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Original article

High patient global assessment scores in patients with rheumatoid arthritis otherwise in remission do not reflect subclinical inflammation

Luisa Brites[a], João Rovisco[a,b], Flávio Costa[g], João Pedro Dinis de Freitas[a], Diogo Jesus[c], Gisela Eugénio[d], Sara Serra[a], Cátia Duarte[a,e], Ricardo J.O. Ferreira[a,f,1], José António Pereira da da Silva[a,e,2,*]

[a] Rheumatology Department, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal
[b] Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[c] Rheumatology Department, Centro Hospitalar de Leiria, Leiria, Portugal
[d] Rheumatology Department, Centro Hospitalar do Baixo-Vouga, Aveiro, Portugal
[e] Faculty of Medicine, Coimbra Institute for Clinical and Biomedical Research (i.CIBR), University of Coimbra, Coimbra, Portugal
[f] Health Sciences Research Unit: Nursing, Nursing School of Coimbra, Coimbra, Portugal
[g] Rheumatology Department, Centro Hospitalar Vila, Nova de Gaia, Portugal

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ABSTRACT

Objectives: To assess whether high patient global assessment (PGA) scores by patients with rheumatoid arthritis (RA) otherwise in remission reflect subclinical inflammation.
Methods: Cross-sectional, single-center study, including consecutive RA patients. Remission states were defined based on the ACR/EULAR Boolean definition: 4V-remission (tender and swollen 28-joint counts (TJC28/SJC28), C-reactive protein (CRP), and PGA all ≤ 1), PGA-near-remission (the same, except PGA > 1), and non-remission (any of TJC28, SJC28, CRP > 1). A blinded expert musculoskeletal ultrasonographer scanned 44 joints, 38 tendon sheaths, 4 bursae on the same day of the clinical evaluation. Each structure was assessed for the presence of Grey Scale synovial hypertrophy (GS) and Power Doppler (PD), both scored using a semi-quantitative scale (0–3 points). The Global OMERACT-EULAR Synovitis Score (GLOESS, 0–132, primary outcome), and a global tenosynovitis/bursitis score (GTBS) were compared between remission states, using non-parametric tests. Different sensitivity analyses comparing GS and PD subscores were performed.
Results: In total, 130 patients (mean age 63 years, 86% female, average disease duration 14 years) were included 40 being in 4V-remission, 40 in PGA-near-remission, 50 in non-remission. 4v-remission and PGA-near-remission presented similar median (IQR) GLOESS, [6 (5–11) and 4 (1–7), $P > 0.05$, respectively] and GTBS [0 (0–1) and 0 (0–2), $P > 0.05$, respectively]. The same was observed in GS, PD scores, and in global synovitis score considering only the 16 joints not included in 28-joint counts. These observations were confirmed in patients with ≤ 5 years disease duration.
Conclusions: Subclinical inflammation is not present among persons with elevated PGA who are otherwise in remission. PGA-near-remission patients would be exposed to the risk of overtreatment if current treatment recommendations were strictly followed. This study supports the need to reconsider the role of PGA in definitions used to target immunosuppressive therapy and to provide a separate and enhanced focus to the patient's experience of the disease.

1. Introduction

Current treatment paradigms in rheumatoid arthritis (RA) recommend that remission or at least low disease activity status should be sought as early and consistently as possible, adjusting immunosuppressive therapy as needed [1,2].

* Corresponding author.
E-mail address: jdasilva@ci.uc.pt (J.A.P.d. da Silva).
[1] Joint last authors.
[2] Joint last authors.

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All definitions of remission endorsed by ACR and EULAR [3] include the patient global assessment of disease activity (PGA). PGA has been consistently identified as the single most common barrier to achieving remission: a condition designated as "PGA-near-remission" or "4V-near-remission" [4,5]. A recent meta-analysis estimated that ~19% (95% CI: 15–23%) of all patients with RA in different clinical settings are in PGA-near-remission, while only 12% (10–15%) are in 4V-remission [6]. Pooled data from 11 recent randomized clinical trials showed a similar rate of PGA-near-remission at 6- or 12-months (19%, 15–22%) [7].

