Recommendations

EULAR points to consider and consensus definitions for difficult-to-manage and treatment-refractory psoriatic arthritis

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ARTICLE INFO

ABSTRACT

Objectives: This study aimed to develop evidence-based points to consider (PtC) and consensus definitions of difficult-to-manage (D2M) and treatment-refractory (TR) psoriatic arthritis (PsA).

Methods: A multidisciplinary international European Alliance of Associations for Rheumatology (EULAR) task force (TF) of 27 members, including rheumatologists, dermatologists, health practitioners, and patient partners, was established, and the EULAR standardised operating procedures, including a systematic literature review and a consensus process, were followed.

Results: The TF formulated 4 overarching principles addressing the proportion of patients with PsA with an unsatisfactory treatment response despite the best standard of care, and for which the causes are likely multifactorial. Six PtC highlight criterion relevant for subsequent definitions including failure to achieve or maintain response to ≥2 biological/targeted synthetic disease-modifying antirheumatic drugs with ≥2 different mechanisms of action; management of signs and symptoms perceived as problematic by the rheumatologist and/or the patient, and evidence of persistent disease activity in the presence of extramusculoskeletal manifestations and/or comorbidities and/or objective evidence of inflammatory activity. Finally, the following 2 definitions were developed: (1) D2M PsA, an umbrella term including drivers such as inflammation, comorbidities, psychosocial or other factors, incorporating (2) TR PsA, defined by persistent disease activity and objective evidence of active inflammation.

Conclusions: EULAR proposes 2 consensus definitions to identify a D2M PsA population, including a TR subgroup. These definitions should now be tested in research studies to understand disease pathogenesis and improve care for people living with PsA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Many people living with psoriatic arthritis (PsA) experience an unsatisfactory treatment response despite the best standard of care (according to European Alliance of Associations for Rheumatology management recommendations) and the availability of multiple efficacious treatment options.
- These clinical scenarios resemble those described in difficult-to-treat (D2T) rheumatoid arthritis and axial spondyloarthritis, where definitions of difficult-to-manage (D2M) and treatment-refractory (TR) have recently been published.
- To date, there are no standardised definitions of D2M and TR PsA.

WHAT THIS STUDY ADDS

- This study provides data-driven points to consider and expert consensus developed definitions of D2M and TR PsA, which incorporate failure to achieve or maintain a response to ≥2 biological/targeted synthetic disease modifying antirheumatic drugs with ≥2 different mechanisms of action, the perception of signs and/or symptoms as problematic by the rheumatologist and/or the patient, and evidence of persistent disease as key elements.

- D2M PsA refers to a wider concept including drivers of persistent signs and symptoms of disease such as inflammation, comorbidities, and psychosocial or other factors.
- TR PsA refers to the subset where persistent disease activity is defined by the objective evidence of active inflammation in the absence of other drivers.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- These definitions of D2M and TR PsA provide a framework to facilitate research in this area, aiming to characterise these populations, test interventions, and guide further research to understand disease pathogenesis and improve the care of people living with PsA.

INTRODUCTION

The treatment of psoriatic arthritis (PsA), a progressive inflammatory disease, is unsatisfactory for many affected individuals, and a cure remains elusive. The multimorbid nature of

PsA, where 90% of patients may have concomitant skin psoriasis (PsO), may ultimately impact treatment choices [1]. Further, the high prevalence of cardiometabolic, mental health morbidities, or the coexistence of other inflammatory and noninflammatory conditions such as gout, osteoarthritis, or fibromyalgia [1] may contribute to management challenges. The recent expansion in the number of disease-modifying antirheumatic drugs (DMARDs) available for PsA and PsO with multiple mechanisms of action (MoA), reflects the advances in the understanding of disease pathogenesis, with management recommendations advocating remission or low disease activity (LDA) as the desirable treatment target for those living with PsA [2]. Yet, current evidence suggests a variable proportion of patients achieving minimal disease activity (MDA) [3], LDA (36%-60%), or remission (13%-42%) depending on the outcome measure used [4]. A common clinical scenario is 'partial' control of symptoms, with dissociation of response between joints and skin, or within the heterogeneous musculoskeletal manifestations of PsA, leading to challenging clinical scenarios of difficult-to-treat (D2T) disease. Real-world data suggest that nearly half of those receiving biological (b) DMARDs will experience at least 1 switch to a different MOA [5], with drug survival and persistence on bDMARDS usually higher for first-line antitumour necrosis factor α (TNFα) agents, but shorter with second-line therapies [6,7] with lower remission rates [8].

Similar challenges in rheumatoid arthritis (RA) led the European Alliance of Associations for Rheumatology (EULAR) to develop definitions and points to consider (PtC) for the management of D2T RA [9,10]. However, these definitions cannot just be extrapolated into PsA, a disease with different aetiopathogenic drivers from RA, less frequently increased inflammation markers, and a multiplicity of tissue targets [11]. At the bedside, a key challenge for patients and clinicians is the need to understand the factors behind treatment nonresponse in those who experience persistent symptoms of ongoing disease activity with objective signs of inflammation despite multiple therapies. In addition, factors beyond drug nonresponse, such as concomitant morbidities together with abnormal pain responses and central sensitisation, contribute to difficulties in the management of PsA.

Data from 2 recent international surveys of rheumatology experts [12,13] and a scoping review by the Group for Research and Assessment of Psoriasis and Psoriatic arthritis (GRAPPA) group [14] suggested that there are a wide range of views on the scope, definition, and concept of what constitutes D2T PsA, highlighting the complexity and nonuniformity of terminology to date and the need for a consensus definition to facilitate research in this area. Recently, consensus definitions were published addressing clinical scenarios of difficult-to-manage (D2M) and treatment-refractory (TR) disease in axial spondyloarthritis (axSpA) [15], a condition more akin and genetically related to PsA.

To address these unmet needs, a EULAR task force (TF) was convened to develop evidence-based PtCs and consensus definitions of D2M and TR PsA with the ultimate intention of improving disease management in these patients.

