Correspondence on: 'EULAR definition of difficult-to-treat rheumatoid arthritis'

We read with great interest the publication entitled 'EULAR definition of difficult-to-treat rheumatoid arthritis', which sought not only to provide a uniform terminology, but also to formulate an adequate definition to classify those patients with difficult-to-treat rheumatoid arthritis (RA).[1] Resolution of this issue promises to be very useful in clinical practice and in the design of studies for future research.

Our group has recently published a study based on the clinical factors that could serve as possible predictors for identifying those patients with RA who are more susceptible to multiple failures to biological therapy.[2] This study was designed and conducted prior to the publication of this paper establishing the definition of difficult-to-treat RA. Based on previous works published on this concept,[3–8] we defined 'multi-refractory' patients as those who have received ≥2 biologic disease-modifying antirheumatic drugs (bDMARDs) with different mechanism of action or ≥3 bDMARDs with the same target. This definition seemed to us the most appropriate option for the classification of difficult-to-treat patients in terms of drug use.

As the European League Against Rheumatism (EULAR) group of experts did, we did not include in our definition of multi-refractory RA the number of previous conventional DMARDs (cDMARDs), although it is worth mentioning that 39 of the 41 (95%) multirefractory patients in our cohort were treated with ≥2 cDMARDs before starting biological therapy. Finally, we decided not to include this in our definition since failure to a first cDMARD does not always lead to the use of a second cDMARD, but rather is associated with bDMARDs, especially if poor prognostic factors are present. In any case, it seems quite logical that patients who failed several cDMARDs are at higher risk of failing several bDMARDs. In general, we observed that 96% of our patients met the suggested criteria of difficult-to-treat RA as proposed by the EULAR group of experts.

Regarding the second point in the EULAR definition of difficult-to treat RA, characterisation of active/progressive disease was defined if the patient presented persistent clinical activity (moderate disease activity by Disease Activity Score 28-Erythrocyte Sedimentation Rate (DAS28-ESR) or Clinical Disease Activity Index (CDAI)), signs or symptoms of active disease, inability to taper glucocorticoid treatment, rapid radiographic progression or a reduction in quality of life. Our cohort included patients who had discontinued bDMARD treatment due to primary or secondary inefficacy based on the DAS28-ESR.

Additionally, the most novel finding arising from our study concerns the baseline/early features that can be used to identify risk factors for multiple failures to biological therapy. In our work, we found that being younger when starting bDMARD therapy, the presence of erosions, baseline DAS28-ESR and delta-DAS28-ESR <1.2 (6 months after starting the first bDMARD) were all associated with multirefractoriness. Early detection of these factors is key to identifying difficult-to-treat patients with RA. This is particularly true in terms of the beginning of bDMARD therapy and in aiding clinicians in better determining which patients' disease activity warrants closer surveillance.

The third point, which is closely related to the complexity of the patient's perception, is very important since too often we only focus on objective parameters and tend to be more permissive when the patient's subjective perception is taken into account. The chronicity of RA, the structural and residual affectation that leads to chronic pain or functional limitation, fibromyalgia and depression associated with RA also constitute a group of conditioning factors that complicate treatment strategies.[9–11] Indeed, it does seem necessary to weigh all of these factors when deciding on the appropriate treatment, which may not necessarily be pharmacologically based. At this point in our study we did not consider individual clinical perception as a main outcome; rather, we essentially focused on refractoriness and the challenges of treating patients from a pharmacological standpoint. However, we observed that the mean global patient assessment at baseline was higher in multirefractory patients than in those who were non-refractory (53.2±22.1 vs 29.5±19.0, p<0.001). Moreover, the Health Assessment Questionnaire at baseline was also higher in those patients who experienced inefficacy to multiple biologics (1.5±0.7 vs 1.0±0.5, p=0.003).

Finally, thanks to the advances this field is undergoing, and the increasingly successful management of difficult-to-treat RA now being carried out, rheumatologists will be better able to assess this group of patients. A consensus-based definition will enable us to evaluate patients homogeneously. In addition, with further strides in research we will be able to conduct comparability studies between different cohorts, thus leading to common preventative and treatment strategies for situations that have long been so frustrating for both patients and clinicians.

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