We have argued for the exclusion of PGA from the definitions of remission targeting therapy [6,8,9] essentially because it mainly reflects subjective domains of RA (pain, function, fatigue) and comorbidities, and is only poorly related to more "objective" measures of inflammation, especially at low levels of disease activity [8,10–12]. This suggests that PGA cannot be changed by additional immunosuppressive treatment once inflammation is abrogated. Consequently, patients in PGA-near-remission, on in low disease activity driven by PGA, would be put at risk of overtreatment if the current recommendations were followed strictly [8,9,13].

This proposal has been met with controversy, based on the argument that PGA can distinguish between active and control treatment in clinical trials [3], supporting the hypothesis that PGA scores > 1 in near-remission reflect subclinical inflammation [8,14].

We herein directly test this hypothesis, for the first time, through extensive musculoskeletal ultrasound (MSUS) evaluation of joint and soft tissue inflammation in RA patients at different ACR/EULAR Boolean remission states.

2. Methods

2.1. Study design and population

This was an observational, cross-sectional study, including consecutive adult patients fulfilling the ACR/EULAR 2010 classification criteria for RA, followed in a single tertiary center. Individuals would be eligible if they fulfilled one of the remission status definitions described below in the previous and in the current visit, at least 3 months apart. They would be ineligible only if unable to score PGA unaided or unwilling to participate.

The primary outcome of interest was the comparison of the Global OMERACT-EULAR Synovitis Score (GLOESS), as defined below, between patients in Boolean 4V-remission and in PGA-near-remission.

2.2. Data collection

Patients were asked to score the PGA using the formulation recommended by ACR/EULAR [3]: "Considering all the ways your arthritis has affected you, how do you feel your arthritis is today?" in a visual analogue scale (VAS), anchored from 0 (best possible) to 100 mm (worst possible). A quantified clinical assessment of 28 joints was performed by the consultant rheumatologist on the same day, who also provided a Physician's Global Assessment of disease activity. This was followed by an US examination, performed by another rheumatologist, blinded to the clinical and laboratory evaluation.

Demographic, clinical and laboratory data were collected from medical records.

Remission status was classified following the ACR/EULAR Boolean-based definition [3]: "4V-Remission": TJC ≤ 1, SJC ≤ 1, CRP ≤ 1 mg/dL, and PGA ≤ 1/10; "PGA-near-remission" [8]: similar but PGA > 1; "Non-remission": Any of TJC28, SJC28 and CRP > 1, irrespective of PGA. Disease Activity Score in 28 joints (DAS28), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) scores were computed from the relevant individual factors.

The sonographic assessment included 44 joints, 38 tendon sheaths and 4 bursae [15]. Each structure was assessed for the presence of Grey Scale synovial hypertrophy (GS) and Power Doppler (PD), both scored using a semi-quantitative scale (0 to 3 points) [16–18]. A scoring matrix (Online material, Table S1) was used to determine a GS/PD composite score per individual structure (0 to 3 points). The scores obtained in the 44 joints were summed to calculate the GLOESS (0–132) as described by D'Agostino et al. [19]. A similar strategy was adopted to calculate the Global Tenosynovitis/Bursitis scores (GTBS) (0–126): the sum of the individual scores obtained in the 38 tendon sheaths and 4 bursae examined. For details on assessed structures, US examination and scoring see Online material (data S1).

2.3. Statistical analysis

Categorical variables were described as proportions and continuous data using mean (standard deviation) or median (interquartile range), as appropriate. A total sample size of 111 patients had been estimated as required using GPower, considering an effect size of 0.30, an $\alpha = 0.05$, and a power of 80%. Because MSUS results were non-normally distributed, the Kruskal–Wallis test was used to compare the remission groups, with *post hoc* pairwise adjusted comparisons.

We performed a number of sensitivity analyses. As the GS has been shown to be more reliant than PD in the assessment of US inflammation, we performed a sensitivity analysis comparing the sum of GS scores and the sum of PD scores independently for joints, tendon sheaths, and bursas (Online material, Table S1). Also, considering the fact that the difference in the synovitis US score might be driven mainly by joints not included in the clinical 28-joint count, we compared the PDUS synovitis score considering only the 16 joints included in the 44-joint assessment but not in the 28-joint count. Because disease duration may be a confounder, a third sensitivity analyses included only the patients with a disease duration ≤ 5 years.

