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# **Title:** Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients

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**Short title**: Drivers of PGA in RA near-remission

**Abstract**

Objectives: American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) Boolean remission in rheumatoid arthritis (RA) is frequently not obtained solely due to a patient global assessment (PGA) >1/10 (a condition often designated as near-remission). This study aimed to assess which domains of impact could explain elevated PGA in near-remission patients.

Methods: Ancillary analysis of data from three cross-sectional studies in patients with established RA. Three disease activity states were defined: remission (tender and swollen joint counts, C-Reactive Protein and PGA all ≤1), near-remission (idem but PGA>1) and non-remission. Physical and psychological domains were assessed using the RA Impact of Disease (RAID: 0-10 numeric rating scales) as explanatory factors of PGA. Univariable and multivariable linear regression analyses were performed to explain PGA.

Results: 1588 patients (79.1% females) were analysed. Mean (standard deviation) disease duration was 13.0 (9.8) years and 28-joint Disease Activity Score (DAS28-4v) was 3.2 (1.4). Near-remission [mean PGA=3.6 (1.9)] was more frequent (19.1%) than remission (12.3%). Scores of disease impact RAID domains were similar in near-remission and non-remission patients. In near-remission, PGA was explained ($R^2_{adjusted}$=0.55) by pain (β=0.29), function (β=0.23), physical wellbeing (β=0.19) and fatigue (β=0.15).

Conclusion: Near-remission was more frequent than remission. These patients, despite having no signs of significant inflammation, report an impact of disease similar to the non-remission patients. PGA in near-remission seems to be driven by physical rather than psychological domains. Selecting the best therapy for these patients requires a better understanding of the meaning of PGA, both globally and in individual patients.

**Key Words**: Rheumatoid arthritis, patient global assessment, patient reported outcomes, disease activity, remission, near-remission, psychological distress, psychological factors, outcomes, disease impact.

## Introduction

Disease remission (or at least low disease activity) is the therapeutic target for patients with rheumatoid arthritis (RA) in current treatment recommendations [1, 2]. Remission is defined according to the American College of Rheumatology (ACR) /European League Against Rheumatism (EULAR) criteria [3], which, in the Boolean-based definition require that tender joint count of 28 joints (TJC28), swollen joint count (SJC28), C-Reactive Protein (CRP, in mg/dl), and patient global assessment (PGA, 0–10 scale) are all ≤1.

The condition where patients fail to reach remission solely because of PGA has been designated as "near-remission" [4]. These patients have no signs of significant joint inflammation since joint counts and CRP are ≤1 but evaluate their disease (using PGA) above 1/10. In published studies, 21%-31% of RA patients were in near-remission [4-6]. Following current treatment recommendations [1, 2] this state of near-remission could justify reinforcement of immunosuppressive therapy. However, this may not be the best choice if the reason for not achieving remission is not inflammatory activity. In these cases, "adjuvant" therapies, such as analgesics, antidepressants or self-management programs might be more appropriate. To select the most adequate intervention in such cases, it is essential to understand why patients without signs of significant inflammatory activity do not achieve a PGA ≤1.

In RA patients, PGA appears to be not only influenced by RA disease activity, but also by sociodemographic features, country/culture, psychological factors, and comorbidities, with emphasis on fibromyalgia [7]. However, no data are available on the meaning of PGA in the specific condition of near-remission.

The aims of this study were to assess which domains of impact may explain the elevated PGA in near-remission patients, and to assess which domains of health better discriminate between disease activity states.

## Patients and methods

### *Study design and setting*

This was an ancillary analysis of three studies of patients with established RA: i) baseline data from the Rheumatoid Arthritis Impact of Disease (RAID) elaboration database [8], an international (12 European countries) observational study in 2008-2009; ii) baseline data from COMEDRA [9], a French multicentre clinical trial in 2011; iii) and CoimbRA (Coimbra Rheumatoid Arthritis cohort), a Portuguese, cross-sectional observational study in 2015 [10].

### *Participants*

In all three studies consecutive adult patients were included if they had definite RA (ACR 1987 revised criteria or ACR/EULAR 2010 classification criteria) and were able to complete questionnaires. For COMEDRA, additional inclusion criteria were: age limit of 80 years, a stable disease (for at least 3 months), and having no planned surgery in the 6 months following study baseline. Written consent was obtained according to the declaration of Helsinki for all studies, as well as approval from ethical committees, as previously reported [8-10].Here, patients were analysed if they had RAID [8] and remission components available [3].

### *Patient global assessment*

PGA was assessed in the three studies using the same formulation[3] - “Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?", using either a 0-100 visual analogue scale (VAS) or a 0-10 numeric rating scale (NRS) (in COMEDRA).

