



HAL
open science

Overtreatment in rheumatoid arthritis: are there reasons for concern?

Ricardo J O Ferreira, Laure Gossec, Jose Antonio Pereira da Silva

► To cite this version:

Ricardo J O Ferreira, Laure Gossec, Jose Antonio Pereira da Silva. Overtreatment in rheumatoid arthritis: are there reasons for concern?. *RMD Open*, 2022, 8 (2), pp.e002212. 10.1136/rmdopen-2022-002212 . hal-03957906

HAL Id: hal-03957906




<https://hal.science/hal-03957906v1>

Submitted on 26 Jan 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

EDITORIAL

Overtreatment in rheumatoid arthritis:
are there reasons for concern?Ricardo J O Ferreira ^{1,2,3} Laure Gossec ^{4,5}
Jose Antonio Pereira da Silva ^{2,6}

To cite: Ferreira RJO, Gossec L, da Silva JAP. Overtreatment in rheumatoid arthritis: are there reasons for concern?. *RMD Open* 2022;**8**:e002212. doi:10.1136/rmdopen-2022-002212

Received 7 April 2022

Accepted 18 September 2022



► <http://dx.doi.org/10.1136/rmdopen-2021-002013>



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

¹Nursing Research, Innovation and Development Centre of Lisbon (CIDNUR), Higher School of Nursing of Lisbon, Lisboa, Portugal

²Rheumatology, Centro Hospitalar e Universitário de Coimbra EPE, Coimbra, Portugal

³Health Sciences Research Unit: Nursing (UICISA: E), Nursing School of Coimbra, Coimbra, Portugal

⁴Sorbonne Université, Institut Pierre Louis d'Epidémiologie et de Santé Publique, INSERM, Paris, France

⁵Rheumatology, Pitié Salpêtrière hospital, AP-HP, Paris, France

⁶Clínica Universitária de Reumatologia, and i-CBR Coimbra Institute for Clinical and Biological Research, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

Correspondence to

Dr Ricardo J O Ferreira;
ferreira.rjo@gmail.com

The concise report by Paulshus Sundlisæter *et al* published in this issue of *RMD Open*¹ provides a significant contribution to the ongoing discussions regarding the definition(s) of remission in rheumatoid arthritis (RA) and their implications when applied as targets in clinical practice. The authors compared patients in American College of Rheumatology/ European Alliance of Associations for Rheumatology (ACR/EULAR) Boolean remission and in 'near-remission' regarding the use of biological disease-modifying antirheumatic drugs (bDMARDs), the incidence of adverse effects and the presence of subclinical inflammation.¹ This is an ancillary analysis of data from the ARCTIC trial, which tested the systematic use of ultrasound in the follow-up of patients with early RA treated in a tight control regimen.² The remission status was defined at the 2years time point.¹

In this editorial, we will discuss four main findings of that paper, as we interpret it:

1. Patient Global Assessment (PGA) of disease activity is the main single obstacle to Boolean remission, explaining 59% of all cases of near-remission, followed by tender joint count (22%).
2. The status of 'PGA-near-remission' represents an important proportion of all patients 'otherwise in remission', even under a tight-control targeted strategy.
3. A PGA>1 or tender joint count >1 in patients who are otherwise in remission do not reflect subclinical inflammation.
4. PGA may drive unwarranted treatment escalations with an associated increase in the rate of adverse events.

The first two observations are well aligned with previous reports. The concept of 'near-remission' was used originally by Studenic *et al* (Austria)³ and Veermer *et al* (The Netherlands),⁴ soon after the publication of the ACR/EULAR remission criteria for RA⁵ to

represent patients who failed to reach remission solely due to one of four criteria of the Boolean definition being >1. Those two studies showed that PGA was responsible for 61% and 67% of all near-remission cases, respectively.^{3,4} Of all RA patients included in these clinical cohorts, 31%³ and 21%⁴ failed Boolean remission solely due to PGA, a condition later coined as PGA-near-remission⁶ (ie, tender and swollen 28-joint (TJC28/SJC28) and C reactive protein (CRP) all ≤1, but PGA >1/10). Recent systematic reviews determined a 19% prevalence of PGA-near-remission in RA for both clinical trials⁷ and cohorts,⁸ representing 45% and 60%, respectively, of all patients otherwise in remission. This percentage was of 21% in the study of Paulshus Sundlisæter *et al*¹

