

**COMMENT:****The dual target strategy: a proposal to mitigate the risk of overtreatment and enhance patient satisfaction in rheumatoid arthritis**

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With great interest we read the viewpoint from Prof. Landewé,<sup>1</sup> calling for more caution, research, and debate regarding the risks of overdiagnosis and overtreatment in rheumatology. Strongly agreeing with the overall message, especially that "(...) overtreatment is hardly discussed but likely present", we would like to contribute to this discussion by raising an issue that touches base on two paradigms listed by Prof. Landewé: remission and evidence-based rheumatology.

There is now ample evidence that a substantial proportion (12 to 38%) of patients with rheumatoid arthritis (RA) does not achieve the status of remission according to disease activity indices, solely because of a patient global assessment (PGA) score >1 (0 to 10 scale, 10=worst).<sup>2 3</sup> If the elevated score on PGA does not reflect disease activity, additional immunosuppressive agents cannot improve the status of these patients, as inflammation is already essentially abrogated. Elevated PGA, therefore, may induce the risk of overtreatment when applying disease indices or Boolean-based criteria to define the treatment aim, which is remission or at least at low disease activity (LDA) according to current treatment recommendations.<sup>4 5</sup> Naturally, patients who still report relevant disease symptoms despite the absence of significant inflammation need to be appropriately assessed and supported to address disease impact, but this probably calls for adjuvant interventions, rather than reinforcement of immunosuppressive therapy.<sup>6 7</sup>

This has led to our recent proposal that the management of RA should be guided by a dual treat-to-target strategy (dual T2T): one representing the control of inflammation (biological remission) and the other the control of disease impact (symptom remission).<sup>8</sup> Remission of inflammation often also results in symptom remission, but not always.<sup>2 8</sup>

Given that the relationship between PGA and disease activity is not consistent, especially around the cut-offs of disease activity indices for LDA and remission,<sup>8</sup> it is proposed that the definition of biological remission should not include PGA, but that it should be defined by the number of swollen and tender joints and CRP, i.e. 3-variable remission. This proposition is further supported by the evidence that, overall, PGA is driven by multiple factors beyond inflammation<sup>9 10</sup>, including non-inflammatory pain, limitation in physical function, fatigue, depression, and comorbidities,<sup>2 8</sup> as well as by socio-economic and cultural factors.<sup>11</sup> Recent research has demonstrated that patients vary enormously in their interpretation of the question and as many as 40% of them find scoring of PGA confusing.<sup>12 13</sup> This is accrued by the existence of several different formulations of PGA, which, in itself, may influence the remission rate in 4.7 to 6.3%<sup>14</sup>.

Symptom remission, an important outcome from patient's perspective,<sup>15 16</sup> would, in this proposal, be served better by an instrument capable of measuring and discriminating the underlying causes of on-going disease impact, so as to guide the selection of appropriate interventions. Currently, the best-suited instrument for this purpose seems to be the Rheumatoid Arthritis Impact of Disease score (RAID)<sup>17 18</sup> with its seven domains, individually considered adequate to guide treatment decisions.<sup>18</sup> Whatever the instrument chosen, treatment decisions must always be based on two-way communication and shared decision-making between the patient and the caring team.<sup>19</sup>

We believe that this novel strategy, i.e. dual T2T and the use of 3-variable remission and RAID, would significantly reduce the risk of overtreatment. Step-up of treatment strategies according to recommendations would still be used until biological remission is achieved. If, at this stage, symptom remission is not achieved, adjuvant therapy may be considered, according to the most affected domains of impact according to RAID. Actually, these domains of impact should be considered from the beginning, not only because patient well-being is a core objective of treatment but also because some of them, e.g. depression, may actually diminish the probability of achieving the biological target.<sup>20</sup>

It has been argued that "the remission criteria are designed for research and for optimum specificity, and not for use in treat-to-target schemes",<sup>21</sup> but this does not preclude their frequent use in clinical settings. It has also been put forward that "most rheumatologists in practice do not need new instruments to decide which patients are most likely have residual disease and are in need of switching their treatment as opposed to patients with comorbidities that confound the interpretation of their RA symptoms".<sup>22</sup> Prof. Landewé argues, conversely, that "sometimes (...) guidelines are too rigidly pursued by clinicians who may ignore the needs of individual patients".<sup>1</sup> In fact, the EULAR recommendations for the management of RA state that treatment must be based on a shared decision with patients and that decisions on immunosuppressive treatment should take structural damage, comorbidities or contraindications into account.<sup>4</sup> The risk of overtreatment would be further diminished if recommendations specifically address major aspects that may "confound" the practicing rheumatologist.

We believe that the proposal presented herein represents an important step forward in this direction. It also highlights the need to keep the patients' perspective and needs at the bull's eye of the treatment target, underlining the importance of an holistic approach to patient assessment and treatment, in order to achieve optimal results.<sup>19</sup> In clinical trials,

the improved relationship between the 3-variable disease index/remission criteria and disease activity would result in a more accurate determination of the actual efficacy and value of disease-modifying medications.

Additional evidence is needed to fully support this paradigm shift, namely by investigating whether exclusion of PGA negatively affects the relationship between remission and structural damage progression – the crunch of the matter, after all. Work is underway.<sup>23</sup>

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