In a secondary analysis, we also tested the association between GLOESS, PGA and Physician's global assessment (PhGA), using Spearman's coefficient correlation (r_s). r_s values < 0.30 were considered poor, 0.30–0.59 fair, 0.60–0.79 moderate, ≥ 0.80 very strong [20]. Statistical analysis was performed using IBM SPSS Statistics, V.23 and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patients' characteristics

Recruitment of consecutive patients took place from September 2019, until the prespecified numbers of participants in the different remission status were achieved, by mid-October 2020. Only 4 eligible patients were excluded (3 declined participating and one was unable to reliably fulfill the PGA unaided). We included 130 patients, presented in Table 1. Similar characteristics were observed in the 4V-remission and PGA-near-remission groups, except for the PGA's value (per definition). PGA scores were similar for patients in PGA-near-remission and in Non-remission. The proportion of patients classified as being in low-disease activity as opposed to remission, by the combined indices of disease activity (SDAI and CDAI) was much larger in the near-remission than in the 4v-remission group.

Table 1
Sociodemographic and clinical characteristics of the study participants ($n = 130$).

Variables	Overall ($n = 130$)	A. 4V-remission ($n = 40$)	B. PGA-near-remission ($n = 40$)	C. Non-remission ($n = 50$)
Age, mean (SD) years	63 (12)	61 (14)	62 (12)	66 (10)
Caucasian, *n* (%)	130 (100)	40 (100)	40 (100)	50 (100)
Female, *n* (%)	109 (84)	33 (83)	36 (90)	40 (80)
Education level, *n* (%)				
Illiterate	10 (8)	2 (5)	3 (8)	5 (10)
Elementary school	84 (65)	24 (60)	26 (65)	34 (68)
Secondary school	18 (14)	6 (15)	5 (13)	7 (14)
Bachelor's degree or higher	18 (14)	8 (20)	6 (15)	4 (8)
Disease duration, median (IQR) years	14 (6–22)	13 (5–17)	15 (6–22)	16 (8–27)
Rheumatoid factor positive, *n* (%)	85 (65)	26 (65)	26 (65)	33 (66)
Anticitrullinated protein antibody positive, *n* (%)	76 (59)	21 (53)	22 (55)	33 (66)
CRP mg/dL, mean (SD)	0.7 (1.0)	0.3 (0.5)	0.2 (0.2)	1.3 (1.4)
ESR mm/hour, mean (SD)	13 (12)	11 (11)	10 (10)	16 (14)
TJC28, median (IQR)	0 (0–1)	0 (0–0)	0 (0–0)	1 (0–2)
SJC28, median (IQR)	0 (0–2)	0 (0–0)	0 (0–1)	2 (1–3)
PGA 0–100 mm, median (IQR)	30 (10–57)	0 (0–10)	48 (30–58)	50 (39–70)
PhGA 0–100 mm, median (IQR)	0 (0–20)	0 (0–0)	0 (0–9)	20 (10–30)
SDAI, 0–86, mean (SD)	7.5 (8.9)	1.1 (1.1)	6.1 (3.5)	13.8 (9.2)
Remission, *n* (%)	47 (36)	38 (95)	8 (20)	1 (2)
LDA, *n* (%)	52 (40)	2 (5)	31 (78)	19 (38)
MDA, *n* (%)	29 (22)	0	1 (2)	28 (56)
HDA, *n* (%)	2 (2)	0	0	2 (4)
CDAI, 0–76, mean (SD)	6.8 (7.6)	0.8 (0.9)	5.9 (3.5)	12.5 (8.9)
Remission, *n* (%)	41 (32)	37 (95)	3 (8)	1 (2)
LDA, *n* (%)	60 (46)	3 (5)	36 (90)	21 (42)
MDA, *n* (%)	25 (19)	0	1 (2)	25 (50)
HDA, *n* (%)	4 (3)	0	0	3 (6)
DAS28-CRP (4V), 0–9.4, mean (SD)	2.5 (1.1)	1.5 (0.4)	2.1 (0.4)	3.4 (1.0)
Remission, *n* (%)	76 (59)	40 (100)	32 (80)	4 (8)
LDA, *n* (%)	29 (22)	0	8 (20)	21 (42)
MDA, *n* (%)	21 (16)	0	0	21 (42)
HDA, *n* (%)	4 (3)	0	0	4 (8)
DAS28-CRP, 0–9.4, mean (SD)	2.3 (0.9)	1.7 (0.4)	1.7 (0.4)	3.1 (0.9)
Remission, *n* (%)	93 (71)	38 (95)	39 (98)	16 (32)
LDA, *n* (%)	20 (15)	2 (5)	1 (2)	17 (34)
MDA, *n* (%)	15 (12)	0	0	15 (30)
HDA, *n* (%)	2 (2)	0	0	2 (4)

CRP: C-reactive protein; DAS28: disease activity score in 28 joints; ESR: erythrocyte sedimentation rate; HDA: high disease activity; IQR: interquartile range; LDA: low disease activity; MDA: moderate disease activity; PGA: patient's global assessment; PhGA: physician's global assessment; SD: standard deviation; SDAI: simplified disease activity index; CDAI: clinical disease activity index.

