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ORIGINAL ARTICLE

Phrasing of the patient global assessment in the rheumatoid arthritis ACR/EULAR remission criteria: an analysis of 967 patients from two databases of early and established rheumatoid arthritis patients

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Abstract

The ACR/EULAR Boolean remission criteria for rheumatoid arthritis (RA) include a strict cutoff for patient global assessment (PGA, value ≤ 1/10). Near-remission corresponds to remission for joint counts and C-reactive protein but with PGA > 1. The objective was to explore whether the contribution of PGA to remission and near-remission varied according to the wording of the PGA and in relation to disease duration. In patients with early arthritis ($N = 731$, French ESPOIR cohort) or established RA ($N = 236$ patients from across Europe), frequency of remission versus near-remission was assessed according to the phrasing used for PGA (global health versus disease activity). In 967 patients (mean [standard deviation] age 49.7 [12.7] years, 76.7% women), remission was infrequent: range 12.9–16.7% (according to wording of PGA) in early RA and 6.8–7.2% in established RA. Near-remission was more frequent: 13.0–16.8% in early RA and 13.1–13.6% in established RA. The ratio of remission to near-remission was higher in the early arthritis cohort (0.8–1.3 versus 0.5–0.5 in established RA). Using the disease activity PGA led to more remission and less near-remission than the global health PGA in the early arthritis cohort (12.9 vs 16.7% near-remission, respectively, $p = 0.047$) but not in established RA. The proportion of patients who can be classified as remission or near-remission differs in early RA compared to establish RA and depends upon the formulation of the PGA question. PGA referring to disease activity and not global health may be preferred in early disease, if the objective is more alignment with inflammation assessment.

Keywords Outcome measures · Pain · Patient-reported outcome measures · Quality of life · Remission · Rheumatoid arthritis

Key messages

1. Boolean remission is a state that is difficult to reach in RA, and PGA is the main limiting component: more than half of the patients with joint counts ≤ 1 and normal acute phase reactants are not attaining remission only because of PGA levels.
2. Among patients with normal/low joint counts and CRP, more patients did not reach remission because of PGA results in a cohort of established RA than in a cohort of early arthritis, indicating more discordance between PGA and objective criteria in established RA.
3. Remission was more frequent when using the disease activity PGA than the global health PGA in early arthritis, indicating disease activity PGA results are closer to examination and acute phase reactant results, than global health, at least in early disease.

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Introduction

The American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Boolean remission criteria for rheumatoid arthritis (RA) include the absence of visible inflammation (swollen 28 joint count (SJC_{28}) ≤ 1 and tender 28 joint count (TJC_{28}) ≤ 1), a low C-reactive protein (CRP) (≤ 1 mg/dl) but also a very low level of symptoms with a strict cutoff for patient global assessment (PGA, value ≤ 1 on a 0–10 scale) [1]. Patients reaching remission for joint counts and CRP according to this definition, but not for PGA (i.e. with PGA > 1) are sometimes termed in 'near-remission' [2–5]. Several studies have indicated that PGA is often a limiting factor for remission and that near-remission is a frequent status [2–4]. Why then do we observe this discordance or disagreement between physical examination and acute phase reactants on the one hand and PGA on the other hand?

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The phrasing used for patient-reported outcome measures may modify the response [6–10]. PGA may be formulated in several ways and may cover many concepts. Two main formulations are frequently used, one which may be seen as referring to 'global health' and one which may be seen as referring to 'disease activity' [11]. Although outcomes at the group level are similar, these formulations have different drivers and may categorise individual respondents differently [9, 10]. The authors of the ACR/EULAR remission criteria proposed the phrasing 'Considering all of the ways your arthritis has affected you, how do you feel your arthritis is today?' [1]. However, this was not supported by any examination of the consequence of adopting this specific formulation. The original studies from which the remission criteria were derived mostly used the phrase 'Considering all the ways your arthritis affects you, mark 'X' on the scale for how well you are doing' which does not refer to disease activity and might therefore be categorised as a global health [11]. In clinical practice, cohort studies and clinical trials, many phrasings of PGA are used, often interchangeably [11]. Thus, exploring the effect of different wordings on the prevalence of remission is of interest. Taking advantage of data collected for other purposes, we sought to compare different categories of wordings although unfortunately exact wordings differed between our data sources. We hypothesised that wordings referring to disease activity might align more closely with physician assessments and hence classify more patients as in remission and less patients as in near-remission.

