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Concise report

The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion

Marloes Vermeer[1,2], Hillechiena H. Kuper[2], Arie E. van der Bijl[3], Henriëtte Baan[4], Marcel D. Posthumus[5], Herman L. M. Brus[6], Piet L. C. M. van Riel[7] and Mart A. F. J. van de Laar[1,2]

Abstract

Objectives. The provisional ACR/European League Against Rheumatism (EULAR) definition of remission in RA requires a score of $\leqslant 1$ on the patient global assessment (PGA, 0–10 scale). We explored the relation between the PGA criterion and the patient's clinical disease state in an observational dataset.

Methods. Data of 512 newly diagnosed RA patients of the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort were analysed. Both 28-joint counts and more comprehensive joint counts (tender joint count-53, swollen joint count-44) were used.

Results. ACR/EULAR remission was present in 20.1% of the patients when using 28-joint counts and in 17.4% of the patients when applying more comprehensive joint counts. In 108 patients, the PGA score was >1 despite fulfilment of the remaining criteria (TJC28, SJC28 and CRP in mg/dl $\leqslant 1$). Residual disease activity was observed in 31.5% (34/108) and median (interquartile range) scores on PGA, pain and fatigue were 2.4 (1.8–4.0), 2.0 (1.1–3.0) and 2.7 (1.3–5.0), respectively. Applying more comprehensive joint counts showed comparable results. In 19.5% (100/512) of patients, disease activity was absent (TJC53 = 0, SJC44 = 0, and CRP $\leqslant 1$). In 41% ($n = 41$) of these patients, the PGA score was >1. Receiver operating characteristic analysis showed moderate accuracy of the PGA to discriminate between fulfilment and no fulfilment of all remaining criteria.

Conclusion. Frequently, patients did not meet the PGA criterion despite a good clinical disease state. Apparently the PGA is not solely influenced by RA disease activity. In patients with marked divergence between the PGA and objective clinical measurements, caution should be taken when applying the provisional ACR/EULAR definition of remission.

Key words: rheumatoid arthritis, remission, disease activity, patient global assessment, patient-reported outcomes.

CLINICAL SCIENCE

[1]Arthritis Centre Twente, Department of Psychology, Health and Technology, University of Twente, [2]Department of Rheumatology and Clinical Immunology, Medisch Spectrum Twente, Enschede, [3]Department of Rheumatology, Isala Klinieken, Zwolle, [4]Department of Rheumatology, Ziekenhuisgroep Twente, Almelo, [5]Department of Rheumatology and Clinical Immunology, University Medical Center Groningen, Groningen, [6]Department of Rheumatology, TweeSteden Ziekenhuis, Tilburg and [7]Department of Rheumatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

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Correspondence to: Marloes Vermeer, Arthritis Centre Twente, Department of Psychology, Health and Technology, Faculty of Behavioural Sciences, University of Twente, PO Box 217, 7500 AE Enschede, The Netherlands. E-mail: m.vermeer@gw.utwente.nl

Introducton

The therapeutic goal in RA should be remission [1], which can be generally defined as 'the state of absence of disease activity in patients with a chronic illness, with the possibility of return of disease activity' [2]. Remission is associated with less radiological progression and better functional outcome [3].

The ACR and European League Against Rheumatism (EULAR) recently proposed new definitions of remission in RA for clinical trials [4–6]. The Boolean-based definition requires a tender joint count (TJC) $\leqslant 1$, swollen joint count

(SJC) $\leqslant$1, CRP $\leqslant$1 mg/dl and patient global assessment (PGA) $\leqslant$1 (on a 0–10 scale) [6].

The PGA asks the patient to give an overall assessment of how the arthritis is doing, thereby integrating a number of dimensions related to RA disease activity. In daily clinical practice it is frequently observed that patients score higher on the PGA than would be expected on the basis of their clinical disease activity [7–9]. This assumes that the PGA is not exclusively related to the clinical disease process of RA, in contrast to TJC and SJC and acute-phase response. Therefore, it is disputable whether a PGA score of $\leqslant$1 should be a prerequisite for remission.

The purpose of the present study was to apply the provisional ACR/EULAR Boolean-based definition of remission in daily clinical practice and to explore the relation between the PGA remission criterion ($\leqslant$1) and the patient's clinical disease state.

