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COMMENTARY

Difficult to Treat and Refractory to Treatment in Psoriatic Arthritis

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ABSTRACT

Psoriatic arthritis (PsA) is a complex and chronic inflammatory condition in which the achievement of the best possible disease control has been proposed as the treatment target, which includes the possibility of reaching remission in all disease domains. However, due to the complexity of this multidomain disease, some patients may still have high disease activity in one or more domain and a high burden of disease, potentially leading to various treatment changes and to difficulty with the overall management. In this paper, we overview the concept of patients with difficult-to-treat PsA and the concept of patients with refractory-to-treatment PsA by providing a distinction between these two concepts and the possible implication for the management of patients with PsA.

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INTRODUCTION

Psoriatic arthritis (PsA) is a complex and chronic inflammatory condition with the involvement of different domains and associations with related diseases such as inflammatory bowel diseases, uveitis, and different comorbidities [1]. The achievement of the best possible disease control has been proposed as the treatment target, which includes the possibility of reaching remission or at least low disease activity in all disease domains [2]. These clinical targets usually range between 40 and 70% of patients with PsA, both in clinical trials and in the routine clinical practice context, given the current pharmacological treatments [3, 4]. However, due to the complexity of this multidomain disease, and despite significant improvements in the treatment of PsA, some patients may still present residual disease activity or high disease activity and burden of disease, potentially leading to various treatment changes [5, 6]. Of note, about 30% of patients with PsA in observational studies did not achieve the target endorsed by the treat-to-target recommendation [4], and, in long-extension follow-up clinical trials, the rate of patients treated with first-line biologic or targeted synthetic DMARDs who did not achieve minimal disease activity

ranged from 30 to 40% [4]. This rate is even higher if we consider patients resistant to first-line biologic drugs who were enrolled in second or even further lines of treatment [7, 8]. Furthermore, a discrepancy between patients and physicians in their perspectives on PsA treatment priorities has been found, confirming that objective clinical disease control is not always perceived as such by patients [9, 10].

Finally, PsA is a multidomain disease in which, even after controlling the disease activity in one domain, some others could still be "active," leading to a change in treatment strategy.

Moreover, related diseases (uveitis and inflammatory bowel disease) and comorbidities may have an important impact on disease burden and disease activity and should be taken into account in the evaluation of PsA [11–13]. This, in turn, can lead to more difficult management of these patients.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

DIFFICULT TO TREAT AND REFRACTORY TO TREATMENT: ANY DIFFERENCES?

Overall, the clinical scenario in which patients with PsA fail to achieve a condition of good disease control after multiple treatments could be in keeping with the concept of "difficult-to-treat" (D2T) PsA. This concept was originally developed for rheumatoid arthritis (RA), which encompasses the presence of persistence of symptoms and/or signs despite the failure of at least two biological or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) (after failing csDMARD treatment) with different mechanisms of action as well as the management of signs and/or symptoms perceived as problematic by the rheumatologist and/or the patient (see Table 1 for the full definition) [14].

However, the definition provided for a patient with RA needs to be further validated, discussed, and applied to PsA; some conceptual concerns will be raised due to the differences in terms of clinical phenotype and disease progression. These concerns have recently been raised in relation to axial spondyloarthritis [15]. First, given the multidomain nature of PsA and the various definitions used, axial involvement may be present in 5–70% of patients [16], and the use of csDMARDs is not recommended in these patients [16]. This, in turn, could be one of the main limitations of "importing" the D2T proposal for RA.

There are also limitations regarding the role of imaging: ultrasound or magnetic resonance imaging are still not routinely used to assess inflammation in therapeutic decision-making [17, 18]; the presence of inflammatory signals can even be found in patients in clinical remission, so this may not be, in itself, a reason for treatment escalation [19].

Furthermore, an inability to taper steroids and rapid radiographic progression does not seem to be generally applicable in the context of PsA, since the use of systemic steroids is not generally recommended, and the features of bone damage in PsA are quite different to those in a "pure" erosive disease such as RA [16, 20].

Of note, in clinical practice, the concept of D2T may assume a "dynamic" nature rather than a "static" one. Some patients may fulfill the definition and remain in this state for the whole duration of follow-up, while others may have fluctuations. In fact, with the availability of new and different treatment strategies, changes in disease status corresponding to a good response may be observed when other treatment lines are chosen [21].