A second issue for PGA (and indeed other patient-reported outcome measures) is that interpretation of the question by the patient may depend on disease duration. A response shift caused by increasing familiarity with symptoms and changes in patient expectations [12] might result in lower PGA scores in general. However, progressive irreversible structural damage (related to disease duration) might increase PGA when related to global health but not when related to disease activity. We hypothesised that structural changes would have a greater effect than response shift, and so increasing disease duration would increase the number of patients in near remission compared to those in remission. In this regard, disease duration and subsequent changing expectations can be considered as 'contextual factors' in relation to assessment of PGA [13].

The objectives of the present study were therefore to explore the contribution of PGA to remission compared to near-remission when using different wordings of PGA and to test whether this differs in recent-onset compared to established RA.

Methods

Cross-sectional analyses were performed on data extracted from the existing database for ESPOIR [14] and from the RA Impact of Disease (RAID) validation study [15]. Patients were included in the current analyses if they had completed questions with both PGA phrasings (see below) and if information about all other components of ACR/EULAR remission (i.e. SJC_{28}, TJC_{28} and CRP) was available [1]. Ethics board approvals were obtained in Montpellier, France for ESPOIR and in each country (if required) for RAID, as previously described [14, 15].

Patients and disease duration

Early arthritis cohort: The ESPOIR cohort is an ongoing French multi-centre national prospective observational cohort of early arthritis patients in 20 centres [14]. At entry patients had two or more swollen joints, joint swelling for more than 6 weeks but less than 6 months, no previous disease-modifying drugs including glucocorticoids and no definite diagnosis of a disease other than RA or undifferentiated arthritis [14]. They may or may not have fulfilled classification criteria for RA. In the present study, the data analysed are from the second visit, 6 months after entry.

Established RA cohort: Data from across-sectional observational international study to validate the RAID questionnaire were analysed [15]. Patients with definite RA according to the American College of Rheumatology 1987 criteria, of more than 2 years' duration and whatever their disease and treatment status, were included in 2008–2009 in the rheumatology departments of tertiary-care centres in 12 countries across Europe.

PGA phrasings

PGAs were those used by the authors of the original studies and were assessed as 0–100 visual analogue scales where 0 was on the left and indicated a better health status in both studies. Two main phrasings were compared, and the questions were not consecutive in the forms the patients completed. The 'global health' PGA in the early arthritis cohort was formulated as follows: 'Mark an X on the scale to indicate how your health is today' with anchors 'best state of health' and 'worst state of health'. In the established RA cohort, it was formulated as follows: 'Considering all the ways in which illness and health conditions may affect you at this time, please mark how you are doing' with anchors 'very well' and 'very poorly'. The 'disease activity' PGA in the early arthritis cohort was formulated as follows: 'How active do you consider your arthritis?' with anchors 'inactive disease' and 'active disease'. In the established RA cohort, it was formulated as follows: 'In general, how active has your rheumatic condition been?' with anchors 'not active at all' and 'extremely active'. In the established RA study, the wordings were translated by the investigators.