METHODS

Steering committee and TF

This project was conducted according to the EULAR standardised operating procedures (SOPs) for developing recommendations and PtCs [16]. After approval from the EULAR Council, the Convenor (HM-O) and co-convenor (SS) formed the steering committee (SC), which also included a senior methodologist (PMM), a comethodologist (AS), 1 predoctoral (SRH) and 1 postdoctoral (GH) fellow, and 2 emerging EULAR Network (EMEUNET) representatives (XM and CM), who contributed to the SC and supported the fellows with the literature review and data analysis. The TF comprised a total of 27 members which, aside from the SC, included 14 rheumatologists, 2 dermatologists, 2 patient research partners from people with arthritis/rheumatism, and 1 health psychologist from 15 countries in Europe, Canada, and South America, with equal gender representation (Fig 1). Nonpatient members had significant expertise in the clinical management and research of psoriatic disease including clinical trials, patient registries, imaging, basic science, and genetics. Five of these and the 2 EMEUNET fellows were recruited via a competitive application process following an open call to EULAR countries.

Target audience

The primary target users of these PtCs and definitions are clinicians and health professionals (HPRs) and researchers in

EULAR QoC019 Task Force Composition
Points to consider for the definitions of Difficult-to-Manage and Treatment-Refractory PsA

eular
fighting rheumatic & musculoskeletal diseases together

- 27 members
- 16 Countries (map)
- 2 Methodologists
- 1 Librarian
- 4 Fellows (2 EMEUNET)

- 22 Rheumatologists
- 2 Dermatologists
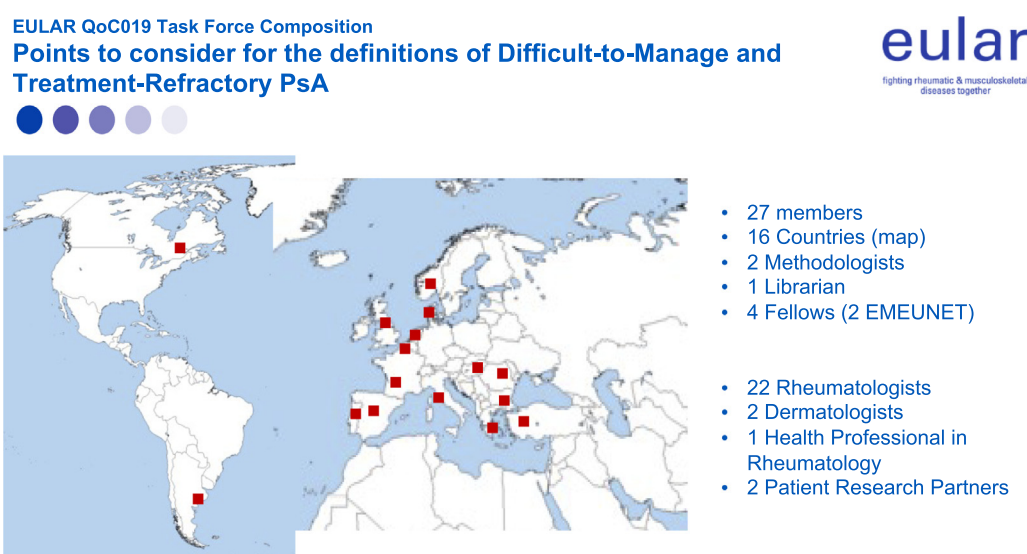- 1 Health Professional in Rheumatology
- 2 Patient Research Partners

Figure 1. Schematic representation of QoC019 task force membership.

rheumatology [16]. Because a research agenda has also been formulated to highlight unmet needs in D2M and TR PsA, these PtCs and definitions are expected to have a significant impact in research underpinning the frame for future studies/trials. As such, they will be of interest to policy makers, scientists, pharmaceutical and health insurance companies, and others, as well as to people living with PsA and their carers, in the context of shared and informed decision making.

TF meetings and project methodology

A total of 3 TF meetings were needed to finalise the project. The first meeting took place online on 18 January 2024, where the TF members discussed the background of the project, including the existing evidence, and agreed on the main remit. After discussing the methodological aspects, and despite concerns about potential data scarcity, the TF agreed that a systematic literature review (SLR) [17] should be performed to inform this work. Research questions were discussed and formulated, and later refined by the SC and methodologists, after which the SLR was performed with the help of a librarian.

Consensus finding

The results of the SLR [17] together with a draft of overarching principles (OAPs), PtCs, and possible definitions formulated by the SC were presented to the rest of the TF members during a second, face-to-face meeting on 4 November 2024, in London, UK. A third meeting took place online on 25 November 2024 to allow for further discussions and agreement on nomenclature and final wording of the proposed definitions, as well as implementation and research agenda. A total of 26, 25, and 26 TF members participated in these meetings, respectively.

A voting process (by raised hands) was applied, with a majority of at least 75% being required to accept each OAP, PtC, and definition. If not achieved, further discussions and potential rewording ensued requiring at least more than two third of votes on a second ballot; followed, if needed, by a final round, which required >50% acceptance. If no agreement was reached after the 3rd round, the statement was rejected [16]. The level of evidence (LOE) according to the Oxford Centre for Evidence-Based Medicine system [18] was added to each PtC. In addition, through an online, anonymous vote utilising a Google poll, each member indicated their level of agreement (LOA) with the statement on a numerical rating scale ranging from 0 to 10 (0 = completely disagree to 10 = completely agree). The mean and SD of the LoA, together with the percentage of members with an agreement of ≥8, are presented.

Proposed nomenclature and definitions

There was considerable debate from the first meeting regarding nomenclature. The group acknowledged that the terminology referring to 'difficult to treat' initially chosen for this project was historic and inherited from RA, and that PsA was a different pathological entity with its own idiosyncrasies [11]. The patient representatives in the TF noted that there might be a risk that some patients will feel that it is not the disease that is D2T, but the person themselves, if the terminology 'D2T' is used. However, they also noted that alternative terms (such as complex, challenging, etc.) are no better, also come with potential connotations, and are less well understood whereas the term 'difficult' is widely used, and embedded in the literature. Therefore, the TF agreed that it is important that clinicians and other

HPRs are aware of these perceptions, and clearly explain to their patients that the term 'difficult' is being applied to the disease itself and not to the individual, which should give reassurance and limit anxieties related to the terminology.

