability when remission at 12 months rather than 6 months was evaluated (data not shown). Moreover, if progression of radiological damage was defined as a ΔmTSS of ≤1 instead of 0, this did not alter the results (data not shown). However, sustained remission between 6 and 12 months had a slightly better predictive ability for good outcome in terms of stable HAQ and TSS combined compared to remission at either 6 or 12 months: LR+ were 3.0 (1.0–9.3) for sustained Boolean remission and 2.85 (1.1–7.3) for sustained Boolean without CRP remission.

Discussion

This study of 4 clinic-based early rheumatoid arthritis cohorts revealed variable rates of remission. The Boolean definition was confirmed to be the most stringent (3, 4, 7, 8) and CRP status could be omitted without penalty to the remission rates or the capacity to predict good outcome. As a whole, predictive ability was limited but in line with the data from established RA cohorts (3).

Strengths of this study include the replication of the methods and tests used in the original remission paper (3), allowing a good comparison of the results. Moreover, the results of 4 rather different European early arthritis cohorts were combined in one paper, which demonstrates the performance of the new criteria in different settings.

Although there are major differences between the cohorts, the results of predictive validity are largely the same; a state of remission as defined by one of the four proposed ACR/EULAR criteria increases the likelihood of a low and stable HAQ score in the near future. The likelihood of remission to result in stability of radiographic damage was less convincing, because the low radiographic damage and progression in early RA patients in general make it hard to differentiate between disease

Table V. Prevalence of remission and good outcome.

	Amsterdam n=468					Leuven n=63					Nijmegen n=120					Vienna n=71				
Follow-up visit	0	3	6	12	24	0	4	8	12	24	0	3	6	12	24	0	3	6	12	24
TJC28 ≤1, %	14	38	42	42		13	44	57	52		8	20	25	30		24	X	62	62	
SJC28 ≤1, %	5	26	34	44		5	46	52	54		4	6	9	12		21	X	59	76	
PtGA ≤1, %	6	18	21	24		10	23	24	25		4	8	12	11		5	X	31	34	
PhGA ≤1, %	X	X	X	X		3	53	58	50		8	9	26	39		21	X	58	73	
CRP ≤1, %	37	69	76	75		33	84	84	84		49	58	69	43		47	X	75	79	
DAS-28 CRP remission, %			57				54						11					44		
Boolean remission, %	0*	4	7	9		0	14	19	13		0	2	2	3		2	X	17	23	
Boolean remission minus CRP, %	0*	6	8	11		0	16	19	14		0	2	2	4		1	X	18	27	
SDAI	X	X	X	X		29.4 (15)	9.3 (7.5)	8.7 (7.1)	9.4 (7.1)		X	X	X	X		21.0 (13.3)	X	9.4 (9.3)	8.5 (8.4)	
SDAI remission, %	X	X	X	X		0	20	32	18		X	X	X	X		2	X	27	35	
CDAI	X	X	X	X		26.9 (14.1)	8.6 (7.2)	7.9 (6.7)	8.7 (6.9)		X	X	X	X		18.6 (10.9)	X	8.5 (9.1)	7.6 (8.4)	
CDAI remission, %	X	X	X	X		0	22	32	18		X	X	X	X		3	X	28	32	
Radiological progression between year 1 and 2					0 (0-2)					0 (0-1)					2 (0-5)					n/a
Good radiological outcome, %					61					64					40					n/a
Good HAQ outcome, %					33					22					28					74
Good radiological AND good HAQ outcome, %					20					16					14					n/a

*Prevalence of Boolean remission baseline in the Amsterdam cohort =0.2%.

activity states. Only in the Nijmegen cohort, which included patients from 1985 to 2003, radiographic stability in remission was observed. However, only two patients in this cohort reached remission, both attaining good long-term outcome. The small number of patients reaching remission in this cohort is most likely due to the inclusion period and the subsequent differences in treatment strategies. When the prevalence of remission before and after the year 2000 in the Amsterdam cohort is studied we see a similar pattern, with only 2% of patients reaching remission at 6 months before 2000 compared to 10% of patients after the year 2000. Recent findings from the NOR-DMARD study show a similar prevalence for ACR/EULAR remission at 6 months (15). Another recent study from Finland by Rannio *et al*. (16) using a treat to target approach reported high Boolean remission rates in RA patients of 27% at three months and 16% at both three and twelve months, underscoring the effectiveness of modern therapy approaches. As mentioned in the previous paragraph, lower remission rates were found in cohorts with a less recent inclusion period and therefore longer disease duration and less intensive treatment strategies. Beside these established predictors associated with remission, other barriers that prevent patients from achieving remission could be present. Tymms *et al*. (17) identified rheumatologist-recorded barriers to disease control in patients with moderate or high disease activity, when there was no adjustment to DMARD therapy. Irreversible joint damage, patient preferences and non-inflammatory musculoskeletal pain were the most frequent recorded barriers. These possible explanations for not treating-to-target and therefore lower remission rates are well recognised in daily clinical practice but less well documented in study settings. In early disease, however, joint damage is mostly low and also non-inflammatory musculoskeletal pain is less frequent.