Patients and methods

Patients

Data were used from the Dutch Rheumatoid Arthritis Monitoring (DREAM) remission induction cohort study, an ongoing multicentre prospective observational cohort study in daily clinical practice in The Netherlands [10]. Inclusion criteria were age $\geqslant$18 years, a clinical diagnosis of RA, symptom duration (defined as the time from first reported symptom onset to diagnosis of RA) $\leqslant$1 year, DAS in 28 joints (DAS-28) $\geqslant$2.6 [11], and no prior DMARDs and prednisolone use. Patients were treated according to a treat-to-target strategy aiming at remission (DAS-28 $<$2.6), with therapy consisting of DMARDs (initial monotherapy, followed by combination therapy), followed by biologic agents in case of persistent disease activity.

This study was approved by the ethical review board of the Medisch Spectrum Twente Hospital and written informed consent was obtained from all patients.

Measures

ACR/EULAR remission

The ACR/EULAR committee has proposed two definitions of remission in RA for clinical trials: a Boolean-based definition and an index-based definition [6]. The Boolean-based definition requires fulfilment of four criteria: TJC $\leqslant$1, SJC $\leqslant$1, CRP $\leqslant$1 mg/dl and PGA $\leqslant$1 (on a 0–10 scale) at any time point. The index-based definition is defined as a simplified disease activity index (SDAI) $\leqslant$3.3 at any time point. As the physician global assessment was not assessed in this cohort, the SDAI could not be calculated.

According to the ACR/EULAR committee, the use of 28-joint counts is sufficient; however, arthritis in joints not included in the 28-joint counts (ankles, feet) will inevitably influence the patient's perception of his/her RA disease activity. It could be expected that a more comprehensive joint assessment is more accurate for the evaluation of remission. Therefore, in this study, ACR/EULAR remission was evaluated using 28-joint counts (TJC28 and SJC28) as well as more comprehensive joint counts (TJC53 and SJC44).

Patient-reported outcomes

For the patient assessment of disease activity (PGA), pain and fatigue, a horizontal 10-cm visual analogue scale (VAS) with scores ranging from 0 (best) to 10 (worst) was used. The wording of questions and anchors were as follows: for the PGA, 'Considering all of the ways your arthritis affects you, mark ''X'' on the scale for how well you are doing' ('very well' to 'very poor'), in accordance with the ACR core set of disease activity measures for RA [12]; for pain, 'How much pain did you experience as a result of your arthritis in the past week?' ('no pain at all' to 'unbearable pain'); and for fatigue, 'How fatigued were you as a result of your arthritis in the past week?' ('not fatigued at all' to 'extremely fatigued').

Statistical analyses

In the present study we included patients with a 6-month follow-up assessment enrolled from January 2006 to July 2010. Only observations without missing data in the ACR/EULAR remission criteria were selected for our analyses. The cohort provided more data on the patient assessment of disease activity and pain than on the patient assessment of fatigue. Descriptive statistics were undertaken to explore the relation between the PGA remission criterion ($\leqslant$1) and the patient's clinical disease state. Correlations between the patient assessment of disease activity, pain and fatigue were calculated using the Spearman's rank correlation coefficient. The receiver operating characteristic (ROC) curve and the area under the curve (AUC) with S.E. were used to evaluate the ability of the PGA to discriminate between fulfilment of all of the remaining remission criteria (TJC, SJC and CRP all $\leqslant$1) and no fulfilment of all of the remaining remission criteria (at least one $>$1). The optimal cut-off points were identified by selecting the value showing optimal sensitivity and specificity [13]. Statistical analyses were performed using the statistical software package SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

A 6-month follow-up assessment was present in 512 patients with very early RA. Mean (S.D.) age at inclusion was 58.6 (14.3) years, 63.1% (n = 323) of patients were female, median [interquartile range (IQR)] symptom duration was 14 (8–26) weeks, 61.2% (309/505) of patients were RF positive, 58.8% (273/464) had anti-CCP antibodies and mean (S.D.) DAS-28 was 5.0 (1.1).

Prevalence of ACR/EULAR remission

ACR/EULAR remission based on 28-joint counts was observed in 20.1% of patients. When applying the ACR/EULAR definition using more comprehensive joint counts, remission was observed in 17.4% of patients.