Further discussion highlighted that any terminology should not refer specifically to drug therapy, as the word 'treatment' tends to be associated with pharmacological interventions whereas 'management' encompasses the wider multidisciplinary approach, including holistic and nonpharmacologic elements. In this context, the management may be affected by direct and indirect disease-related factors leading to loss of response to therapy, intolerance, and others. Importantly, the TF discussed the need to specifically differentiate within the wider D2M group, the subgroup of patients with true biological nonresponse, as indicated by failure to respond to multiple drugs with different MoA and objective evidence of ongoing inflammation, as shown by physical examination, peripheral blood markers, or imaging. It was agreed that this latter group represents a true D2T population with refractory disease, and to avoid confusion with the established RA terminology, and to minimise concerns around the terms D2T and D2M being used interchangeably, the TF agreed to utilise the terminology of 'treatment refractory (TR)' PsA for this situation. This terminology is aligned with that published in axSpA [15].

At the third and final meeting, once the proposed PtCs had been discussed and agreed (Table 1), the TF voted to change the historic terminology of D2T, initially developed for RA, and agreed unanimously (100%) to develop the following 2 definitions to be used in PsA: (1) D2M PsA, a wider concept which includes drivers such as inflammation, comorbidities, psychosocial or other factors, and (2) TR PsA defined by persistent disease activity and objective evidence of active inflammation (Table 2).

RESULTS

Overall, the TF formulated 4 OAPs that underpin the unmet clinical need addressed and possible contributing factors, and 6 PtCs towards the definitions (Table 1). The PtCs summarise the respective criterion identified in the SLR and are presented in the order in which they were formulated. Each of the OAP and PtC formulated will be discussed independently, explaining the reasoning behind each PtC and supporting evidence.

OAPs

Each OAP was voted in favour by 100% of members.

A. *A proportion of patients with a confirmed diagnosis of PsA have an unsatisfactory treatment response despite current best standard of care.*

This first OAP highlights the motive underpinning the current project by stating an unmet need observed in clinical practice. Therapeutic responses in PsA vary widely depending on the different outcome measures utilised, and are often considered unsatisfactory by the patient and/or their clinician. Data from real-world registries and clinical trials show similar prevalence of MDA at 6-month follow-up 30% (95% CI: 21%-41%, $I^2 = 85\%$) vs 32% (95% CI: 26%-39%, $I^2 = 79\%$, respectively) [3] with 1 observational study reporting 33% MDA at baseline in those who discontinued their first TNFi and 42% in those who continued [19]. In the ReFlap (remission/flare in PsA) multicentre study [20] of 410 patients, 56.8% of whom were on

Table 1

Overarching principles and points to consider for the definitions of difficult-to-manage and treatment-refractory PsA

	Overarching principles	LoE	LoA (SD)*	% LoA ≥ 8
A	A proportion of patients with a confirmed diagnosis of psoriatic arthritis have an unsatisfactory treatment response despite the current best standard of care.	NA	9.8 (0.51)	100
B	Unsatisfactory treatment response despite the best standard of care has significant impact on patients' health status, including well-being and societal functioning.	NA	9.8 (0.49)	100
C	Unsatisfactory treatment response may be multifactorial, including ongoing inflammation, joint damage, extramusculoskeletal manifestations, comorbidities, and psychosocial factors.	NA	9.4 (1.68)	92
D	Establishing the reasons for ongoing signs and symptoms is essential to optimise further management.	NA	9.7 (0.62)	100
	Points to consider			
1	Failure to achieve or maintain response to ≥2 b/tsDMARDs with ≥2 different mechanisms of action according to the EULAR recommendations for the management of PsA should be used to define D2M and TR PsA.	2	9.5 (0.86)	96
2	Failure to achieve or maintain low disease activity should be used to define D2M and TR PsA.	2	9.1 (1.74)	88
3	The presence of active extramusculoskeletal manifestations should be considered to define D2M and TR PsA.	5	9.8 (0.51)	100
4	Objective evidence of inflammatory activity, namely clinical signs, elevated acute phase reactants and/or imaging findings suggestive of inflammation can be used to define D2M and TR PsA.	3	9.5 (1.14)	96
5	The presence of comorbidities should be considered when interpreting disease activity measurements and when defining D2M and TR PsA.	5	9.7 (0.60)	100
6	The perception of disease management as problematic by the patient and/or physician should be considered when defining D2M and TR PsA.	3	9.1 (2.01)	96

b/tsDMARD, biological/targeted synthetic disease modifying antirheumatic drugs; D2M, difficult to manage; LoA, level of agreement; LoE, level of evidence; NA, not applicable; PsA, psoriatic arthritis; TR, treatment refractory.

* Level of agreement out of 10. Average of 26 responses, 1 response missing.

biologics, LDA was attained by 25.4% (MDA) to 43.9% (patient-perceived LDA), and remission by 12.4% (very LDA [VLDA]) to 36.1% (physician-perceived remission) [20]. A recent report from the Finnish Quality Register showed remission rates on bDMARD to range from 17% (ACR [American College of Rheumatology]/EULAR Boolean definition), 30% for cDAPSA (clinical Disease Activity Index for Psoriatic Arthritis) to 73% (DAS28 [Disease Activity Score]) in patients with PsA, which were similar to RA [21].

Further, drug persistence is variable, with 30% to 40% of patients discontinuing their first biological/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARD) after 1 year [22]. A large European database reported that approximately half of >14 000 patients with PsA who initiated their first TNFi in routine care were in DAS28 remission (22% in Disease Activity in Psoriatic Arthritis score [DAPSA] remission) after 6 months, with three-quarters still on the drug after 1 year, although considerable heterogeneity in baseline characteristics and outcomes across registries was observed [23]. Other real-world studies in Europe and the USA have shown that women with PsA are more likely to discontinue TNFi therapy and have shorter drug survival than men [19,24].

