Dual-target strategy: fostering person-centered care in rheumatology

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Rheumatoid arthritis (RA) is a prototypical condition in rheumatology, often used to test innovative treatments and management concepts. The impressive advances observed over the last decades regarding early diagnosis, biological agents, and treatment strategies, led to equally impressive improvements in outcomes, especially regarding rates of remission and prevention of structural damage. However, somewhat paradoxically, these improvements in clinical outcomes have not always been twined by enhancements in patient-reported outcomes and well-being.

In this editorial, we discuss some of the patient's unmet needs, the inclusion of the patient's perspective in the definition of targets, and a dual-target strategy proposal, aimed at improving person's-centred care and reducing the burden of the disease.

THE TREAT-TO-TARGET STRATEGY - WHAT HAVE WE LEARNED?

The positive results of adopting a T2T strategy in RA are known uncontroversial. Its guiding principles have been cornerstone in the European and American treatment recommendations since 2010 and 2012[1, 2]. Achievements and limitations of T2T, one decade after its proposal were recently reviewed by Prof. Josef Smolen, his most prominent advocate[3]. A critical persisting question refers to how strict one must be in pursuing the treatment target (remission or a low disease activity (LDA) state)? Prudence is generally recommended and the clinician is advised to take into consideration a number of circumstances, including patient factors, such as comorbidities[3].

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This highlights the crucial importance of the definition of remission and LDA. The provisional definitions proposed conjointly by the ACR and EULAR recommend the use of either a Boolean-based definition or a composite index[4]. Although these definitions were primarily designed for clinical trials, their use in clinical practice was already predicted by the authors and they were implicitly adopted in treatment recommendations.

THE DISCORDANCE BETWEEN PATIENT'S AND PHYSICIAN'S GLOBAL ASSESSMENT

The patient global assessment of disease activity (PGA) is the single patient-reported outcome measure (PROM) included in all definitions of remission. The physician global assessment (PhGA) is included only in SDAI and CDAI.

In the current issue of the ARP, Brites *et al.*[5] assessed the PGA-PhGA discordance (i.e. difference > |20mm|) and its determinants, using data from a Portuguese sample of 467 patients (69% in remission or LDA). In six of every ten cases (62%) there was discordance, and in 95% of these instances, patients scored higher. In multivariate analysis, pain was the most relevant correlate of PGA, while physicians valued mainly the swollen joint counts (SJC28). These results are in line with a previous meta-analysis, which on top of these variables, underlined the contribution of physical function to patients' and laboratory measures to physicians' scores[6].

This interpretation is reinforced by the high prevalence of patients who fail to achieve ACR/EULAR Boolean-based remission solely due to a PGA >1/10, i.e. having SJC28, TJC28, and CRP (in mg/dl) all ≤1. This status, termed PGA-near-remission[7], was observed in 19% of all patients included in clinical cohorts[8] and randomised trials[9], compared to 12% and 23% of patients achieving "full" remission, respectively. The PGA-near-remission rate in clinical cohorts indicates that as many as 61% of all patients otherwise in remission

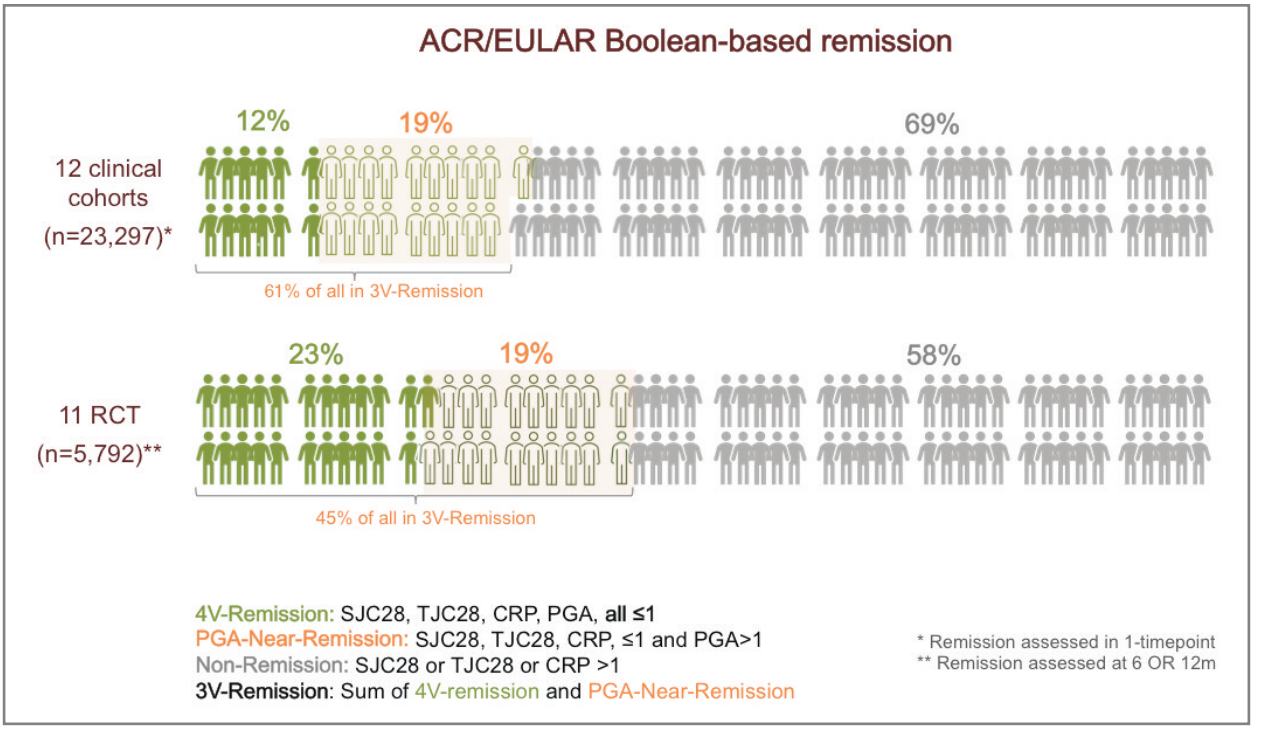

FIGURE 1. Meta-analyses of the proportion of patients with RA failing ACR/EULAR Boolean-based remission solely due to Patient Global Assessment of disease activity (PGA) in clinical cohorts and randomised controlled trials.