Table 1 Fulfilment of the criteria of the provisional ACR/EULAR Boolean-based definition of remission in RA in 512 patients based on 28-joint counts and more comprehensive joint counts

	ACR/EULAR remission based on TJC28/SJC28 ($n = 512$)	ACR/EULAR remission based on TJC53/SJC44 ($n = 512$)
Remission	103 (20.1)	89 (17.4)
Non-remission, fewer than three of four criteria fulfilled	251 (49.0)	287 (56.0)
Non-remission, three of four criteria fulfilled	158 (30.9)	136 (26.6)
Variables not fulfilling the criterion of $\leqslant 1$		
PGA	108/158 (68.4)	80/136 (58.8)
SJC	33/158 (20.9)	34/136 (25.0)
CRP	13/158 (8.2)	10/136 (7.4)
TJC	4/158 (2.5)	12/136 (8.8)

Values are presented as *n* (%).

Absence of ACR/EULAR remission

Data for the 409 patients who did not fulfil the ACR/EULAR remission criteria (based on 28-joint counts) were evaluated. In 158 patients, three of the four criteria were fulfilled. The variable not meeting the remission cut-off point was in 68.4% of PGA, 20.9% of SJC28, 8.2% of CRP and 2.5% of TJC28 (Table 1). When more comprehensive joint counts were used, comparable results were found (Table 1).

Residual disease activity

Residual disease activity not captured by the 28-joint counts was present in 31.5% (34/108) of the patients who had a high PGA score (>1) despite low TJC28 and SJC28 and normal CRP. The use of more stringent criteria allowing no minimal residual disease activity (TJC53 = 0, SJC44 = 0 and normal CRP) showed that of the 100 patients fulfilling these criteria, only 59% (59/100) fulfilled the PGA criterion of $\leqslant 1$.

Experience of pain and fatigue

In patients who had a high PGA score (>1) despite low TJC28 and SJC28 and normal CRP, the distribution of the PGA scores showed wide ranges beyond the cut-off point for remission (Fig. 1A). The distributions of the scores on the patient assessment of pain ($n = 108$) and fatigue ($n = 53$) are presented in Fig. 1B and C, respectively. These figures show that a considerable number of patients experienced pain and fatigue despite minimal inflammation. The median (IQR) scores for the patient assessment of disease activity, pain and fatigue were 2.4 (1.8–4.0), 2.0 (1.1–3.0) and 2.7 (1.3–5.0), respectively. Overall, the PGA correlated highly with the patient assessment of pain ($\rho = 0.820$, $P = 0.000$) and moderately with fatigue ($\rho = 0.528$, $P = 0.000$).

Discriminative ability of the PGA

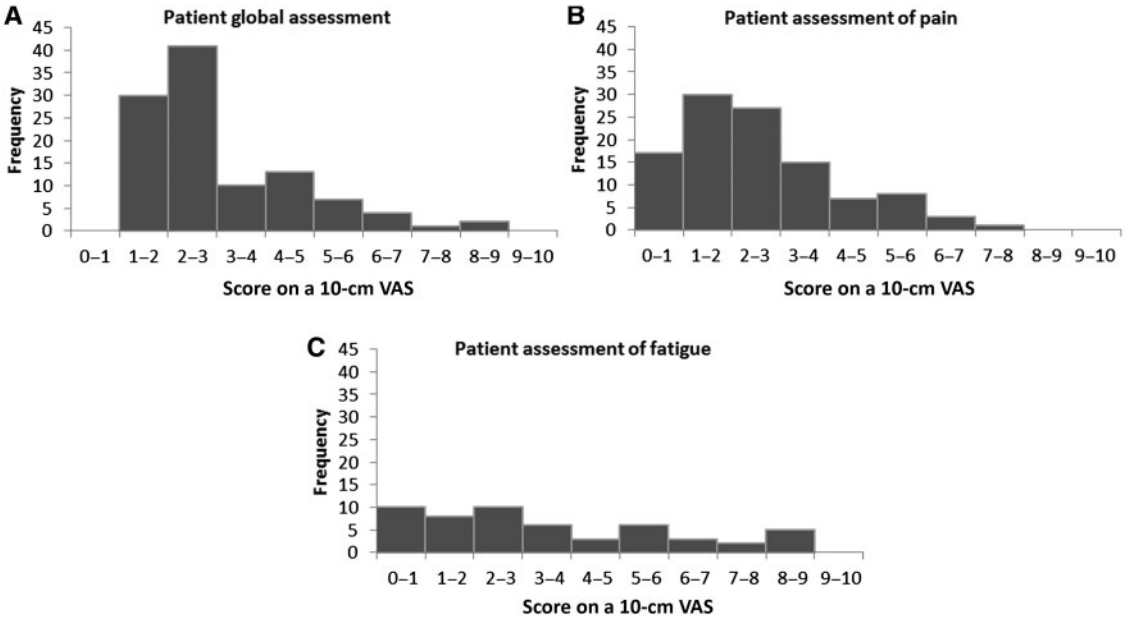
The ROC curve analysis showed moderate accuracy of the PGA to discriminate between the fulfilment of the TJC28, SJC28 and CRP remission criteria *vs* no fulfilment of all three remaining criteria (at least one >1), with an AUC (S.E.) of 0.73 (0.02). The optimal cut-off point of PGA in differentiating the two conditions was estimated at 2 (74% sensitivity and 65% specificity). When applying more comprehensive joint counts, comparable results were found (data not shown).