By referring to 'patients with a confirmed diagnosis of PsA', this OAP firmly anchors the need for these OAPs, PtCs, and definitions to be applied solely when there is diagnostic certainty. Indeed, misdiagnosis may be more common in the context of seronegative arthritis, namely PsA or axSpA when compared with RA or other autoimmune conditions where serum biomarkers or antibodies can aid the clinical diagnosis [25,26]. When considering reasons for treatment nonresponse, the clinical diagnosis should always be considered and reassessed.

The word 'proportion' was chosen over 'subset' as the latter implies the possibility of a specific endotype, for which there is a lack of evidence, and it was felt to be a term more accurate than 'number'. Although 'proportion' describes a percentage of the whole cohort of PsA, the true value is yet to be elucidated with estimates currently reported in the literature ranging between 2.9% and 68.4%, reflecting the varied definitions utilised [17].

Current management recommendations in PsA are in line with the principles of treat to target [27], yet the reference to best standard of care was made as this is a broader concept, and it is acknowledged that, as opposed to RA, no single target or specific outcome measure is used universally in PsA, reflecting the complex and multifaceted nature of PsA. This is similar to OAP B of the latest update of the EULAR recommendations for the management of PsA, which highlights that the treatment of PsA should aim at best care based on a shared decision between the patient and the rheumatologist, considering efficacy, safety, patient preferences, and cost [2]. For similar reasons, the TF felt that referring to 'unsatisfactory' was more accurate than 'sub-optimal care' or 'treatment' because there needs to be agreement on the measure to decide what is suboptimal, which is currently not available in PsA. Suboptimal can also have negative connotations and may be perceived as judgmental or critical by both patient and physician.

Although not a perfect term, 'unsatisfactory' was felt to capture the patient and physician's opinion, which patient partners agreed with. It is important to consider that to estimate the PsA disease to be D2T or manage, an adequate 'trial' of pharmacologic therapy must first be undertaken. Consideration was given to real-world scenarios in whereby noncompliance may occur, which may be influenced by psychological and social factors. Whereas this would represent a D2M scenario, it was agreed that it did not represent drug nonresponse.

B. *Unsatisfactory treatment response despite the best standard of care has a significant impact on patients' health status, including well-being and societal functioning.*

This OAP acknowledges the consequences of having an unsatisfactory treatment response in PsA, with discussion

generated about how this impact could be captured, not only in patients but on their relatives, healthcare systems, and the global economy. The SLR revealed a lack of evidence in this respect when addressing the research question on long-term outcomes associated with D2M/treat disease [17]. Similarly, there is a lack of data on the impact of unsatisfactory treatment response, although current evidence shows that achieving MDA is associated with less fatigue and better health-related quality of life (HRQoL), mental well-being, and work productivity than not reaching MDA [28,29]. Further, failure to achieve MDA in the first year after PsA diagnosis is associated with worse patient reported outcomes (PROs) that persist over time [30]. Overall, patients with PsA who achieve clinical disease control (MDA or VLDA, and DAPSA, psoriatic arthritis disease activity score, and Routine Assessment of Patient Index Data LDA or remission) are more likely to achieve improvements and normative values in PROs and QoL measures, reinforcing the concept of disease control as a treatment target in PsA [31−33]. Patient partners and representatives in the panel favoured including the term 'societal' as it was intended to be broader than simply social functioning. The TF felt that it was important to include this OAP, and the order of the phrasing was chosen to try to capture the impact on the patient first and foremost.

C. *Unsatisfactory treatment response may be multifactorial, including ongoing inflammation, joint damage, extramusculoskeletal manifestations, comorbidities, psychosocial, and other factors.*

The TF discussed the appropriateness of considering health status vs treatment response, ultimately opting for the latter, as it was felt that 'health status' would be too broad a concept. Overall, the group felt strongly that joint damage should be included as a specific point rather than other end-organ damage (eg, cardiovascular disease, hypertension, etc.) and that no single comorbidity should be singled out, as each may have a different impact at the individual level. This also applies in the context of extramusculoskeletal manifestations (EMMs) such as PsO, inflammatory bowel disease (IBD), or uveitis, which are immunogenetically related to PsA and form part of its manifestations. Indeed, most people with PsA would meet the multimorbidity definition, as 90% of people with PsA seen in rheumatology clinics also have PsO [1].

Comorbidities, particularly cardiometabolic disorders, such as obesity and metabolic syndrome, are prevalent in PsA, with studies showing that patients with these comorbidities experience more severe disease, poorer quality of life, and increased treatment discontinuation [1,34]. Underlying inflammation is thought to contribute to this risk. Obesity, reported in nearly 30% of patients with PsA, carries a greater risk for cardiovascular related morbidity and mortality, through alteration in the production of cytokines (TNF, interleukin [IL]-6) and adipokines (eg, leptin, adiponectin) also linked to low-grade chronic systemic inflammation [35,36]. Metabolic dysfunction-associated steatotic liver disease (MASLD) is also prevalent in the context of chronic inflammation, which contributes to excess lipid accumulation in the liver, worsened by central adiposity, that can interfere with drug metabolism causing intolerance and/or increased side effects [37]. Other comorbidities such as fibromyalgia, central pain sensitisation, osteoarthritis, and gout can contribute to ongoing symptoms of pain, which can impact accurate assessment of disease activity and treatment response [38,39] and lead to misinterpretation of treatment failure.

Mental health can be significantly affected in PsA [40]. Further, evidence shows that comorbid anxiety and depression are associated with higher disease activity and pain [41]. The psychosocial impact of experiencing an unsatisfactory treatment response was discussed in some detail by the TF members. The term psychosocial is meant to broadly capture different aspects of the disease's impact, not only in an individual's mental health, but also in their personality, coping strategies, etc., in addition to health and lifestyle factors.

