Remission in Early Rheumatoid Arthritis — A Comparison of New ACR/EULAR Remission Criteria to Established Criteria

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ABSTRACT. ***Objective.*** To describe the frequency of remission in an early rheumatoid arthritis (ERA) cohort.

Methods. The frequency of remission was evaluated, based on 8 definitions including the Boolean-based American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria.

Results. Of 369 patients, remission at 12 months ranged from 18% according to the ACR/EULAR clinical trial criteria to 40% according to the 28-joint Disease Activity Score (DAS28) < 2.6. Higher tender joint count, swollen joint count, and physician global scores were seen for DAS28-based definitions, and patient global assessment (PtGA) scores were almost 5-fold higher for DAS28 remission.

Conclusion. Remission is achievable in ERA but its frequency differs according to the remission definition applied. Adoption of the new ACR/EULAR definition will limit the number classified as in remission, especially if the PtGA criteria are rated high for reasons other than inflammatory arthritis. (J Rheumatol First Release April 15 2012; doi:10.3899/jrheum.111341)

Key Indexing Terms:
RHEUMATOID ARTHRITIS CLINICAL REMISSION DISEASE ACTIVITY SCORE

Frequent assessments of disease activity in rheumatoid arthritis (RA) are necessary to gauge and direct the therapeutic response. Achieving low disease activity, especially remission, is associated with favorable outcomes[1].

Some remission definitions are strict but unattainable, while other remission cutoffs allow for residual disease activity[2,3]. The heterogeneity among remission definitions makes comparability between and within cohorts problematic.

The American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) created a new clinical remission definition that is stringent, achievable, and could be used as the primary outcome of clinical trials and routine practice[4]. Testing these new remission criteria in RA cohorts was encouraged to determine their practicality for daily use.

Our aim was to describe the occurrence of clinical remission in an early RA (ERA) cohort according to these new ACR/EULAR criteria and other established remission definitions.

MATERIALS AND METHODS

Patient population. Consecutive patients with inflammatory arthritis enrolled in the Canadian early ArThritis CoHort (CATCH), who had a minimum of 12 months of followup (n = 664), no missing data (n = 436), and fulfilled the 1987 ACR classification criteria for RA (n = 369), comprised the study population. CATCH is an early inflammatory arthritis cohort that has recruited patients since 2006 as described[5].

Remission definition. Eight remission definitions were evaluated: (1) 28-joint Disease Activity Score (DAS28, using the erythrocyte sedimentation rate) < 2.6; (2) DAS28 score < 2.0; (3) Simplified Disease Activity Index (SDAI) score ≤ 3.3; (4) Clinical Disease Activity Index (CDAI) score ≤ 2.8; (5) ACR/EULAR clinical trial (Trial) definition requiring a tender joint count (TJC) ≤ 1, plus swollen joint count (SJC) ≤ 1, plus patient global assessment of disease (PtGA) ≤ 1 on a 0–10 cm scale, plus C-reactive protein (CRP) ≤ 1 mg/dl using 28/28 TJC/SJC; (6) a variant of the Trial definition using 68/66 TJC/SJC; (7) ACR/EULAR clinical practice (Practice) definition, which omits the CRP using a 28/28 TJC/SJC; and (8) a variant of the Practice definition using 68/66 TJC/SJC.

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Statistical analysis. The frequency of remission by each definition at baseline, 6 months, and 12 months was evaluated. The strength of agreement between definitions was measured by κ statistics[6].

RESULTS

The 369 patients had moderate to high disease activity according to mean DAS28, CDAI, and SDAI scores at baseline (Table 1). Combination disease-modifying antirheumatic drug (DMARD) therapy was the most common initial treatment and was maintained at 12 months (range 78%–80%). At 1 year, biologic use was low (range 3%–6%) and occurred exclusively with combination therapy.

Table 1. Baseline characteristics of patients with rheumatoid arthritis (n = 369) with ≥ 12 months of followup. Data are mean ± SD and median (IQR) unless otherwise indicated.