The number of patients reaching remission at 6 months limits the results of this study. Pooling of datasets would increase the power to detect a signal in the data; however, due to the high heterogeneity in patient characteristics and collection of outcome measures this was deemed unacceptable. Despite the acknowledgement of the need for uniform data collection across rheumatology practices over the years (18, 19, 20, 21), heterogeneity continuous to be high, limiting the opportunity to draw meaningful conclusions and advance rheumatology research.

The development of the ACR/EULAR remission criteria was a step forwards,

Table VI. Predictive ability of remission at six months for good functional and radiographic outcome.

	Prevalence of good outcome in patients[#]			
Amsterdam	In remission	Not in remission	LR+	*p*-value*
Stable HAQ				
Boolean	53 (17/32)	31 (136/436)	2.3 (1.2-4.6)	0.013
Boolean without CRP	47 (17/36)	32 (136/432)	1.8 (1.0-3.4)	0.059
Stable Sharp				
Boolean	69 (22/32)	60 (263/436)	1.4 (0.7-2.9)	0.339
Boolean without CRP	67 (24/36)	60 (261/432)	1.3 (0.7-2.5)	0.456
Both stable				
Boolean	38 (12/32)	18 (80/436)	2.5 (1.2-4.8)	0.015
Boolean without CRP	33 (12/36)	19 (80/432)	2.0 (1.1-3.9)	0.043
Leuven (4 months)	In remission	Not in remission	LR+	*p*-value*
Stable HAQ				
Boolean	33 (3/9)	20 (11/54)	1.8 (0.5-6.3)	0.405
Boolean without CRP	40 (4/10)	19 (10/53)	2.3 (0.8-7.1)	0.140
SDAI	42 (5/12)	19 (9/47)	2.3 (0.9-6.1)	0.118
CDAI	46 (6/13)	17 (8/46)	2.8 (1.1-6.9)	0.040
Stable Sharp				
Boolean	67 (6/9)	63 (34/54)	1.2 (0.3-4.2)	0.830
Boolean without CRP	60 (6/10)	63 (34/53)	0.9 (0.3-2.7)	0.804
SDAI	67 (8/12)	60 (28/47)	1.3 (0.4-3.8)	0.650
CDAI	62 (8/13)	61 (28/46)	1.0 (0.4-2.7)	0.965
Both stable				
Boolean	33 (3/9)	7 (4/54)	4.0 (1.3-13.0)	0.043
Boolean without CRP	30 (3/10)	8 (4/53)	3.4 (1.1-10.0)	0.066
SDAI	33 (4/12)	6 (3/47)	3.7 (1.5-9.8)	0.020
CDAI	31 (4/13)	7 (3/46)	3.3 (1.3-7.9)	0.027
Nijmegen	In remission	Not in remission	LR+	*p*-value*
Stable HAQ				
Boolean	100 (2/2)	26 (31/118)	∞	0.021
Boolean without CRP	100 (2/2)	26 (31/118)	∞	0.021
Stable Ratingen				
Boolean	100 (2/2)	36 (42/118)	∞	0.053
Boolean without CRP	100 (2/2)	36 (42/118)	∞	0.053
Both stable				
Boolean	100 (2/2)	13 (15/118)	∞	0.005
Boolean without CRP	100 (2/2)	13 (15/118)	∞	0.005
Vienna	In remission	Not in remissio	LR+	*p*-value*
Stable HAQ				
Boolean	100 (12/12)	69 (41/59)	∞	0.005
Boolean without CRP	100 (13/13)	69 (40/58)	∞	0.003
SDAI	95 (18/19)	69 (35/51)	5.8 (0.8-40)	0.012
CDAI	96 (19/20)	67 (34/51)	6.5 (0.9-45)	0.006

[#]Values in the first 2 columns are percentages, with absolute proportions in parentheses.
*p-value from χ^2 analysis using logistic regression, in which the independent variable was remission and the dependent variable was HAQ, Sharp or the combination of HAQ and Sharp.
∞ mathematical infinity.

intended to create international consensus on the way to measure remission. Remission has been defined in many ways and in the recent past most frequently by a cut-off of the disease activity score in 44 or 28 joints (DAS, DAS28). However, studies have shown that this measure of disease activity does not perform well as a measure of remission, as residual disease activity is often observed (23, 24).