Other important factors are the presence of contraindications or poor drug adherence, ie, the extent to which a patient takes a drug as prescribed by the health care provider [42]. Poor adherence is estimated to occur in about half the population with on regular bDMARD drug therapy and including apremilast [43], and contributes to suboptimal clinical outcomes [44].

D. *Establishing the reasons for ongoing signs and symptoms is essential to optimise further management.*

This OAP refers to the need for exploring the reasons for ongoing clinical signs and/or symptoms in patients with PsA who are treated with the best standard of care. Both patient partners and clinicians agreed on the importance of evaluating the presence of objective signs of inflammation, such as swollen or tender joints, elevated C-reactive protein (CRP), or imaging evidence of inflammation, since confirmation of ongoing inflammatory drive is needed to guide treatment interventions [2,11].

Points to consider

1. *Failure to achieve or maintain response to ≥2 b/tsDMARDs with ≥2 different mechanisms of action according to the EULAR recommendations for the management of PsA should be used to define D2M and TR PsA.*

The TF also felt it was equally relevant to consider the failure to achieve and the failure to maintain a response independently, as these represent different concepts. Failure to achieve a response may be seen in 30% of patients commencing a bDMARD and is normally considered a primary nonresponse to that therapy [3,4]. Because this nonresponse is likely to be underpinned by the specific molecular or biological endotype, a different treatment MoA (ie, a different biological therapeutic target) may be considered as an alternative b/tsDMARD. By contrast, the inability to maintain a response implies the loss of an initially acceptable response, which may trigger or require a change of therapy, often within the same treatment class.

Because the SLR showed a limited amount of evidence on the optimal number of conventional synthetic (cs)DMARDs to be considered [17], there was agreement on focusing this PtC around b/tsDMARDs. In addition, csDMARDs may not be indicated as first-line treatment in every clinical scenario, for instance, those presenting with isolated or primarily axial disease [2]. With regards to the number of b/ts-DMARDs, the evidence so far pointed towards considering a minimum of 2 advanced therapies with different MoAs when defining a D2M or TR scenario. There was discussion within the TF as to the suitability of utilising a cut-off of 2, with some members expressing concern that >50% of their PsA cohorts may have switched or cycled through more than 2 ts/bDMARDs. It was also noted that the current literature [17] is more likely to refer to a cut-off of 2, as many published studies in PsA applied the RA definitions in their cohort descriptions [17]. In the end, the group agreed to

refer to 2 b/tsDMARDs since the available evidence refers to a minimum of 2 rather than 3 or more, considering that the intention with these PtCs and definitions is to be as inclusive as possible rather than too restrictive, and that the proposed definitions of D2M and TR PsA have elements beyond the number of drugs or specific MoAs.

The TF also considered it important to align this PtC to the EULAR management recommendations [2] so the statement is anchored on an agreed and widely implemented standard of care in order to avoid confusion as to the number of individual drugs and drug classes mentioned. Since the EULAR management algorithm places csDMARDs as first-line therapy in PsA and accommodates combined csDMARD use [2], this PtC implicitly incorporates the concept that a D2M or TR scenario includes prior and/or concomitant exposure to csDMARDs. This PtC was voted positively by 18/20 (90%) with 2 members abstaining.

2. Failure to achieve or maintain LDA should be used to define D2M and TR PsA.

Current management recommendations refer to LDA or remission as a desirable target [2]; however, this remains aspirational as 60% to 70% of patients fail to achieve this target based on phase 3 trial data or real-world observational studies [4]. The SLR [17] looked at other possible cut-offs referring to LDA, such as VLDA, which appeared even more restrictive, with only 1% to 5% of those defined as D2T in the reported studies achieving VLDA or MDA [3]. Other outcome measures, such as DAPSA with cut-offs for remission and LDA reported to align well with physician and patient-perceived remission were also evaluated [20]. Nevertheless, when combining the number of drugs (ie, ≥2 b/tsDMARDs) with ≥2 different MoA, alongside the LDA cut-off, the prevalence appeared to be around 8% to 30% [17], which was more aligned with the clinical impression of the TF experts and supports the fact that these definitions are not applicable to the majority of people living with PsA.

There was agreement on leaving this PtC as a broad concept, as it represents a PtC, and not a formal definition. In this context, the TF group agreed to emphasise a state of 'low disease activity' as desirable, without specifying a particular outcome measure. Although MDA and low DAPSA having been previously recommended by EULAR [19], the limitations of these and other outcome measures need to be taken into consideration [45].

It is important to highlight that at the time of formulating a definition, several different aspects need to be considered, such as disease activity and patient perception of their disease status, among others. Treatment failure history was felt to be an independent criterion in defining D2M and TR PsA. This PtC was voted on by 21 of 21 members (100%).

3. The presence of active EMMs should be considered to define D2M and TR PsA.

EMMs are part of the disease process in PsA and other spondyloarthritis (SpAs) with shared genetic and molecular immunopathology. Although skin PsO may be considered an intrinsic clinical manifestation of the disease process in PsA, its presence is not universal. This, together with other less prevalent clinical features such as IBD and uveitis, can contribute, when present, to the disease burden [46,47]. Many of the current b/tsDMARDs are known to work across different tissues and organs with proven efficacy in skin and joints, as well as uveitis and IBD in some cases [2]. Yet, it is common in clinical practice to see a divergence of response between the different disease components as is the case with IL-17 and IL-23 inhibitors, for which deeper levels of response have been reported in skin than joints [48,49], or certain clinical scenarios where there may be concomitant active IBD precluding the use of certain agents, ie, IL-17 inhibitors. In addition, paradoxical emergence of EMMs with these treatments has been observed, such as the development of skin PsO after TNF inhibitors for IBD, the mechanism of which is not fully understood [50]. In clinical practice, these differing scenarios require complex, often individualised, treatment decisions that may include multiple drug switching to find the best options. The complexity of clinical presentations influencing management decisions led the group to favour the use of the word 'should', as it was deemed important to consider the presence of EMMs when making treatment decisions in PsA reflecting the need for individualised treatment approaches.