Characteristic	
Demographic	
Age, yrs, mean ± SD	52.1 ± 14.2
White, n (%)	299 (81)
Other, n (%)	70 (19)
Female sex, n (%)	265 (72)
Current smoker, n (%)	70 (19)
Ex-smoker, n (%)	165 (45)
Never smoked, n (%)	134 (36)
Clinical	
Symptom duration, mo, mean ± SD	6.3 ± 3.2
TJC in 28 joints	8.4 ± 6.5, 7 (10)
TJC in 68 joints	12.8 ± 9.3, 11 (12)
SJC in 28 joints	8.1 ± 6.1, 6 (9)
SJC in 66 joints	10.3 ± 8.0, 8 (11)
PtGA, cm (0–10 cm scale)	5.7 ± 2.9, 6 (5)
PhGA, cm (0–10 cm scale)	5.2 ± 2.4, 5 (4)
DAS28 score	5 ± 1.5, 5.1 (2.1)
CDAI score	27.3 ± 14.6, 25 (11.3)
SDAI score	28.3 ± 15, 26.7 (12)
M-HAQ score, mean ± SD	1.0 ± 0.7
Erosive disease	94 (31)*
Laboratory	
ESR, mm/h	27.3 ± 22.3, 20 (19.3)
CRP, mg/l	1.4 ± 1.8, 0.65 (1.6)
RF-positive, n (%)	223 (63)**
ACPA-positive, n (%)	198 (70)†
Treatment initiated within first 3 mo, n (%)	
No DMARD	7 (2)
Use of MTX alone	48 (13)
Use of non-MTX DMARD	40 (11)
Use of combination therapy (MTX or LEF ± SSZ ± HCQ)	280 (76)
Use of biologic agent	22 (6)
Use of oral glucocorticoid	113 (31)

* Data available for 301 patients. ** Data available for 355 patients. † Data available for 283 patients. ACPA: anticitrullinated protein antibodies; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS28: Disease Activity Score 28 joints using ESR; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; HCQ: hydroxychloroquine; IQR: interquartile range; LEF: leflunomide; M-HAQ: modified Health Assessment Questionnaire; MTX: methotrexate; PhGA: physician global assessment of disease; PtGA: patient global assessment of disease; RF: rheumatoid factor; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; SSZ: sulfasalazine; TJC: tender joint count; VAS: visual analog scale.

Few patients were in remission at baseline. By 6 months, the percentage achieving remission ranged from 14% to 30%; by 12 months it reached 18%–40%, depending on definition (Table 2). Differences between indices showed a similar pattern at both 6 and 12 months. Remission was most frequent for DAS28 < 2.6, followed by the CDAI, ACR/EULAR clinical practice definitions, and SDAI.

We investigated agreement among the definitions. Agreement between all ACR/EULAR criteria variants and the DAS28-based criteria was fair to moderate (κ range 0.39 to 0.55), but for the SDAI and CDAI, substantial (κ range 0.73 to 0.81).

There were no major differences in patient characteristics for those meeting remission by the various definitions (Table 3). Higher TJC and SJC were seen for patients in DAS28-based remission. Physician-reported global assessment scores were between double and 4-fold higher for DAS28 < 2.6 when compared to other criteria. PtGA scores were about 5-fold higher for DAS28 < 2.6 in comparison to ACR/EULAR variants.

DISCUSSION

At 1 year, we found that 40% of patients with ERA were classified in DAS28 remission, whereas remission was nearly half that for SDAI, CDAI, and the ACR/EULAR clinical practice definitions. Occurrence of remission at all timepoints was lowest for the ACR/EULAR clinical trial criteria, making it the most stringent remission definition.

Our results echo the work of others, demonstrating higher response rates when DAS28 < 2.6 is used and lower responses when index-based definitions or ACR/EULAR variants are applied[7,8]. We found an overall higher occurrence of remission than did other cohorts, which may be due to shorter disease duration and higher use of combination therapy in our population.

We observed higher joint counts and PtGA scores among patients in DAS28 remission. However, because most patients in DAS28 remission had between 0 and 5 swollen joints, factors other than inflammatory pain, such as osteoarthritis, fatigue, comorbidities, and joint damage, may cause some to persistently score high on this component[9,10,11]. In this setting, despite a low number of active joints and normal acute-phase reactants, ACR/EULAR remission will not be achieved. An attempt to understand factors associated with PtGA is needed when applying these new remission definitions, because these factors may have implications for treatment.

Our study had some limitations. We evaluated the cross-sectional occurrence of remission and did not study whether sustained remission differs according to the definitions. Further, we did not investigate the association between remission and physical functioning or radiographic joint damage. A recent observational study found joint damage occurred even

Table 2. Remission [n (%)] according to each definition at baseline, 6 months, and 12 months of followup.