*Remission definitions*

Four different Boolean-based concepts of remission were used in this study: a) the ACR/EULAR Boolean remission (TJC28, SJC28, CRP mg/dl, and PGA all ≤1) [3], b) near-remission (TJC28, SJC28, and CRP mg/dl all ≤1; and PGA>1), c) non-remission (TJC28 or SJC28 or CRP mg/dl >1, irrespective of PGA), and d) "3variable (3v)-remission" [11] (TJC28, SJC28, and CRP mg/dl all ≤1; PGA excluded from consideration).

*Explanatory factors of PGA*

The seven domains of the RAID score [8] were used as possible factors to explain PGA: i.e., physical (pain, function, and physical wellbeing), psychological (emotional wellbeing and coping/self-efficacy), and mixed domains (fatigue and sleep) [12]. Each domain is assessed by a NRS, ranging from 0 (no impact) to 10 (high impact).

*Other data collection*

Age, gender, disease duration, current biologic agent (yes/no), health assessment questionnaire (HAQ), physician global assessment (PhGA) and 28-joint Disease Activity Score with 4 variables (DAS28-4v) were also assessed for patient's characterization.

*Statistical analyses*

Descriptive analyses, Student’s t-test to compare disease activity states and Hedges' g effect size (ES) were performed using IBM® SPSS® Statistics version 20.0 software.

The ES assessed the discriminant capacity of impact domains to distinguish the disease activity states. To determine the drivers of PGA in near-remission patients, univariable (Pearson's correlation coefficient) and multivariable analyses (linear regression, backward method) were used.

## Results

*Patient characteristics*

The evaluable population comprised 1588 patients (RAID=348; COMEDRA=936; CoimbRA=304), who presented typical established RA, with long disease duration (*Table 1*). Patients from COMEDRA and RAID were often treated with biologic disease modifying drugs (74.7% and 50.0%, respectively). Disease activity was on average, low in COMEDRA and in CoimbRA and moderate in RAID (*Table 1*). All aspects of disease impact presented mean values around 3.5 on 0-10 scales, except for fatigue (mean=4.3, standard deviation, SD=2.8) where higher numbers reflect worst status (*Table 1*).

*Remission rates and PGA cut-offs*

ACR/EULAR Boolean-based remission was achieved by only 195 (12.3%) patients (6.0% in RAID, 15.6% in COMEDRA and 9.2% in CoimbRA). Overall, 303 (19.1%) patients were in near-remission (14.4% in RAID, 14.6% in COMEDRA and 38.2% in CoimbRA). Near-remission was at least as frequent as remission (COMEDRA) and up to four times more frequent (CoimbRA). Overall, 498 (31.4%) of all patients had no signs of inflammation as currently assessed, i.e. were in 3v-remission (*Table 1*).

In the near-remission group (n=303), mean PGA was considerably above the ACR/EULAR Boolean cut-off of ≤1 (mean=3.6, SD=1.9), with 70.3% and 43.9% of patients having a score above 2 and 3, respectively (*Supplementary Figure S1*).

*Impact domains according to disease activity states*

*Table 2* presents disease impact domains according to remission status. In non-remission patients (n=1090), all the disease impact domains had mean values above 3.4, with coping, sleep, and emotional wellbeing scoring lower/better than physical domains. Conversely, in remission patients (n=195), only fatigue (mean=1.3) and physical wellbeing

(mean=1.1) presented means >1.

Mean values of disease impact measures were very similar for patients in near-remission and in non-remission, except ($p<0.05$) for pain, physical wellbeing and function domains (*Table 2*).

Mean scores of disease impact measures were markedly different between patients in remission and those in near-remission ($p<0.001$ in all cases) (*Table 2*). These two groups are brought together under the concept of 3v-remission, whose values of disease impact are, as expected, in-between the two (*Table 2* and *Supplementary Table S1*).

*Drivers of PGA in near-remission patients*

In the 303 near-remission patients, PGA presented moderate ($r_p=0.47$, emotional wellbeing) to good ($r_p=0.68$, pain) correlation with disease impact domains (all $p<0.001$) (*Supplementary Table S2*). In multivariable analysis, PGA was explained ($R^2_{adjusted}=0.55$) by pain ($\beta=0.29$), function ($\beta=0.23$), physical wellbeing ($\beta=0.19$) and fatigue ($\beta=0.15$).

*Main drivers of differences of impact between disease activity states*

Although both remission and near-remission patients had SJC28, TJC28 and CRP ≤1, all mean values of impact domains were statistically higher in near-remission (Supplementary *Figure S2*). Within these, physical and mixed domains of impact (pain, physical wellbeing, function and fatigue) presented greater effect sizes (around 1.53) than psychological ones (still with high effect sizes >1.0). The same trend was found for comparisons between other disease activity groups but with lower effect sizes (Supplementary *Figure S2*). Global scores (PGA and RAID score) were better discriminants than individual RAID domains only when comparing remission with near-remission patients (Supplementary *Figure S2*).