Remission definitions

Remission was defined according to the ACR/EULAR Boolean remission criteria: $SJC_{28} \leq 1$ and $TJC_{28} \leq 1$ and CRP ≤1 mg/dl and PGA ≤ 1/10. As PGA was assessed here on a 0–100 scale and as suggested by an expert who developed the remission criteria, a value < 15/100 was considered as remission since it would be rounded to 1/10 [1]. Near-remission was defined as $SJC_{28} \leq 1$ and $TJC_{28} \leq 1$ and CRP ≤1 mg/dl, but with PGA ≥ 15/100. For the present analysis, a status of 'no visible inflammation' was defined as $SJC_{28} \leq 1$ and $TJC_{28} \leq 1$ and CRP ≤1 mg/dl, irrespective of the PGA value. 'No visible inflammation' thus includes patients in remission and near-remission.

Statistical analyses

Descriptive statistics used means and standard deviation (SD) or median and interquartile range (IQR) as appropriate and mean values were compared by *t* tests. PGA scores and remission/near-remission frequencies were analysed in each cohort and according to both phrasings of PGA. Agreement between the two phrasings of PGA was assessed through graphs, intra-class correlations (ICC) and kappa for attainment of remission. The ratios of remission to near-remission were calculated in each cohort.

In the early arthritis cohort, additional analyses were run according to fulfilment or not of the 2010 ACR/EULAR RA classification criteria. Sensitivity analyses were performed according to disease activity status and, to explore the strictness of the cutoff, using a cutoff of PGA < versus ≥ 25/100. Fisher's exact tests were computed throughout with no imputation of missing data. Analyses were performed on SAS, the Statistical Analysis System version 9.3.

Results

Patients

In total, 731 of the 813 early arthritis ESPOIR patients and 236 of the 505 established RA patients (none of whom had early arthritis of less than 6 months duration) had all data available and were included in the present analyses. Of the included early arthritis patients 608 (83.2%) satisfied the ACR/EULAR 2010 classification criteria [15]. As anticipated, at the time point considered (i.e. second visit in ESPOIR and baseline visit in RAID) established RA patients were older (mean age 48.8 (SD 12.4) years vs 54.6 (SD 12.3) years, in early vs established RA, respectively), were more likely to have RF or anti-CCP antibodies (49.9 vs 79.6%), were more likely to have erosions (17.5 vs 69.5%) and had greater functional loss (mean HAQ 0.54 (SD 0.56) vs 1.13 (SD 0.75)). Mean duration of symptoms was 9.4 ± 1.8 months and 12.4 ± 10.4 years; 76.3–77.7% were female (Table 1). Disease activity in both groups was in the moderate to high range according to the disease activity score.

PGA values

Mean and median values of PGA scores for the early arthritis cohort and the established RA cohort are shown in Table 2. They were higher (corresponding to a worse status) in the international established RA patients than in the French early arthritis cohort for both formulations and higher (i.e. worse) with the disease activity formulation than with the global health formulation, in the established RA cohort (Table 2 and supplementary Fig. S1). The agreement between the two formulations was moderate at the individual patient level: ICC 0.56 [95% confidence interval 0.56, 0.61] and supplementary Fig. S2).

Because the differences in PGA scores between established RA and early arthritis may have resulted from established RA patients having more active disease (Table 1), mean and median PGA scores were also compared in patients with no visible inflammation (TJC_{28}, SJC_{28} and CRP all ≤ 1) (Table 2).

PGA using both formulations was lower in these patients than in the whole group of early arthritis and established RA patients. In these patients with no inflammatory signs, the

