Reexamining Remission Definitions in Rheumatoid Arthritis: Considering the 28-joint Disease Activity Score, C-reactive Protein Level, and Patient Global Assessment: Comment on the Article by Felson et Al

Ricardo J. O. Ferreira, Paco M. J. Welsing, Johannes W. G. Jacobs, Laure Gossec, Mwidimi Ndosi, Pedro M. Machado, Désirée Heijde, José A. P. Silva

Reexamining remission definitions in rheumatoid arthritis: considering the Twenty-Eight-Joint Disease Activity Score, C-reactive protein level, and patient global assessment: comment on the article by Felson et al

Ferreira, R.J.O.; Welsing, P.M.J.; Jacobs, J.W.G.; Gossec, L.; Ndosi, M.; Machado, P.M.; ... ; Silva, J.A.P. da

Arthritis Care & Research
Vol. 74, No. 3, March 2022, pp 501–503

American College of Rheumatology
Empowering Rheumatology Professionals

LETTERS

DOI 10.1002/acr.24843

Reexamining remission definitions in rheumatoid arthritis: considering the 28-joint Disease Activity Score, C-reactive protein level, and patient global assessment: comment on the article by Felson et al

To the Editor:

We read with great interest the editorial by Felson et al on definitions of remission in rheumatoid arthritis (RA), recently published in *Arthritis Care & Research* (1). The article gives a comprehensive and historical overview of the development of remission criteria and provides a well-founded critique of remission criteria based on the 28-joint Disease Activity Score (DAS28). The DAS28 has been primarily developed and validated for evaluations at the group level, i.e., for measuring effects in clinical trials. However, in almost forgotten earlier times, when patient remission was rarely achieved, there was a need for a single index, expressing disease activity of the individual patient, and the only instrument available was the 44-joint Disease Activity Score (2). When biologics became available in many countries of Europe, the use of the DAS28 as a single index of disease activity was also stimulated by health authorities and insurance companies, requiring DAS28 proof of active RA and documented previous treatment failure (or contraindication) of conventional synthetic disease-modifying antirheumatic drugs, before allowing reimbursement of an expensive biologic drug. Since then, remission has proved to be an achievable goal, and for clinical trials and for individual patients, DAS28 cutoffs have been used for this purpose, especially in Europe, although their limitations for evaluations at the individual patient level have indeed been recognized (3).

Moreover, we agree with Felson et al that patient global assessment (PtGA) is a valuable assessment. However, we feel compelled to clarify the misunderstanding that seems to persist regarding our relatively simple proposal. We do not suggest merely eliminating PtGA from the definitions of remission; we suggest that a second target, based on valid and discriminative patient-reported measures of disease impact, be adopted, in parallel but separated from the existing target for inflammatory disease activity, which, we believe, could be refined by the exclusion of PtGA. Although Felson et al cite our article (4), they do not depict our proposal for this dual-target strategy and its conceptual framework, summarized in the conclusions of that article. Following our proposal, the patient's perspective would become more valued, rather than being ignored.

We disagree with the interpretation of the evidence provided by Felson et al to support the concept that PtGA should be kept as a component of the American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) definitions of remission. Although PtGA and measures of clinical disease activity are correlated at high levels of disease activity, contributing to the ability of PtGA to distinguish active treatment from placebo in the context of clinical trials, they are only poorly, if at all, correlated at low levels of disease activity (5,6), precisely when the practicing clinician needs to make difficult decisions regarding escalating or maintaining immunosuppressive/immunomodulatory therapy. Thus, while the inclusion of PtGA may facilitate the distinction between treatments in clinical trials, we are concerned regarding the implications of including PtGA as an element of composite definitions of remission used to tailor immunosuppressive/immunomodulatory therapy in clinical practice and the potential risk of overtreatment that this practice entails. As many as 45–61% of all patients with RA (in clinical trials [4] and cohort studies [7]) who are otherwise in remission fail to meet the Boolean definition of remission solely because of a too high PtGA score. These patients, in so-called PtGA near-remission, are exposed to the risk of overtreatment, because their disease cannot be improved by additional immunosuppression/immunomodulation. However, they still endure a significant impact of nondisease activity manifestations and outcomes of the disease (8), which were recently touched upon in the EULAR points to consider for the management of difficult-to-treat RA (9). The use of the ACR/EULAR remission definitions in clinical practice was explicitly predicted in the original 2011 report (10), and the definitions have been extensively adopted as part of the treat-to-target strategy. Thus, the implications of these definitions are more extensive than those for clinical trials only.

The assertion that PtGA reflects subclinical inflammation is, in our view, unsupported by evidence. We, and in fact, some of the authors of the editorial themselves, have shown no correlation between PtGA and joint damage accrual (11). We have also demonstrated that in patients who are in PtGA near-remission there is no evidence of inflammation in other joints or synovial structures, through extensive ultrasonography assessment (12). It is difficult to envisage what room is left for the consideration in the editorial that "…the patient global assessment reflects components of disease activity that are otherwise not captured, …as inflammation in joints not included in a 28-joint count, such as the feet and ankles." This is, therefore, not the reason "why high patient global assessment scores, even when 28-joint counts are low, identify patients at high risk of later functional loss" (1). This may be simply and better explained by the fact that function is a major

determinant of PtGA, irrespective of inflammatory disease activity, as repeatedly reported (5,6,8,13). These publications are the basis of our dual-target strategy proposal, which, we hypothesize, may result in more accurate and comprehensive definitions of remission. We proposed the dual target to comprise 1) biologic remission, which will be sharper and more sensitive to help guide immunosuppressive/immunomodulatory therapy in individual patients in clinical practice, and 2) patient remission, also addressing all other important aspects of nondisease activity manifestations, of outcomes of the disease, and of medication adverse effects (disease impact), and will thus be more informative than the current 1-item PtGA. Surely, this approach highlights the importance of patients' perspective, as it ensures that clinicians address both the disease activity and the disease impact aspects accordingly.