**Discussion**

Several important findings emerged from this first study exploring disease impact in different Boolean disease activity states. It was confirmed that ACR/EULAR Boolean-based remission is very stringent (12.3% of all patients). Near-remission, i.e., failing to reach remission solely due to PGA, was at least as frequent as, and up to four times more frequent than remission. Because of the influence of PGA, the percentage of patients classified as in remission was reduced from 31.4% (3v-remission) to 12.3%. The scores of the diverse domains of impact in near-remission patients were similar to patients in non-remission and PGA was high in these patients (mean=3.6) Pain, physical wellbeing, function and fatigue were the impact domains that better differentiated remission from near-remission states. These results were confirmed by multivariable analyses, supporting the conclusion that high PGA in near-remission patients is driven by physical factors (which might represent subclinical inflammatory activity) and does not especially reflect psychological aspects including anxiety or distress, or fibromyalgia, contradicting common beliefs [7, 13].

This study has strengths and weaknesses. A weakness may be the relatively low percentage of patients in remission, which might limit the power. Using different multicultural cohorts imposes some cautions in the interpretation of results. However, it allowed a greater sample and permitted to analyse multicultural differences in PGA and its impact on the classification of remission. How PGA is measured and its relatively "unclear" cut-offs and formulations are another issue [7]. Using the same formulation in the three studies strengthened this pooled analysis. Some relevant comorbidities such as fibromyalgia, depression, or radiological damage were not assessed, although psychological distress and function were assessed through the RAID questionnaire [8]. Further studies might explore their influence on PGA. Finally, other measures of quality of life than the RAID would have strengthened the paper.

One recent study explored PGA determinants in different levels of disease activity [14], but using tertiles of Disease Activity Score (DAS28) instead of remission [3], and the small sample rendered assessment of remission not feasible and a DAS28<4.2 was adopted.

The ratio of near-remission versus remission rates was variable between studies, from 1/1 to 4/1 patients. Possible reasons to explain this difference could include culture, which may affect PROs [15]. Other reasons could be differences in the provision of patient education, psychological support, and patient expectations between countries. Near-remission rate differences could also be affected by reliability of joint counts [16]. SJC and TJC may miss subclinical inflammation in joints [17], and totally ignores inflammation in other structures, such as tenosynovitis, which the patients can still perceive and value. The use of ultrasound [18] or sensitive CRP measurement [19] rather then current methods should be further explored, specially in patients in near-remission.

As expected, patients in remission had a low disease impact. Fatigue was, among this group of patients and also among all, the domain with highest mean score, underlining its importance in the impact of RA, even in patients in remission [20].

The findings reported herein have important implications for clinical practice. Patients in near-remission presented high levels of symptoms with mean scores around 3.5. Although a higher cut-off for PGA in the definition of remission would certainly increase the number of remissions, it would not make clinical sense in patients whose high PGA is not related to residual inflammation but to structural damage, or an unrelated comorbidity, such as osteoarthritis, depression or fibromyalgia. Such patients would require adjunctive tailored interventions (e.g. patient education, physiotherapy, analgesics, antidepressants, or cognitive behavioural therapy) and not the reinforcement of disease-modifying medication recommended to those not achieving remission. Such special requirements are briefly

addressed in the EULAR recommendations, which state: "once any patient has reached a low disease activity that is close to remission, the individual disease activity variables have to be considered in detail before major therapeutic changes are made." [1]. However, no specific guidance is given for such cases. Another important issue is when to stop or taper immunosuppression – is the target then remission or also near-remission? The present results support the idea that PGA poses problems when used in the 'combined' definition of remission. Perhaps having two separate definitions of remission: one for the purposes of defining the target of immunosuppressive therapy (excluding PGA) and another patient-based, would make sense.

The impact of disease from the patient's perspective should continue to be taken very seriously, but this would be better served by an instrument that allows the identification of the specific cause of persistent impact and thus, guide adjunctive therapy. The RAID [8], taking its individual dimensions separately, may well be a good solution to this need.

**Key messages**:

- Boolean remission in rheumatoid arthritis (RA) is very stringent (achieved by only 6.0% to 15.6% of patients) whereas 14.4 to 38.2% of patients failed to reach remission solely because of patient global assessment (PGA) >1 (near-remission).
- Near-remission patients reported high disease impact, similar to the non-remission patients, indicating that absence of signs of inflammation does not equate to full abrogation of disease impact as reflected by current measures.
- High PGA in near-remission patients did not reflect more the psychological aspects than the physical aspects of impact as reported by patients.

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