3.2. Musculoskeletal ultrasound scores

GLOESS scores were similar in the PGA-near-remission [median 4 (IQR 1–7)] and in the 4V-remission group [6 (IQR 5–11)] ($P > 0.05$), both being significantly lower than in the non-remission group [13 (5–19)] (Table 2). No statistically significant differences were found between the 4V-remission and PGA-near-remission regarding the MSUS scores for synovitis, tenosynovitis or bursitis (Table 2). The Maximum GLOESS scores were 27 and 26 in patients in 4V-remission and PGA-near-remission, respectively.

3.3. Sensitivity analyses by ultrasound features

The GS and PD scores were similar for PGA-near-remission and 4V-remission (Table 2). The composite synovitis score for the 16 joints excluded from 28-joint counts was statistically lower in the PGA-near-remission compared to the 4V-remission.

3.4. Sensitivity analyses by disease duration

Twenty-eight patients had ≤ 5 years of disease duration ($n = 11$ in 4V-remission, $n = 8$ in PGA-near-remission, $n = 9$ in non-remission) allowing for non-parametric comparisons. Results were similar to those obtained in the complete sample (Online material, Table S2).

3.5. Secondary analysis: association between GLOESS, PGA and PhGA

Considering the total sample, the correlation between GLOESS and PGA was not statistically significant ($P > 0.05$). The correlation with PhGA was fair ($r_s = 0.34$, $P < 0.001$).

4. Discussion

This study compared US findings in patients in Boolean-based remission status and in PGA-near-remission. After an extensive joint and periarticular tissue evaluation, we found no significant differences between these two groups. The observation of some US synovitis in patients in clinical remission, especially GS, replicates other reports [14,21,22].

The hypothesis that a high PGA score in near-remission patients might be explained by subclinical joint inflammation or inflammatory activity in structures not examined in 28-joint counts (tendon sheaths, bursae and 16 other joints, namely from the feet) is not supported by our results. The similarity between groups in both GS and PD scores further indicates that the degree of inflammation does not differ between persons in 4V-remission and PGA-near-remission.

We recognize that the average disease duration is quite long in our global sample which may allow for additional potential causes of high PGA. This would not exclude these patients from the risk

Table 2
Comparison of ultrasound scores between Boolean remission states. All values are median (IQR).

Ultrasound score	A. 4V-remission ($n = 40$)	B. PGA-near-remission ($n = 40$)	C. Non-remission ($n = 50$)
Global joint scores			
GLOESS composite scores (0–132)	6 (5–11)	4 (1–7)	13 (5–19)$^{\#\#\#}$
Grey scale (0–132)	7 (4–10)	5 (3–9)	14 (6–19)$^{\#\#\#}$
Power Doppler (0–132)	0 (0–2)	0 (0–1)	1 (0–6)$^{\#\#}$
Global Tenosynovitis/Bursitis scores			
GTBS composite scores (0–126)	0 (0–1)	0 (0–2)	2 (0–6)$^{\#\#}$
Grey scale (0–126)	0 (0–1)	0 (0–2)	2 (0–6)$^{\#\#}$
Power Doppler (0–126)	0 (0–0)	0 (0–0)	0 (0–1)
GLOESS 16 joints (0–48)[a]	5 (3–8)**	2 (0–5)	3 (2–7)

GLOESS: global OMERACT-EULAR synovitis score, 44 joints; GTBS: global tenosynovitis and bursitis score; *: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$ in comparisons between group A vs. group B; $^{\#}$: $P < 0.05$; $^{\#\#}$: $P < 0.01$; $^{\#\#\#}$: $P < 0.001$ in comparisons between group C vs. group B. The global tenosynovitis/bursitis scores were calculated by summing the individual scores of the 38 tendon sheaths and 4 bursae examined. The Kruskal–Wallis test with *post hoc* pairwise adjusted comparisons was used.