In summary, we agree with many of the points made in the editorial by Felson et al, but we feel that it distorts our proposal by omitting to mention the patient remission aspect, which is what makes it a dual target: a holistic strategy that empowers patients and promotes health by allowing patients to gain greater control over decisions and actions affecting their health, a World Health Organization recommendation since the Ottawa conference in 1986.

Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr.24843&file=acr24843-sup-0001-Disclosureform.pdf.

Ricardo J. O. Ferreira, PhD
Centro Hospitalar e Universitário de Coimbra and Nursing School of Coimbra
Coimbra, Portugal
Paco M. J. Welsing, PhD
Johannes W. G. Jacobs, PhD
University Medical Center
Utrecht, The Netherlands
Laure Gossec, PhD
Sorbonne Université–INSERM and Pitié Salpêtrière hospital, AP-HP
Paris, France
Mwidimi Ndosi, PhD
University of the West of England
Bristol, UK
Pedro M. Machado, PhD
University College London, University College London Hospitals NHS Foundation Trust, and Northwick Park Hospital, London North West University Healthcare NHS Trust
London, UK
Désirée van der Heijde, PhD
Leiden University Medical Centre
Leiden, The Netherlands
José A. P. da Silva, PhD
Centro Hospitalar e Universitário de Coimbra and University of Coimbra
Coimbra, Portugal

1. Felson DT, Lacaille D, LaValley MP, Aletaha D. Reexamining remission definitions in rheumatoid arthritis: considering the twenty-eight–joint Disease Activity Score, C-reactive protein level, and patient global assessment [editorial]. Arthritis Care Res (Hoboken) 2022;74:1–5.
2. Van der Heijde DM, van 't Hof MA, van Riel PL, Theunisse LA, Lubberts EW, van Leeuwen MA, et al. Judging disease activity in clinical practice in rheumatoid arthritis: first step in the development of a disease activity score. Ann Rheum Dis 1990;49:916–20.
3. Jacobs JW, Ten Cate DF, van Laar JM. Monitoring of rheumatoid arthritis disease activity in individual patients: still a hurdle when implementing the treat-to-target principle in daily clinical practice [editorial]. Rheumatology (Oxford) 2015;54:959–61.
4. Ferreira RJ, Welsing PM, Jacobs JW, Gossec L, Ndosi M, Machado PM, et al. Revisiting the use of remission criteria for rheumatoid arthritis by excluding patient global assessment: an individual meta-analysis of 5792 patients. Ann Rheum Dis 2020;80:293–303.
5. Ferreira RJ, Duarte C, Ndosi M, de Wit M, Gossec L, da Silva JA. Suppressing inflammation in rheumatoid arthritis: does patient global assessment blur the target? A practice-based call for a paradigm change. Arthritis Care Res (Hoboken) 2018;70:369–78.
6. Ferreira RJ, Carvalho PD, Ndosi M, Duarte C, Chopra A, Murphy E, et al. Impact of patient's global assessment on achieving remission in patients with rheumatoid arthritis: a multinational study using the METEOR database. Arthritis Care Res (Hoboken) 2019;71:1317–25.
7. Ferreira RJ, Santos E, Gossec L, da Silva JA. The patient global assessment in RA precludes the majority of patients otherwise in remission to reach this status in clinical practice. Should we continue to ignore this? Semin Arthritis Rheum 2020;50:583–5.
8. Ferreira RJ, Dougados M, Kirwan JR, Duarte C, de Wit M, Soubrier M, et al. Drivers of patient global assessment in patients with rheumatoid arthritis who are close to remission: an analysis of 1588 patients. Rheumatology (Oxford) 2017;56:1573–8.
9. Nagy G, Roodenrijs NM, Welsing PM, Kedves M, Hamar A, van der Goes MC, et al. EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis 2022;80:20–33.
10. Felson DT, Smolen JS, Wells G, Zhang B, van Tuyl LH, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum 2011;63:573–86.
11. Studenic P, Felson D, de Wit M, Alasti F, Stamm TA, Smolen JS, et al. Testing different thresholds for patient global assessment in defining remission for rheumatoid arthritis: are the current ACR/EULAR Boolean criteria optimal? Ann Rheum Dis 2020;79:445–52.
12. Brites L, Rovisco J, Costa F, Freitas JPD, Jesus D, Eugénio G, et al. High patient global assessment scores in patients with rheumatoid arthritis otherwise in remission do not reflect subclinical inflammation. Joint Bone Spine 2021;88:105242.
13. Craig ET, Perin J, Zeger S, Curtis JR, Bykerk VP, Bingham CO III, et al. What does the patient global health assessment in rheumatoid arthritis really tell us? Contribution of specific dimensions of health-related quality of life. Arthritis Care Res (Hoboken) 2020;72:1571–8.

DOI 10.1002/acr.24842

Reply

To the Editor:

We read with interest the letter by Ferreira and colleagues in response to our editorial about the measurement of remission in