Further, input from multiple specialties and the wider multidisciplinary team may be required to address these challenging, multimorbid clinical scenarios, with the rheumatologist well placed to coordinate care [51]. This PtC was voted by 20 of 21 (95%), with 1 abstaining.

4. Objective evidence of inflammatory activity, namely clinical signs, elevated acute phase reactants, and/or imaging findings suggestive of inflammation can be used to define D2M and TR PsA.

This PtC aligns with OAP D and highlights the need to confirm the presence or absence of current inflammation to guide appropriate pharmacologic and nonpharmacologic interventions. In the presence of persistent signs and symptoms of PsA, establishing objective evidence of inflammation is needed to identify those considered as having TR PsA, who have ongoing symptoms and signs of disease despite multiple therapies. Clinical signs of active inflammation may be heterogeneous and include peripheral arthritis, enthesitis, dactylitis, and potentially also highly suggestive 'inflammatory' axial symptoms even in the absence of convincing imaging findings. Indeed, although imaging may help identify persistent or refractory inflammation, ie, ultrasound findings of Doppler signal in synovial joints or bone oedema on MRI in sacroiliac joints or axial skeleton, it may not be useful or sufficient in all cases, particularly when the level of inflammation is low and therefore difficult to visualise [52,53]. It was also recognised that access to advanced musculoskeletal imaging may not be universal. Further, radiographic progression, a consequence of disease activity and a 'surrogate' for severity in RA, may only be useful in small joint symmetric PsA phenotypes, and data on longitudinal imaging in PsA are lacking, particularly for those with large joint oligoarticular disease, or isolated entheseal or axial phenotypes [54]. By contrast, persistent symptoms in the absence of current inflammation may suggest that other treatment strategies, beyond DMARDs and including nonpharmacologic interventions, may be indicated. This PtC was voted on by 20 of 21 (95%), with 1 abstaining.

5. The presence of comorbidities should be considered when interpreting disease activity measurements and when defining D2M and TR PsA.

This PtC stems from OAPs C and D. Comorbidities are important contributors to disease severity, can limit treatment options, and affect treatment response and its assessment, potentially contributing to both scenarios of D2M and TR PsA [1]. When

assessing these, it is important to differentiate those comorbidities that may contribute to ongoing inflammation (ie, obesity, fatty liver disease, metabolic syndrome, dyslipidaemia, and gout) from those that mimic PsA (osteoarthritis), chronic pain syndromes, and others, and to utilise the specific disease assessment tools as appropriate. As such, the TF felt it important to highlight this as a standalone PtC towards the definitions of D2M and TR PsA. This PtC was voted by 21 od 21 (100%)

> 6. *The perception of disease management as problematic by the patient and/or physician should be considered when defining D2M and TR PsA.*

There is evidence suggesting a disconnect or misalignment between patients' and physicians' assessment of disease, including perspectives on treatment priorities and goals in PsA, which is associated with increased disease activity, greater disability, and poorer HRQoL [55]. Although there are differences at the global level, with higher levels of treatment satisfaction and alignment reported in Latin America, there is a considerable clinical and quality-of-life burden, especially when misalignment occurs [56]. This reflects the fact that traditional outcomes, designed for clinical trials, do not always capture the full impact of disease in each individual, ie, on their work or social lives. Like the definition of D2T RA [9], the TF felt it was essential for this concept to be included as a criterion in the definition of D2M and TR PsA. The wording was carefully chosen to refer to management rather than treatment, to encompass the fact that nonpharmacological interventions may be needed. Another important consideration raised by the patient partners was that referring to 'the perception of disease management as problematic', emphasises that the concepts of D2M and TR PsA relate to the disease being D2M, rather than the patient. This PtC was agreed on unanimously (19/19%-100%).

Criteria for definitions and ranking order

Four individual criteria were chosen as essential toward the definitions of D2M and TR PsA (Table 2).

Criterion 1. Treatment failure history

This criterion refers to treatment failure history as discussed in PtC1, anchoring the definitions to existing management algorithms that are followed globally and emphasising the relationship of these definitions and the EULAR guidelines [2]. This will lead the treating clinician to reappraise the diagnosis when faced with a scenario of inadequate treatment response. The reference to 'failure to achieve or maintain' a response to at least 2 b/tsDMARDs with ≥2 different MoAs, with the potential to be classified as D2M PsA, is linked to phase III of the management algorithm of the 2023 management recommendations [2]. Like the D2T RA definition, this criterion was felt to be the most clinically relevant to start off the definitions and applies to both the D2M and TR PsA clinical scenarios. However, an important differentiator between the D2M and TR groups is the definition of treatment failure, which includes any type of primary and secondary failure, including immunological reactions such as biological drug immunogenicity and the formation of antidrug antibodies, drug nontolerance or nonadherence, or discontinuation because of side effects/intolerability/contraindications/comorbidities, etc., when considering a D2M scenario. However, TR PsA refers solely to primary and secondary failure likely to be underpinned by intrinsic differences in tissue-specific pathways but not discontinuation due to side effects, intolerability, or drug contraindications.

Criterion 2. Clinical perception

This criterion stresses the importance of considering the clinical perception of both the patient and their rheumatologist or HPR on whether the disease management is felt as problematic, as outlined in PtC 6. It underpins the need for a personalised approach and the importance of shared decision-making in order to optimise the management of their PsA [57]. Due to its clinical relevance, this was felt to be an essential criterion to add to the definitions, and as such, it was voted unanimously to be ranked as number 2.

Criterion 3. Evidence of persistent disease by the patient and their clinician

This criterion highlights the need to demonstrate evidence of ongoing disease activity in those people with PsA who fulfil criteria 1 and 2. Following PtC 2, 3, and 4, evidence of persistent disease can be established by the presence of 3 points: (1) failure to achieve or maintain LDA (regardless of whether this is driven by inflammation, comorbidities, psychosocial or other factors), (2) the presence of active EMMs of PsA, and (3) the objective evidence of inflammatory activity, namely clinical signs, elevated acute phase reactants and/or imaging findings suggestive of inflammation. At least one of these points (a, b or c) is needed to apply criterion 3 in the definition of D2M.