Table 1 Characteristics of 967 early arthritis and established RA patients

	Early arthritis *N* = 731	Established RA *N* = 236
Age, years	48.8 (12.4)	54.6 (12.3)
Female gender, *N* (%)	558 (76.3)	183 (77.9)
Disease duration, years	0.8 (0.2)	12.4 (10.4)
Higher education, *N* (%)	234 (32.0)	79 (37.0)
RF or anti-CCP positivity, *N* (%)	365 (49.9)	184 (79.6)
Erosive status on hand/ft X-rays, *N* (%)	128 (17.5)	148 (69.5)
Health assessment questionnaire (0–3)	0.54 (0.56)	1.13 (0.75)
Tender joint count (0–28)	4.4 (5.8)	6.1 (6.8)
Swollen joint count (0–28)	2.4 (3.3)	4.1 (4.8)
DAS28-ESR	3.39 (1.40)	4.29 (1.65)
C-reactive protein, mg/dl	0.87 (1.99)	0.96 (1.42)
Pain visual analogue scale (0–100)	32.7 (11.5)	32.7 (18.5)
Fatigue visual analogue scale (0–100)	34.0 (11.5)	17.0 (12.3)

Results are presented as mean (standard deviation) unless otherwise indicated and pertain to the second visit in ESPOIR and baseline data in RAID. Percentages are calculated on available data. DAS28-ESR: disease activity score on 28 joints based on erythrocyte sedimentation rate. RF/CCP: rheumatoid factor/cyclic citrullinated protein. Higher education: studies above the level of end of high school. Erosive status: at least one typical erosion according to the investigator. Pain and fatigue VAS are scored 0 when absent and 100 for highest levels

Table 2 PGA levels (0–100), according to disease duration and to the phrasing used, in the whole population and in patients with no inflammatory signs (TJC ≤ 1, SJC ≤ 1 and CRP ≤ 1)

PGA formulation		Early arthritis			Established RA (236)	Early arthritis with TJC < =1, SJC < =1 and CRP < =1			Established RA with TJC ≤ 1, SJC ≤ 1 and CRP ≤ 1 (48)
		No definite RA (111)*	RA (608)*	Combined (731)		Non-RA (48)*	RA (163)*	Combined (217)	
Global health	Mean	30.3	31.2	30.8	40.1	26.9	23.4	23.8	27.1
	SD	18.1	18.6	18.5	23.2	18.6	16.9	17.3	19.4
	Median	30	30	30	40[a]	20	20	20[c]	26[d]
	IQR	15, 41	20, 48	15, 45	20, 55	10, 40	10, 30	10, 30	10, 38
Disease activity	Mean	30.4	35.7	34.8	48.5	20.3	19.6	19.5	29.4
	SD	25.1	26.9	26.7	25.6	20.8	21	20.8	21.2
	Median	25	30	30	50[a, b]	15	13	13[c, e]	30[d]
	IQR	9, 49	12, 55	11, 53	30, 70	4, 31	4, 27	3, 28	10, 50

PGA was scored 0 when excellent and 100 for worst status

*Some patients had missing data for RA criteria and thus do not appear as no definite RA or RA

Statistical tests compared mean values

[a] $P < 0.05$ comparing established RA to early arthritis

[b] $P < 0.05$ comparing PGA disease activity formulation to global health formulation

[c] $P < 0.05$ comparing early arthritis with TJC ≤ 1, SJC ≤ 1 and CRP ≤ 1 to early arthritis

[d] $P < 0.05$ comparing established RA with TJC ≤ 1, SJC ≤ 1 and CRP ≤ 1 to established RA

[e] $P < 0.05$ comparing PGA disease activity formulation to global health formulation in patients with TJC ≤ 1, SJC ≤ 1 and CRP ≤ 1

early arthritis patients tended to score disease activity PGA lower than global health PGA (mean 19.5 (SD 20.8) versus mean 23.8 (SD 17.3)) whereas both phrasings gave similar results in established RA. PGA levels were similar in early arthritis patients who did or did not fulfil the ACR/EULAR classification criteria (Table 2).

Contribution of PGA and disease duration to remission

The prevalence of ACR/EULAR Boolean remission was low (Table 3). A greater proportion of patients were in remission in early arthritis than in established disease: 12.9 vs 6.8% using global health PGA and 16.7 vs 7.2% using disease activity PGA ($P < 0.05$ for both comparisons). Comparing formulations of the PGA, a greater proportion of patients were in remission in the early arthritis group when using the disease activity PGA, but this was not the case in the established RA patients. Agreement between the global health and disease activity classifications was low (kappa = 0.02 to 0.13, with a kappa for the whole population of 0.11 (95% confidence interval, 0.02; 0.19); data not shown).