Furthermore, in our recent work, we aimed to adapt the D2T criteria to use with our group of patients and to evaluate the possible associated factors. Even with the limitations discussed above, we found that patients with D2T are those with a high number of comorbidities, obesity, the presence of fibromyalgia and a long time from diagnosis to first bDMARDs, suggesting that attention should be paid to these factors in the management of patients [22].

In this context, when examining the potential applicability of the definition of D2T to PsA, it is clear enough that this concept is not

Table 1 EULAR definition of D2T rheumatoid arthritis [16]

1. Treatment according to European Alliance of Associations for Rheumatology (EULAR) recommendation and failure of ≥ 2 b/tsDMARDs (with different mechanisms of action) after failing csDMARD therapy (unless contraindicated)
2. Signs suggestive of active/progressive disease, defined as ≥ 1 of:
a. At least moderate disease activity (according to validated composite measures including joint counts, for example, DAS28-ESR > 3.2 or CDAI > 10)
b. Signs (including acute phase reactants and imaging) and/or symptoms suggestive of active disease (joint related or other)
c. Inability to taper glucocorticoid treatment (below 7.5 mg/ day prednisone or equivalent)
d. Rapid radiographic progression (with or without signs of active disease)
e. Well-controlled disease according to above standards, but still having RA symptoms that are causing a reduction in quality of life
3. The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient
All three criteria need to be present in D2T RA

EULAR European Alliance of Associations for Rheumatology, *D2T* difficult to treat, *DMARDs* disease-modifying anti-rheumatic drugs, *DAS* Disease Activity Index, *ESR* erythrosedimentation rate, *CDAI* Clinical Disease Activity Index, *RA* rheumatoid arthritis

synonymous with severe or refractory disease in a completely interchangeable way.

In fact, our current treatment strategies are mainly designed to interfere with cytokines or intracellular pathways leading to inflammation, with the aim being to suppress inflammatory changes in the synovial joints, skin, entheses, and other tissue (gut, uvea). The assessment of a PsA patient refractory to a single and/or multiple DMARDs should necessarily involve an evaluation of the presence of persistent (proven) inflammation.

However, discordance between the clinically measured disease activity and "deep" remission, including that indicated by imaging or tissue analysis, may be present. In fact, while clinical tools such as the Disease Activity Score for Psoriatic Arthritis (DAPSA) or the Minimal Disease Activity are well-established, validated surrogate measures of disease activity and disease state and are employed for assessing the response to treatment, limitations of these tools are well recognized because they may be driven by subjective components [14, 23, 24]. This was emphasized for RA but it appears to be equally true for PsA, as the clinical manifestations of the disease are difficult to encompass in a single measure, leading to an evident discrepancy in the rate of patients achieving a specific target [25]. Furthermore, secondary damage due to osteoarthritis associated with chronic pain conditions and comorbidities can contaminate the measurement of disease activity and thus could reasonably yield apparent "refractory" drug profiles [11].

In this context, Maya Buch proposed some definitions of refractory disease by categorizing the multifactorial basis of patients with refractory RA. Intrinsic refractory disease with persistent inflammation may be due to an incorrect drug target (with the disease mainly driven by other cytokines) or different pathophysiological features, while pharmacokinetic refractory disease is caused by the development of auto-antibodies (when bDMARDs are used). On the other hand, persistent refractory disease in the absence of tissue inflammation (false refractory disease) may be due to other factors such as pain sensitization or mechanical joint damage [26].