Table 2

EULAR consensus-based definitions of difficult-to-manage and treatment-refractory PsA

	Difficult-to-manage (D2M) PsA	Treatment-refractory (TR) PsA
1	Treatment according to the EULAR recommendations for the management of PsA and failure to achieve or maintain response to ≥2 b/tsDMARDs with ≥2 different mechanisms of action*‡	
2	The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient	
3	Evidence of persistent disease as defined by ≥1 of the below points: a) Failure to achieve or maintain low disease activity (regardless of whether this is driven by inflammation, comorbidities, psychosocial or other factors) b) The presence of active extramusculoskeletal manifestations§ of PsA c) Objective evidence of inflammatory activity, namely clinical signs, elevated acute phase reactants and/or imaging findings suggestive of inflammation	Evidence of persistent disease as defined by ≥2 of the below points, with point [c] mandatory: a) Failure to achieve or maintain low disease activity b) The presence of active extramusculoskeletal manifestations§ of PsA c) Objective evidence of inflammatory activity, namely clinical signs, elevated acute phase reactants and/or imaging findings suggestive of inflammation
4		Other causes, including comorbidities, psychosocial and other factors, excluded as drivers of persistent disease
	*Including primary and secondary failure, or discontinuation because of side effects/ intolerability/contraindications Criteria 1, 2, and 3 are needed to define D2M PsA	‡TR PsA refers specifically to primary and secondary failure, but not discontinuation due to side effects/intolerability/contraindication All 4 criteria are needed to define TR PsA

b/tsDMARD, biological/targeted synthetic disease modifying antirheumatic drugs; EULAR, European Alliance of Associations for Rheumatology; PsA, psoriatic arthritis.
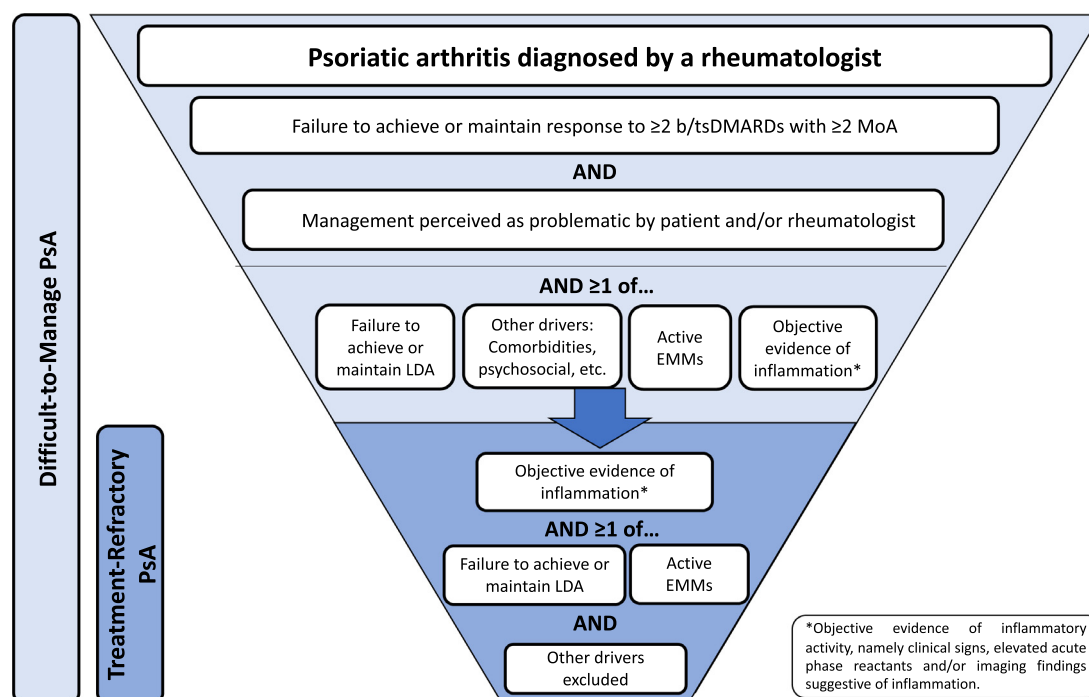
Figure 2. Diagram encompassing the concept of difficult-to-manage PsA, including treatment-refractory PsA. Starting at the top of the truncated pyramid, a clinical situation whereby a patient with a diagnosis of psoriatic arthritis has experienced failure to achieve or maintain response to ≥2 b/tsDMARDs with ≥2 different mechanisms of action; in whom the management of signs and/or symptoms is perceived as problematic by the rheumatologist and who has evidence of persistent disease as defined by either failure to achieve or maintain low disease activity (regardless of whether this is driven by inflammation, comorbidities, psychosocial, or other factors) or the presence of active extramusculoskeletal manifestations of PsA or objective evidence of inflammatory activity, namely clinical signs, elevated acute phase reactants and/or imaging findings suggestive of inflammation, may be considered an scenario of D2M PsA. If there has been primary or secondary treatment failure but not discontinuation due to side effects/intolerability/contraindication, with objective evidence of ongoing inflammatory activity, after other causes, including comorbidities, psychosocial and other factors, have been excluded as drivers of persistent disease, this would be considered a clinical scenario of TR PsA. b/tsDMARD, biological/targeted synthetic disease modifying antirheumatic drugs; D2M, difficult to manage; EMMs, extramusculoskeletal manifestations; LDA, low disease activity; MoA, mechanisms of action; PsA, psoriatic arthritis; TR, treatment refractory.