Contribution of PGA and disease duration to near remission

Near-remission was frequent, indicating that PGA was often a limiting factor to reaching remission (Table 3). The prevalence

Table 3 Frequency of remission and near-remission according to disease duration and to the phrasing used for PGA

PGA formulation	Patient classification	Early arthritis (731)	Established RA (236)
Global health	Remission number (%)	94 (12.9)	16 (6. 8)[b]
	Near remission number (%)	123 (16.8)	32 (13.6)
	Ratio R:NR [95% CI]	0.76 [0.62, 0.93]	0.50 [0.28, 0.81]
Disease activity	Remission number (%)	122 (16.7)[a]	17 (7.2)[b]
	Near remission number (%)	95 (13.0)[a]	31 (13.1)
	Ratio remission : non remission [95% CI]	1.28 [1.07, 1.53][a]	0.55 [0.32, 0.88][b]

Ratio calculated as ratio of remission to near-remission (R:NR) in each cohort using the PGA phrasing and reported with bootstrapped confidence intervals. Fisher's exact test was applied

[a] $p < 0.05$ comparing PGA formulations

[b] $p < 0.05$ comparing established RA and combined early arthritis

of near-remission was dependent on disease duration and on which PGA formulation was used. In established RA, it was similar in both PGA formulations (13.6 and 13.1%), but in early arthritis, it was higher for the global health PGA (16.8 vs 13.0%, $p < 0.05$). However, as noted above, remission was also more frequent in early arthritis and so using the disease activity PGA formulation the ratio of remission to near-remission was higher in early arthritis than in established RA (1.28 vs 0.55, $p < 0.05$) and higher than that using the global health formulation (1.28 vs 0.76, $p < 0.05$).

Sensitivity analysis

Changing the criterion for PGA from 15 to 25 led, as expected, to more frequent remission and less frequent near-remission. The prevalence of near-remission was then 8.5–10.3% in early arthritis and 10.6–11.4% in established RA ($p < 0.001$). In this case also, the disease activity phrasing led to less near-remission in early arthritis than the global health wording, though the difference did not reach statistical significance (19.4% in remission and 10.3% in near-remission with global health versus 21.2 and 8.5%, respectively, with disease activity, $p = 0.36$).

Discussion

The present study sheds light on several important findings relating to the use of PGA in clinical care. We confirm that Boolean remission is a state that is difficult to reach in RA, and that PGA was the main limiting component of Boolean remission: more than half of the patients with 'no inflammation' by joint counts and acute phase reactants were not attaining remission only because of PGA levels. More patients did not reach remission because of PGA results in the international established RA cohort, than in the French early arthritis cohort, potentially indicating the multifactorial nature of PGA particularly in established disease. Finally, remission was more frequent when using the disease activity PGA than the global health PGA in early arthritis. Thus although the published ACR/EULAR remission definition refers to a phrasing which is closer to global health than to disease activity, we suggest using disease activity wordings may lead to more alignment with physicians' assessment of inflammation.

PGA results were generally quite high in this population of patients with moderate disease activity and when we analysed the sub-group of patients with no inflammatory signs ($TJC_{28} <= 1$, $SJC_{28} <= 1$ and CRP <= 1 mg/dl) mean levels of PGA remained high (mean values 19.5 to 29.4, Table 2) indicating a frequent discordance between the objective criteria of inflammation used in the definition of remission and PGA. This was reflected in the high proportion of patients reaching a state of near-remission, confirming previous studies [2–5]. Indeed, near-remission was always more frequent than remission, further indicating the stringency of the PGA criterion in the remission definition.