	DAS28 < 2.6	DAS28 < 2.0	SDAI ≤ 3.3	CDAI ≤ 2.8	ACR/EULAR Trial (28)	ACR/EULAR Trial (66/68)	ACR/EULAR Practice (28)	ACR/EULAR Practice (66/68)
Baseline	21 (6)	6 (2)	2 (1)	2 (1)	3 (1)	2 (1)	3 (1)	2 (1)
6 months	112 (30)	73 (20)	66 (18)	78 (21)	55 (15)	52 (14)	79 (21)	73 (20)
12 months	147 (40)	85 (23)	82 (22)	95 (26)	71 (19)	66 (18)	91 (25)	84 (23)

DAS28: 28-joint Disease Activity Score; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism.

Table 3. Comparison of patient characteristics and core components of remission definitions at 12 months.

Characteristics	DAS28 < 2.6	DAS28 < 2.0	SDAI ≤ 3.3	CDAI ≤ 2.8	ACR/EULAR Clinical Trial (28 joints)	ACR/EULAR Clinical Trial (66/68 joints)	ACR/EULAR Clinical Practice (28 joints)	ACR/EULAR Clinical Practice (66/68 joints)
Age, yrs, mean ± SD	49 ± 13.7	47.8 ± 13.3	50.4 ± 14.3	50.2 ± 13.6	50.4 ± 13.7	50.7 ± 13.7	50.6 ± 14.1	51 ± 13.8
Female, n (%)	104 (71)	58 (68)	57 (79)	65 (68)	53 (75)	48 (73)	64 (70)	57 (68)
Symptom duration, mo, ± SD	18.1 ± 3.1	18.1 ± 3.1	17.8 ± 3.1	17.8 ± 3.1	18.3 ± 3.2	18 ± 3.1	18.2 ± 3.2	18 ± 3.2
Core components								
TJC, n (%)								
0–1	130 (88)	80 (94)	81 (99)	94 (99)	71 (100)	66 (100)	91 (100)	84 (100)
2–3	10 (7)	5 (6)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
4–5	6 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6–10	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
> 10	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
SJC, n (%)								
0–1	129 (88)	77 (91)	82 (100)	95 (100)	71 (100)	66 (100)	91 (100)	84 (100)
2–3	11 (7)	6 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
4–5	5 (3)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
6–10	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
> 10	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
CRP, mg/l, mean ± SD	0.3 ± 0.4	0.26 ± 0.36	0.28 ± 0.3	0.39 ± 0.49	0.25 ± 0.22	0.25 ± 0.22	0.40 ± 0.47	0.38 ± 0.48
PhGA, cm, mean ± SD	0.70 ± 1.2	0.51 ± 1.2	0.20 ± 0.37	0.20 ± 0.40	0.30 ± 0.55	0.26 ± 0.49	0.40 ± 0.72	0.33 ± 0.65
PtGA, cm, mean ± SD	1.5 ± 1.9	1.1 ± 1.6	0.59 ± 0.8	0.59 ± 0.7	0.3 ± 0.4	0.31 ± 0.41	0.36 ± 0.41	0.33 ± 0.4

ACR/EULAR: American College of Rheumatology/European League Against Rheumatism; ACR/EULAR Trial: clinical trial definition based on 28 joints (28) or 66 swollen and 68 tender (66/68); ACR/EULAR Practice: clinical practice definition based on 28 joints (28) or 66 swollen and 68 tender (66/68); CRP: C-reactive protein; DAS28: Disease Activity Score of 28 joints; PhGA: physical global assessment of disease; PtGA: patient global assessment of disease; SDAI: Simplified Disease Activity Index; SJC: swollen joint count; TJC: tender joint count.

among patients meeting strict remission criteria, but that greater time spent in remission was protective against radiographic progression[8]. Other studies have similarly demonstrated that stringent remission criteria did not reduce the percentage of joints with ultrasound synovitis, which has been independently associated with progression of joint damage[12,13]. Thus, the debate continues as to whether clinical criteria are sufficiently sensitive to identify true remission (no synovitis) or whether an accurate remission definition need also include imaging measures of synovitis.

We found that remission is frequently achievable within the first year in an ERA cohort treated with conventional DMARD. Remission varies substantially according to the definition applied. The newly proposed, Boolean-based ACR/EULAR variants are stringent, with achievement of remission limited by the achievability of the PtGA criteria.

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