Discussion

The present study demonstrated that RA patients regularly do not meet the PGA criterion ($\leqslant 1$) of the provisional ACR/EULAR Boolean-based definition of remission in RA, despite a good clinical disease state. This finding was not fully explained by residual disease activity. Pain and fatigue were experienced by a considerable number of patients despite minimal inflammation. Moreover, the accuracy of the PGA to discriminate between fulfilment and no fulfilment of all of the remaining three remission criteria was moderate. Apparently other factors can drive non-remission of the PGA criterion in the absence of evidence of joint inflammation in RA. Patient-reported outcomes (PROs) have been increasingly recognized as important and are now part of the core set of disease activity measures [12]. The use of PROs in defining remission assumes a strict relation with objective clinical disease activity parameters. Kievit *et al*. [14] have shown that the patient's perception of health can be different with equal disease activity, depending on the moment in the disease course. Furthermore, patients with RA often suffer from pain, physical disability, fatigue [15] and symptoms of depression and anxiety due to significant comorbidities, which may influence the patient's perception of how the arthritis is doing [16]. Additionally, in RA patients with concomitant FM, the low threshold of pain sensitivity found in this disease may lead to overestimation of the PGA [17]. Social, cultural and ethnic factors [18–20] as well as the clinical setting (clinical trial or daily clinical practice) may also play a role in the reporting of disease activity.

Some remarks on the present study should be addressed. We used data from an observational cohort study in daily clinical practice. However, the provisional ACR/EULAR definition of remission was defined for trial

FIG. 1 Distribution of (**A**) the patient assessment of disease activity (PGA) ($n = 108$), (**B**) pain ($n = 108$) and (**C**) fatigue ($n = 53$) on a 0–10 VAS in 108 patients who did not meet the PGA criterion of $\leqslant 1$ of the provisional ACR/EULAR Boolean-based definition of remission in RA, despite TJC28, SJC28 and CRP meeting the cut-off point of remission ($\leqslant 1$).



settings. The ACR/EULAR committee suggested a different definition for clinical-based practice that does not require an acute-phase reactant (i.e. TJC $\leqslant 1$, SJC $\leqslant 1$ and PGA $\leqslant 1$), since this is frequently not immediately available in the clinical setting. Obviously the definition that was formulated for clinical practice settings also encounters the problem regarding the PGA, and thus applying this definition would not affect our results.

We acknowledge further research is needed to formally test whether the PGA criterion in its present form or a modification adds discriminatory power over and above that provided by the TJC, SJC and CRP in discriminating between patients with and without clinically relevant radiological progression in trial and observational datasets.

In conclusion, this exploratory study demonstrated that the PGA criterion of the provisional ACR/EULAR Boolean-based definition of remission in RA has limitations in daily clinical practice, because patients that are obviously in clinical remission can score high on the PGA due to other reasons than their RA disease activity. Caution should be taken in patients with marked divergence between subjective and objective clinical measurements when applying the definition.

Rheumatology key messages

- PGA criterion of ACR/EULAR RA remission is often not fulfilled despite minimal inflammation.
- The PGA is not solely influenced by RA disease activity.

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