The conclusion that PGA-near-remission is not associated with subclinical inflammation is supported, in this study, by ultrasound evaluation of 32 joints and MRI of the dominant hand.¹ Of note, 12 joints in the feet, not included in clinical 28-joint counts, were included in the ultrasound evaluation. This imaging data does not support the interpretation that the slightly higher levels of CRP and physician global assessment observed in the PGA-near-remission group (at 2 years follow-up) might reflect the presence of subclinical inflammation. These results confirm the findings of two previous studies addressing this issue (see [table 1](#)).^{9,10} These studies do not support the arguments that high scores of PGA in patients otherwise in remission reflect subclinical inflammation that is not accounted for by currently used 28-joint counts and or laboratory markers.^{11,12} This is reinforced by the demonstration that PGA-near-remission patients do not have worse radiographic progression than patients in 'full' remission.^{5,7,12} Several studies have demonstrated that SJC and CRP are the only items of the Boolean definition that have

Table 1 Summary of studies comparing subclinical findings between patients with rheumatoid arthritis who fulfil the ACR/EULAR Boolean-based remission criteria and the patients in near-remission

Study	Context	Sample characteristics	Definition of ACR/EULAR Boolean Remission, n (%)	Assessment timepoint	Definition of near-remission, n (%)	Image definition(s)	Comparison of sub-clinical image
Paulshus Sundlisæter et al (2022), Norway ¹	DMARD-naïve patients participating in an RCT (ARCTIC), 11 centres	Sample: n=203 (62% female; 54 years median age (42–63); 5 months median disease duration (3–11); 69% RF+; 81% ACPA+)	Definition: SJC≤1/44 AND Ritchie Articular Index (RAI) ≤1 AND CRP≤1 AND PGA≤1 Proportion: 112 (55%)	2 years after study initiation	SJC≤1/44 and CRP≤1 and RAI>1 and/or PGA>1 Proportion: 61 (30%)	Ultrasound: 32 joints, using grey scale (GS, 0–96) and synovitis power doppler (PD, 0–96) according to a semi-quantitative scale (0–3) MRI: dominant hand, using OMERACT scoring system (RAMRIS synovitis, 0–21; RAMRIS bone marrow oedema, 0–75; RAMRIS tenosynovitis, 0–42).	No statistical differences in any score
Brites et al (2021), Portugal ⁹	Observational study, single centre	Sample: n=130 (86% female; 63 years mean age (SD=12); 14 years median disease duration (6–22); 65% RF+; 59% ACPA+)	Definition: SJC≤1/28 and TJC≤1/28 and CRP≤1 and PGA≤1 Proportion: 40 (31%)†	Cross-sectional study	SJC≤1/28 and TJC≤1/28 and CRP≤1 and PGA>1 Proportion: 40 (31%)†	Ultrasound: 44 joints, 38 tendons sheaths, and four bursae using grey scale (GS, 0–132) and synovitis power doppler (PD, 0–132) according to a semi-quantitative scale (0–3), and the Global OMERACT-EULAR Synovitis Score (GLOESS, 0–132, primary outcome).	No statistical differences in any score
Nakabo et al (2020), Japan ¹⁰	Observational study, single centre	Sample: n=402 (81% female; 62 years mean age (SD=13); 13 years mean disease duration (SD=11); 87% RF+; 81% ACPA+)	Definition: same as above Proportion: 118 (29%)	Cross-sectional study	SJC≤1/28 AND TJC≤1/28 AND CRP≤1 AND PGA>1 Proportion: 141 (35%)	Ultrasound: 20 joints, using grey scale (GS, 0–60) and synovitis power doppler (PD, 0–60) according to a semi-quantitative scale (0–3)	No statistical differences in any score