When comparing patients from cohorts with different disease durations, the relative frequency of remission when compared to near-remission was higher in the early arthritis cohort: remission was 0.8 to 1.3 times as frequent as near-remission in early disease, whereas in the established RA cohort, it was 0.5 times as frequent. Furthermore, among patients without visible inflammation, more patients did not reach remission because of PGA results in established RA than in early arthritis. This indicates overall discordance between PGA and objective criteria whatever the disease duration but this was even more so the case in the established RA cohort. Of note, this comparison between cohorts may be influenced by numerous other factors than the disease duration, such as culture (since one population was French and the other was international), treatment options, management processes, etc. However, we believe this finding is of interest and has formulated some hypotheses regarding explanations for these differences. It might be supposed that early arthritis patients would have more expectations and score PGA higher even without inflammation. On the other hand, as PGA also measures many other aspects of health including mental health, comorbidities or overall satisfaction, it might be expected that older patients with a more established and potentially more severe RA (in terms of structural damage) should score PGA higher even in the absence of inflammation [9, 10, 16, 17]. The reference frame may also differ according to disease duration (e.g. comparison to a normal non-RA person versus comparison to previous disease states).

Regarding the phrasing used for PGA, remission was more frequent when using the disease activity PGA than the global health PGA in the early arthritis but not in the established RA cohort. It appears disease activity PGA results are closer to examination (at least when including 28 joints only, as is the case in the remission criteria) [1] and acute phase reactant results, than global health, using the formulations as in the present study, at least in early disease. On the other hand, global health PGA may capture better either joints which are not in the 28-joint count or other aspects of quality of life. Previous studies have indicated different drivers explained PGA according to the wording used: disease activity PGA is more strongly related to joint counts, whereas global health reflected comorbidities and depression to a greater extent [10, 11]. The present study brings additional information in the context of early disease and indicates that in treating to a target of remission, the two wordings should not be used interchangeably [18]. In clinical trials, where the pooled response of the treatment cohort is measured, our results seem to support the equivalence of formulations. However, in the context of treating-to-target an individual patient, the variability observed might make it more attractive to use near-remission as an objective. If remission is considered as 'absence of inflammation', an approach that is supported by

many physicians and inherently implied in the ACR/EULAR definition, then the disease activity wording might be preferred. It would align better with physician examination data (18), but this assumes that such data are adequately comprehensive (for example, the feet are not included in the 28 joint count score). First evidence from qualitative studies into the patient perspective on remission tends to support this approach although more research on the patients' opinion on remission as well as on PGA is needed [11, 19]. If remission is considered as 'absence of symptoms', then global health PGA or a phrasing such as the one proposed by ACR/EULAR for remission can be used and is likely to better align with patient's expectations [1, 19].

A potential limitation of this study is the analysis of two different populations, since these populations have different characteristics and remission frequencies. However, since one of our objectives was to compare remission and near-remission between different disease durations, this was a logical choice. Although many patients were analysed, given the low frequency of remission, some caution is necessary in the interpretation, in particular in established RA. However, several sensitivity analyses were performed and they all confirmed our main findings. The wordings of the questions used to assess PGA in the two patient groups were not identical. We recognise this is a weakness but this reflects the diversity of wordings of PGA used in clinical practice [20]. Furthermore, phrasings were translated by investigators in the established RA cohort and such translations would merit assessment [7].

Here, we have chosen to concentrate on situations of disagreement in assessment of status, where PGA is high when other components of remission are low. However, there are situations where this equilibrium is reversed and it might be of interest to also explore these situations. As the definition of remission rests on assessing only 28 joints and other joints may influence PGA, the results observed here (and indeed in the original proposal for the definition of remission) may only apply in the context of assessing 28 joints [1].

It would be useful to agree on a standardised wording for PGA to be used across studies and to further assess what the PGA is actually measuring. This would also facilitate further exploration of the causes and implications of a status of near-remission

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Compliance with ethical standards

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