[a] Separate analysis of the sixteen joints examined by US but excluded from clinical 28-joint counts.

of overtreatment if treatment recommendations would be strictly followed, and this was the main objective of this study. Nonetheless, we performed a sensitivity analysis in patients with up to 5 years of disease, which showed concordant results.

The sample was recruited in a single center which may question generalizability. However, a recent study from Japan also reported similar levels of US evaluated inflammation in these two groups of patients, although a smaller number of synovial structures was examined [23]. Our sample shows a relatively low level of formal education, which may have influenced the results, although the difficulties and inconsistencies of PGA have also been observed in people with higher formal education [24]. A longitudinal study could have provided further information, namely to assess sustained remission status or to explore if a high PGA may represent patient anticipation, or recent experience, of a flare. We did not perform a formal evaluation of interobserver variability of US examination for this study, but the crucial aspects of experience and blinding of the ultrasonographer were strictly guaranteed. The use of MRI, which is more sensitive than US to assess inflammation, namely when restricted to bone marrow, might be preferable. However, an unpublished study used both MRI and US to assess the presence of subclinical inflammation in patients with different ACR/EULAR Boolean status, including the PGA-near-remission status (based on 44-joints), and found no clinical nor statistically significant differences between the two methods [25]. Conversely, as strengths, we used in an adequately powered sample size, including patients from a clinical setting, with a diversity of disease duration and background treatments. A comprehensive US assessment was performed, although we recognize that GLOESS has not been the object of extensive validation or wide acceptance.

The results described herein are in line with previous observations indicating that PGA is, overall, but most especially in near-remission status, essentially driven by dimensions that do not reflect the concomitant inflammatory process, such as pain, fatigue, physical impairment, depressive symptoms, fibromyalgia, osteoarthritis, to name some [8,10–12,26].

This reinforces the argument that, at least in lower levels of disease activity, PGA scores are not sufficiently related to disease activity to merit inclusion in definitions of remission used to target therapy addressing the inflammatory process [8,9]. This is further supported by recent studies showing that PGA-near-remission and 4V-remission are associated with similar radiographic outcomes, both in clinical practice and in clinical trials [7,27].

In conclusion, these observations should not be interpreted as indicating that the patient's appraisal of their condition is unreliable. They simply indicate that, through PGA, patients are not measuring disease activity/inflammation, but disease impact, which encompasses dimensions independent of inflammation. The problem lies on our decision to include PGA as a measure of inflammation and making it part of the target used to guide immunosuppression. It seems clear that patients in PGA-near-remission would be exposed to the risk of overtreatment if current treatment recommendations were followed strictly [13]. An ambitious and stringent target could reinforce this tendency [28]. This problem affects all definitions of remission adopted by ACR/EULAR (Table 1) [3]. Although the treatment recommendations advise the rheumatologist to carefully explore other reasons for the "unsatisfactory" state of the patient otherwise in remission, this would become clearer if PGA was taken away from the definition of target. Meanwhile, rheumatologists should adopt in clinical practice a more personalized and flexible approach than in RCTs, in order to provide optimal care (pharmacological and non-pharmacological).

The dual target approach [8,9,29], separating a biological remission target, and an equally important and complementary target focused on symptom remission, seems a plausible approach to mitigate this problem and sharpen to biological target while highlighting the crucial role that the patient's experience should play on the assessment and management of RA.

Ethical approval and consent to participate

The study complies with the Declaration of Helsinki and its protocol was approved by the Ethics Committee of Centro Hospitalar e Universitário de Coimbra (CHUC-142-17). All patients signed an informed consent.

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Contribution

Study design: Diogo Jesus, Gisela Eugénio, João Rovisco, Cátia Duarte, Ricardo J. O. Ferreira, J. A. P. da Silva.

Data collection: Diogo Jesus, Flávio Costa, J.P. Freitas, Luisa Brites, João Rovisco, Sara Serra.

Data analysis: Luisa Brites, Ricardo J. O. Ferreira.

Preparation of the initial manuscript: Luisa Brites, Ricardo J. O. Ferreira.

Manuscript revision and final approval: Luisa Brites, João Rovisco, Diogo Jesus, Flávio Costa, J.P. Freitas, Sara Serra, Gisela Eugénio, Cátia Duarte, Ricardo J. O. Ferreira, J. A. P. da Silva.

Disclosure of interest

The authors declare that they have no competing interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2021.105242.

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