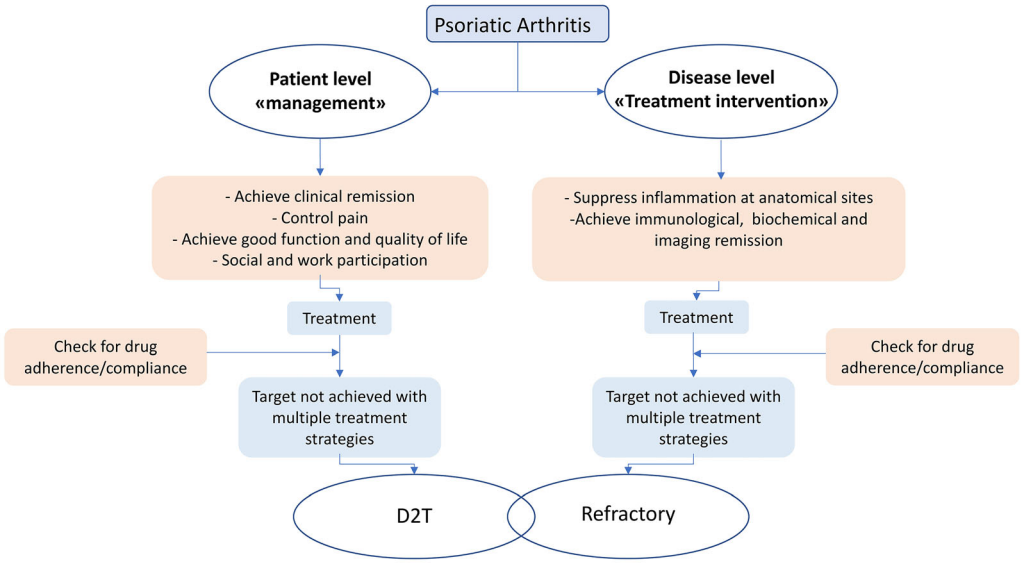

Fig. 1 The D2T and refractory-to-treatment concepts applied in PsA: a proposed clinical algorithm for the definition of patients in clinical practice. *D2T* difficult-to-treat, *PsA* psoriatic arthritis

The same author reported that refractory RA could be stratified into two major categories; persistent inflammatory refractory RA (PIRRA), in which unabated inflammation is evident, and non-inflammatory refractory RA (NIRRA), which lacks discernible inflammation [24].

Within the category of PIRRA, serological status and HLA associations can provide meaningful stratification that can inform potential therapeutic avenues, while NIRRA is typically mediated by ongoing pain and patient-reported outcomes; pain mechanisms might include autoimmune and neuroinflammatory pathways that are independent of joint synovitis [24].

The term "refractory RA" implies treatment-resistant persistent joint and/or systemic inflammation; however, it is often used interchangeably with broader definitions such as "D2T" RA.

In PsA, inflammatory activity may persist in one or more disease domains due to multidrug resistance, clinical and immunologic mechanisms (including anti-drug antibodies), or other factors such as non-adherence. On the other hand, factors such as comorbidity and, in particular, fibromyalgia, degenerative joint disease, anxiety, and depression may play a role, making the patient resistant to multiple treatment strategies. Finally, any uncertainty that patients might have about their condition and treatment may have a role as an apparent reason for treatment failure [27].

D2T may be intended as an umbrella term to describe patients with PsA in which the presence of pre-existing clinical conditions (such as comorbidities, fibromyalgia, and other) may lead to a reduced treatment response with difficult management of the patient's symptoms [22, 28]. On the other hand, patients with refractory PsA may be defined as those in which persistent tissue inflammation despite multiple therapies can be demonstrated, beside other factors.

Obviously, these two definitions are not interchangeable, but they may be complementary because a patient with PsA may satisfy both.

In this view, the terms "D2T" or "refractory" may be applied in the management of PsA if we look at a "patient-centred" (which may encompass the difficulties in the management of patients) or "disease-centred" approach (see Fig. 1).

USEFULNESS OF DISTINGUISHING BETWEEN D2T AND REFRACTORY

Why should it be useful to distinguish between these two definitions? PsA is a very complex and

multifaceted disease in which the assessment of disease activity with clinical, serological, and imaging tools in each domain is not always feasible or simple [1].

Distinguishing between patients with D2T, in which the presence of associated factors such as comorbidities or fibromyalgia may have an impact on the probability of responding to treatment, and a true refractory disease in which, despite the implementation of different treatment strategies, tissue inflammation is still present, gives us the possibility to focus our management on different clinical aspects or treatment targets or even safety issues.

Obviously, a shared and validated definition of D2T and refractory disease in PsA should be defined, and further studies are needed on this intriguing topic.

CONCLUSIONS

In conclusion, the assessment and management of patients with PsA who are not achieving treatment targets after multiple treatment strategies are complex and include the evaluation of the potential concepts of D2T PsA and true refractory PsA. Unfortunately, there is a lack of data and strong evidence that may support a distinction between these definitions of the two concepts. However, the implication for PsA management of the introduction of a definition for RA may be of great interest to the scientific community. The further validation and application of those concepts in clinical trials or the clinical context may help the physician to better understand the disease phenotype and course, which may allow better management of patients with PsA. In this context, more personalized treatment strategies which may include a non-pharmacological [29] approach could be implemented in patients with D2T.

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