(SJC28, TJC28, and CRP ≤1 – termed 3Variable-Remission) still report significant impact of the disease. (Figure 1)

IS PGA, TRULY, A MEASURE OF DISEASE ACTIVITY?

Which are the reasons for these mismatched evaluations? Although concurrent fibromyalgia and health illiteracy are frequent contributing factors[7, 10], the evidence revised above suggest that PGA is more a measure of symptom severity and disease impact than a true reflection of disease activity. It is essentially driven by pain (whatever its origin), physical function, fatigue, sleep, and psychological issues[11]. This becomes more and more decisive as disease activity improves into lower levels of inflammation, where the tough decisions on treatment take place. This explains the ability of PGA to differentiate active treatment from placebo, in clinical trials, the main reason for its inclusion in the Boolean definition of remission[4]. It also explains observations that improvements in PROMs are less pronounced than improvements in the other remission criteria, both at short[12] and long-term[13].

The limitations of PGA are also underlined by observations that many patients are unaware of its purpose and have considerable difficulties in completing it reliably (e.g. scoring high when aiming low)[10, 14].

THE IMPLICATIONS OF THE PGA IN THE DEFINITIONS OF REMISSION IN RA

Patients in PGA-near-remission cannot be expected to improve by additional immunosuppressive therapy, as suggested by a strict reading of the T2T and current treatment recommendations. These patients actually face an unjustifiable risk of overtreatment. They rather require the introduction of adjunctive interventions targeting the uncontrolled domains of disease impact, whatever they are.

It has been argued that PGA represents, in these patients, persistent subclinical inflammation justifying additional treatment.

To test this hypothesis we performed a meta-analysis of individual patient data from 11 RCTs (n>5,700) and found that 3V-remission (the Boolean definition without PGA) is more reliable than the original 4V-remission as a predictor of good radiographic outcome[9]. We have also demonstrated that there is no difference in sub-clinical inflammation between patients in 4V-re-

mission and PGA-near-remission, as assessed by extensive ultrasound examination[15].

In the face of the above mentioned, we questioned the scientific community whether the PGA reflects disease activity closely enough to justify its inclusion in definitions of target used to guide immunosuppressive therapy[7, 16].

Surely, the risk of overtreatment may be averted if the individual clinician analyzes the individual patient's circumstances and declines to increase therapy in patients in PGA-near-remission. Certainly, a wise and committed clinician would also try to understand the reasons behind the high PGA and provide useful advice. Shouldn't this clinical wisdom be incorporated in treatment recommendations?

THE PATIENT'S REPRESENTATION IN CURRENT TARGETS

The patient's perspective in guiding targets is obviously ethically imperative and valuable. This was also in the mind of the ACR/EULAR committee[4].

However, we demonstrated that this is a very poor and limited representation of the patient experience with the disease. PGA is unhelpful to select adjuvant interventions. By using the seven impact domains of the "rheumatoid arthritis impact of disease" (RAID) score, we have demonstrated that all drive a high PGA, although requiring very different interventions[11].

Including the PGA in the guiding target may have a detrimental effect on the physician's attention to the wider spectrum and particularities of patient's experience because patient's perspective is already included in the summative number. Good clinical practice certainly demands the consideration of other PROMs. Shouldn't also this clinical wisdom be incorporated in the definitions of treatment targets?

THE DUAL-TARGET PROPOSAL

Trying to bring together the observations revised and solve the problem outline above we proposed the consideration of a new paradigm: the dual-target strategy[7,16]. In practice, clinicians would simultaneously pursue two targets: one focused on the disease process (the biological target) and the other focused on symptoms and impact (the impact target). The clinician would primarily focus on the biological target in active disease and progressively increase the attention to impact, especially as LDA or remission are achieved or approached.

The "dual" underlines that we do not "simply" propose to disregard the patient's perspective by dropping PGA from the biological target. We, instead, advocate that the patients' experience is brought to a more central place in the clinician's guiding targets and have a better opportunity to become genuinely engaged in shared treatment decisions.

This call for a paradigm change has been somewhat recognised. Some authors actually went even further and questioned if "is it time to banish composite measures for remission in RA?"[17]. Naturally, others have been reluctant in removing the PGA from current definitions[18, 19], despite recognizing PGA's limitations[20]. May we risk to forget the patient's perspective with the 3V-remission definition?

We may not have correctly conveyed the message, namely regarding the second target's nature and fundamental role. This requires adequate and lengthy research as well as careful discussion among different stakeholders. Clear is, as documented, that PGA is not suitable for that purpose because it is useless to guide interventions. We have been working on the suitability of the individual domains of the RAID[11, 21] and found them to be promising, but other instruments may also be applicable or preferable.

Moving beyond the PGA and genuinely assessing and addressing other domains of impact, such as fatigue or psychological distress, will require an enlarged "rheumatology team", endowed with the necessary knowledge, motivation and team spirits to enable effective interventions upon those domains[22]. This strategy will certainly prompt better functional outcomes (among others) and satisfaction, despite the absence of PGA, while significantly diminishing the risk of overtreatment.

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