Moreover, new promising measures based on patient reported outcomes are being studied; the RAPID-3 has shown to be as strict a measure of remission as the ACR/EULAR remission criteria which can predict stable low HAQ scores (25, 26). While innovation and new, improved ways of measuring outcome is always solicited, the current study mainly aims to add to the body of knowledge on the performance of the new ACR/EULAR based remission criteria. In addition, the value of a treat to target approach, in this case remission, is confirmed.

The new remission criteria were developed for use in clinical trials. In a clinical practice setting, treatment strategies change depending on the patient's disease activity state. Therefore, the comparison of good long-term outcome between year 1 and 2 for patients in remission versus patients not in remission at 6 months may not be appropriate because some non-remission patients may achieve remission later on. To account for this, but still focus the analysis on early RA patients, we performed sensitivity analyses (Amsterdam cohort) with remission measured at 12 months as well as sustained remission between 6 and 12 months. Although results for remission at 12 months were highly similar, sustained remission slightly improved the likelihood of achieving a good long- term outcome. As these cohorts were based in practice, treatment strategy was not fixed as in the trials, so that adjustments in treatment after the 6-month assessment could have impacted the results in subsequent follow-up. This could have affected the capability of the remission state at 6 months to predict subsequent good outcome. However, the improved likelihood of reaching good outcome when in sustained remission strengthens the importance of treat-to-target strategies where disease activity is frequently assessed and continuously suppressed by rapidly adjusting treatment, targeted at either low disease activity or remission.

Four other studies examined the predictive validity of the new ACR/EULAR remission definitions in a clinical practice setting. Zhang *et al*. (7) found a similar validity compared to the original paper of Felson *et al*. (3). In this study the remission group was defined as those who ever reached remission during the

study. The actual disease duration of the patients reaching remission is not mentioned in the article, but is probably not compatible with early RA. Lillegraven *et al*. (27) studied remission at baseline, with absence of radiographic progression as outcome. They reported positive likelihood ratios for good radiographic outcome between 1.5 (DAS28-CRP) to 2.6 (ACR/EULAR criteria). The median disease duration for the patients in this cohort was 11 years. Sakellariou *et al*. (8) evaluated remission 12 months after initiation of DMARD treatment and used HAQ stability and absence of power Doppler-positive synovitis (PDPS) at ultrasound examination, but not total Sharp stability, as good long-term outcome. They show good validity of the new definitions in an observational setting, with high likelihood ratios for both the Boolean and SDAI definitions. However, in contrast to our practice-based cohorts, these patients were treated uniformly according to a DAS-steered protocol, more closely resembling clinical trial settings. Interestingly, in the early RA ESPOIR cohort, reaching SDAI remission rather than low disease activity (LDA) resulted in better radiographic outcomes at 3 years (28).

Conclusion

In practice-based settings, the criteria showed predictive validity similar to the original study, but the likelihood ratios were lower than in the original study, possibly because the number of remissions at 6 months were low. Moreover, our data suggest that CRP status adds little information to the classification of remission in early RA. While achievement of ACR/EULAR remission after 6 months of therapy may be too high a target for the majority of early RA patients in routine clinical practice, the current study has validated the proposed definitions for remission in practice (3). Recent studies have indicated that in overall practice more than 15% of patients achieve index-based ACR/EULAR remission (28). Even if achieving higher proportions of patients in stringent remission may currently still be an aspirational goal, low disease activity has been defined as an alternative with good outcomes (30, 31), and such a state can be achieved in a large proportion of patients. Importantly, however, the fact that patients achieving ACR/EULAR remission criteria have excellent functional and structural outcome bolsters the importance of reaching this target especially in early RA, and the expected advances in targeted therapies will hopefully turn this goal into a frequent reality within the next few years.

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