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EDITORIAL

Overtreatment in rheumatoid arthritis: are there reasons for concern?

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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 2 years 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 RA[5] 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-remission[6] (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 trials[7] 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 yars 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 semiquantitative 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 (tempro-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 arthritis[16] and in patients with RA in remission.[17 18] However, the ARCTIC trial[2] 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 trial[2] 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.

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