*Ritchie Articular Index is a graded assessment of 0–3 of the tenderness (0 no tenderness, +1 patient complained of pain, +2 patient complained of pain and winced, +3 patient complained of pain and winced and withdrew) in 26 joint regions (temporo-mandibular, cervical spine, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, metacarpal-phalangeal, proximal interphalangeal, hip, knee, ankle, talocalcaneal, midtarsal and metatarsal)²⁶
†purposive sample.
ACPA+, anticitrullinated protein/peptide antibody positive; CRP, C reactive protein; DMARD, disease-modifying antirheumatic drugs; GS, grey scale; OMERACT, Outcome Measures in Rheumatology; PGA, Patient Global Assessment of disease activity; RAI, Ritchie Articular Index; RCT, randomised controlled trial; RF+, rheumatoid factor positive; SJC, swollen joint count; TJC, tender joint count.

a significant association with long-term radiographic outcome.^{13,14} Of note, in this report on the ARCTIC trial, radiographic damage is not reported.¹

In fact, there is abundant evidence that PGA has a very poor correlation with objective measures of inflammation, especially in lower levels of disease activity (moderate to low disease activity/remission), and may, therefore, misguide treatment decisions made according to these cut-offs.^{6,15} PGA is essentially an indicator of disease impact, driven mostly by fatigue, pain, function and psychological domains, which bear no relationship with disease activity once the inflammatory process has been brought under control (remission).^{6,15}

Taken together, the arguments above question the use of PGA in the definition of targets used to guide immunosuppressive therapy, as this cannot be expected to have additional benefits after remission has been achieved. Furthermore, an elevated PGA coupled with low disease activity provides no clues on the underlying reasons in need of adjuvant therapy.

The fourth remark, addressing the unnecessary treatment escalations driven by PGA and its associated risks, needs to be dissected in detail and seen with caution.

The results of Paulshus Sundlisæter *et al* show that patients in near-remission who miss full remission due to PGA and/or joint tenderness were more frequently prescribed bDMARDs (38 vs 14%, $p < 0.001$) and had more non-serious adverse events (95 vs 73%, $p < 0.001$) than patients in complete remission. Patients in full remission had more serious adverse events than patients in near-remission (5 vs 2%, $p = 0.33$), although absolute numbers were very small ($n = 5$ and 1). These clues of overtreatment are especially important given the absence of objective clinical and imaging signs of inflammation.¹ The low scores observed with MRI (~ 4) are compatible with prior observations in normal people without arthritis¹⁶ and in patients with RA in remission.^{17,18} However, the ARCTIC trial² providing the original data is not aligned with current clinical practice. The target being pursued under tight control in both arms was more stringent than the ACR/EULAR Boolean remission: DAS remission (< 1.6) plus 0 SJC (out of 44) for the control arm and, additionally for the intervention arm, absence of ultrasound power doppler in any assessed joint. This is especially relevant as low disease activity might be argued as a more appropriate target for the population included. The physician was asked to overrule the DAS-based decision in the ultrasound arm and proceed to the next treatment step indicated by the ultrasound score.² Cautionary features highlighted in the current EULAR RA treatment recommendations,¹⁹ namely the consideration of 'patient factors, such as comorbidities and progression of structural damage' were not adhered to, by protocol. All these aspects suggest that the absolute risk of overtreatment is amplified by the protocol well beyond what should be expected in clinical practice.

The fact remains, though, that being in PGA-near-remission was associated with stronger medication and

a higher prevalence of non-serious adverse events than being in full remission. This is relevant, given that all patients were exposed to same treatment protocol, having DAS as the main driver of treatment escalation, without consideration of its individual components. The ARCTIC trial² used the outdated Ritchie articular index to indirectly establish the ACR/EULAR Boolean remission status, which was validated using the 28-joint counts.⁵ However, Paulshus Sundlisæter *et al*¹ confirmed the results by a sensitivity analysis, with predefined methods.² We consider it unlikely that this aspect may have significantly influenced the results.

Data suggestive of overtreatment were also reported in a recent preprint,²⁰ based on post hoc analyses of a supplemental fish oil trial in early RA, following a treat-to-target (T2T) protocol.²⁰ At week 52, patients who had improvement in SJC28 and CRP but not in TJC28 and PGA were prescribed a higher dose of methotrexate (18.5 vs 12.5 mg/week) and more frequently leflunomide (16% vs 4%) than patients who improved all four components of the Disease Activity Score with 28-joints (DAS28).²⁰

The topic of overtreatment was recently highlighted in a viewpoint as a potential consequence of strict pursuance of T2T treatment guidelines.²¹ There is no doubt that managing RA to ensure the early and persistent abrogation of the inflammatory process, as per T2T, provides the best possible outcomes to patients, both in terms of symptoms and long-term structural preservation of joints and internal organs. However, it entails a risk of overtreatment if medication continues to be escalated after objective signs of inflammation have been abrogated. It has been argued that 'common sense' would preclude practicing rheumatologists from reinforcing immunosuppression in patients in PGA-near-remission, irrespective of what recommendations state.^{11,12,22} The actual practice of clinicians in this respect has never been evaluated in real life. However, if this is considered a wise approach, shouldn't recommendations explicitly define and promote it?

Obviously, undertreatment persists as an important (and probably bigger) problem. Adherence rates to T2T principles have been estimated to range from 41% to 79%,^{23,24} often for very good reasons.²⁵ However, this does not imply that overtreatment is not relevant. We believe that it merits concern, especially if it is being fuelled by treatment recommendations, as argued herein. Our perspective is that, as a community, we should continue to promote adherence to T2T and, at the same time, make efforts to refine the target definition as necessary to avoid undesirable overtreatment risks.

How can this be achieved? Increasing the Boolean threshold of PGA from ≤ 1 to ≤ 2 ¹² will only reduce the rate of PGA-near-remission by about 25%, as up to three-quarters of all patients in near-remission have a PGA score higher than 2 and up to 10.¹⁵ Clinicians would still be devoid of information they might use to understand the causes underlying the persistent impact and try to

reduce it. There are ample reasons to consider the exclusion of PGA from the definitions of remission and low disease activity, especially if they are meant to drive the use of immunosuppressive medication. The supporting evidence is reinforced by many of the results reported by Paulshus Sundlisæter *et al*¹

In conclusion, although undertreatment of RA, due to non-complete adherence to T2T, persists as a serious problem in clinical practice, overtreatment, resulting from (too) strict adherence to T2T, needs to be considered and properly investigated.

Twitter Ricardo J O Ferreira @FerreiraRJO

Contributors RJOF and JAPdS wrote the first draft of the manuscript and all authors have critically reviewed it and agreed with the final version.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Ricardo J O Ferreira <http://orcid.org/0000-0002-2517-0247>

Laure Gossec <http://orcid.org/0000-0002-4528-310X>

Jose Antonio Pereira da Silva <http://orcid.org/0000-0002-2782-6780>

REFERENCES

- Paulshus Sundlisæter N, Sundin U, Aga A-B, *et al*. Inflammation and biologic therapy in patients with rheumatoid arthritis achieving versus not achieving ACR/EULAR Boolean remission in a treat-to-target study. *RMD Open* 2022;8:e002013.
- Haavardsholm EA, Aga A-B, Olsen IC, *et al*. Ultrasound in management of rheumatoid arthritis: Arctic randomised controlled strategy trial. *BMJ* 2016;354:i4205.
- Studenic P, Smolen JS, Aletaha D. Near misses of ACR/EULAR criteria for remission: effects of patient global assessment in Boolean and index-based definitions. *Ann Rheum Dis* 2012;71:1702–5.
- Vermeer M, Kuper HH, van der Bijl AE, *et al*. The provisional ACR/EULAR definition of remission in RA: a comment on the patient global assessment criterion. *Rheumatology* 2012;51:1076–80.
- Felson DT, Smolen JS, Wells G, *et al*. American College of Rheumatology/European League against rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Ann Rheum Dis* 2011;70:404–13.
- Ferreira RJO, Duarte C, Ndosi M, *et al*. Suppressing inflammation in rheumatoid arthritis: does patient global assessment blur the target? A practice-based call for a paradigm change. *Arthritis Care Res* 2018;70:369–78.
- Ferreira RJO, Welsing PMJ, Jacobs JWG, *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* 2021;80:293–303.
- Ferreira RJO, Santos E, Gossec L, *et al*. 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.
- Brites L, Rovisco J, Costa F, *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.
- Nakabo S, Tsuji Y, Inagaki M, *et al*. Severe joint deformity and patient global assessment of disease are associated with discrepancies between sonographic and clinical remission: a cross-sectional study of rheumatoid arthritis patients. *Mod Rheumatol* 2021;31:334–42.
- Boers M. Patient global assessment to define remission in rheumatoid arthritis: quo vadis? *Annals of the Rheumatic Diseases* 2020.
- Studenic P, Felson D, de Wit M, *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.
- Navarro-Compán V, Gherghe AM, Smolen JS, *et al*. Relationship between disease activity indices and their individual components and radiographic progression in RA: a systematic literature review. *Rheumatology* 2015;54:994–1007.
- Weinblatt ME, Keystone EC, Cohen MD, *et al*. Factors associated with radiographic progression in patients with rheumatoid arthritis who were treated with methotrexate. *J Rheumatol* 2011;38:242–6.
- Ferreira RJO, Carvalho PD, Ndosi M, *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* 2019;71:1317–25.
- Mangnus L, van Steenberghe HW, Reijnen M, *et al*. Magnetic resonance Imaging-Detected features of inflammation and erosions in symptom-free persons from the general population. *Arthritis Rheumatol* 2016;68:2593–602.
- Møller-Bisgaard S, Horslev-Petersen K, Ejbjerg B, *et al*. Effect of magnetic resonance imaging vs conventional Treat-to-Target strategies on disease activity remission and radiographic progression in rheumatoid arthritis: the IMAGINE-RA randomized clinical trial. *JAMA* 2019;321:461–72.
- Ranganath VK, Motamedi K, Haavardsholm EA, *et al*. Comprehensive appraisal of magnetic resonance imaging findings in sustained rheumatoid arthritis remission: a substudy. *Arthritis Care Res* 2015;67:929–39.
- Smolen JS, Landewé RBM, Bijlsma JWJ, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
- Pisaniello HL, Whittle SL, Lester S. DAS28-P index as a discriminatory measure of poor subjective response to disease-modifying rheumatic drug therapy in early rheumatoid arthritis. *PRE-PRINT* In press 2022.
- Landewé RBM. Overdiagnosis and overtreatment in rheumatology: a little caution is in order. *Ann Rheum Dis* 2018;77:1394–6.
- van Tuyl LHD, Boers M. Rheumatoid arthritis: Remission - keeping the patient experience front and centre. *Nat Rev Rheumatol* 2017;13:573–4.
- Ramiro S, Landewé RB, van der Heijde D, *et al*. Is treat-to-target really working in rheumatoid arthritis? A longitudinal analysis of a cohort of patients treated in daily practice (RA BIODAM). *Ann Rheum Dis* 2020;79:453–9.
- Wabe N, Wiese MD. Treating rheumatoid arthritis to target: physician and patient adherence issues in contemporary rheumatoid arthritis therapy. *J Eval Clin Pract* 2017;23:486–93.
- Tymms K, Zochling J, Scott J, *et al*. Barriers to optimal disease control for rheumatoid arthritis patients with moderate and high disease activity. *Arthritis Care Res* 2014;66:190–6.
- Ritchie DM, Boyle JA, McInnes JM, *et al*. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q J Med* 1968;37:393–406.