Taken together, criteria 1 to 3 are all needed for the definition of D2M PsA (Table 2). However, there are 2 important differentiators when defining TR PsA. Failure to achieve or maintain LDA in TR PsA represents primary or secondary treatment failure. Whereas comorbidities, psychosocial and other factors may coexist with, and even contribute to, ongoing active inflammation, as is the case of obesity, gout [58,59], or smoking [60], these are likely insufficient to cause a true refractory scenario and hence the text does not include the wording 'regardless of whether this is driven by inflammation, comorbidities, psychosocial or other factors' therefore differentiating it from the D2M concept. In addition, demonstrating the presence of ongoing inflammation is essential to define TR PsA (Fig. 2). Hence, 2 of the 3 points of criterion 3 are needed, with point c (namely, clinical signs, elevated acute phase reactants, and/or imaging findings suggestive of inflammation) being mandatory, to define TR PsA. To make this distinction clear and to avoid potential confusion between the definitions of D2M PsA and TR PsA, the TF voted to present these in 2 different columns (16/20 [80%]; Table 2).

Criterion 4. Other possible drivers of persistent disease should be excluded

This criterion follows OAP D and PtC5, highlighting the need to consider other causes contributing to ongoing symptoms and signs of disease, including comorbidities, psychosocial, and other factors that may require additional or specific treatment, to be excluded as drivers of persistent disease to make the definition of TR PsA, complementing criterion 3a. Objective confirmation of active inflammation can be assessed either by clinical signs, an elevated serum CRP, or imaging, which are essential for the definition of TR. It was therefore felt important to differentiate this in the context of TR PsA since comorbidities such as obesity, fatty liver disease, metabolic syndrome, dyslipidaemia, or gout can be proinflammatory, making it difficult to evaluate the cause of an elevated CRP [58] in these patients. In addition, obesity and an elevated body mass index are directly associated with higher disease activity and reduced response to treatment [59]. Smoking is associated with an elevated CRP and higher rates of treatment failure, negatively influencing PsA outcomes [60]. The TF members felt that it was important to consider this as a standalone point towards the definition of TR PsA.

The final wording on the definitions (Table 2, Fig. 2) was agreed by 100% (20/20) of the TF for D2M and 75% (15/20) for TR PsA. Suggested variables to help harmonise their implementation are given in Table 3.

Research agenda and quality indicators

The TF formulated a research agenda (Table 4) and 2 sets of quality indicators for implementation of the proposed definitions as follows:

1. The TR definition is used in at least 2 studies, including both clinical trials of investigational medicinal products (CTIMP) and non-CTIMP/observational studies, within the next 2 to 4 years.
2. The D2M definition is used in 3 studies, within the next 2 to 4 years.

Table 3

Suggested variables to utilise when applying the definitions of D2M and TR PsA

	Suggested variable
Treatment according to the EULAR recommendations for the management of PsA and failure to achieve or maintain response to ≥2 b/tsDMARDs with ≥2 different mechanisms of action	Refer to latest published version of the EULAR recommendations for the management of PsA
The management of signs and/or symptoms is perceived as problematic by the rheumatologist and/or the patient	Physician and Global Assessment of Disease Activity (can be utilised in the absence of specific validated outcome measures)
Low disease activity status	Any validated outcome measure including but not exclusive of DAPSA, MDA, PASDAS, RAPID3, PSAID, etc.
Comorbidities	Proinflammatory comorbidities: ie, obesity, fatty liver disease, metabolic syndrome, dyslipidaemia, gout
	Comorbidities that mimic PsA: ie, osteoarthritis, fibromyalgia, etc.
	Other: cardiovascular disease, chronic pain syndromes, depression, anxiety, etc.
Active extramusculoskeletal manifestations of PsA	Psoriasis,
	Inflammatory bowel disease
	Uveitis
Clinical signs of inflammatory activity	Swollen or tender joints ≥1
	Swollen or tender entheses (clinical count or any validated index) ≥1
	Dactylitis (clinical count or any validated measure) ≥1
	Back pain symptoms
	BSA ≥ 3%
	Nail psoriasis
Elevated acute phase reactants	CRP ≥ 5 mg/L
	ESR as per local values according to age and sex
Imaging findings suggestive of inflammation	Ultrasound findings of Doppler signal in synovial joints or entheses, or validated definitions
	MRI findings of bone marrow oedema, synovitis, etc., on sacroiliac joints or spine or validated definitions

BSA, body surface area; CRP, C-reactive protein; DAPSA, Disease Activity in Psoriatic Arthritis score; ESR, eyrthrocyte sedimentation rate; EULAR, European Alliance of Associations for Rheumatology; MDA, minimal disease activity; MRI, magnetic resonance imaging; PASDAS, Psoriatic Arthritis Disease Activity score; RAPID3, Routine Assessment of Patient Index Data; PSAID, psoriatic arthritis impact of disease.

Table 4

Research agenda

Theme	Research question
Epidemiology	What is the prevalence of D2M and TR PsA
Pathogenesis	To explore the molecular basis and underlying endotype of TR PsA-
Contextual factors	Is biological sex related or a determinant of D2M and TR PsA?
	What is the socioeconomic impact of D2M and TR PsA?
Contributing factors	What are the factors contributing to D2M and TR PsA and their interactions
	To explore the number of drugs and MOAs needed to accurately define TR PsA
	Are there any differences between classes of b/tsDMARDs contributing to D2M and TR PsA?
Assessment	Which outcome measures align with and best capture D2M and TR PsA?
	Is there a temporal timeframe to apply to the definitions of D2M and TR PsA?
	How do the D2M/TR status change over time?
Treatment	To develop EULAR management guidelines for D2M and TR PsA
	What are the best treatment strategies for D2M/TR PsA: ie, combination therapy or alternative strategies including non-pharmacological interventions?
	What is the value of therapy sequencing in the management of D2M/TR PsA?
	Are different strategies (eg, starting with 1 or the other b/tsDMARDs) expected to alter the course of D2M PsA at the individual level?
Imaging	What is the role of new imaging techniques in the detection of subclinical entheseo-synovial inflammation in PsA?

b/tsDMARD, biological/targeted synthetic disease-modifying antirheumatic drugs; D2M, difficult to manage; EULAR, European Alliance of Associations for Rheumatology; PsA, psoriatic arthritis; TR, treatment refractory.

DISCUSSION

The EULAR TF developed a set of OAPs and PtC and 2 definitions of D2M and TR PsA suitable for use in clinical trials, and potentially in clinical practice, aimed to characterise these PsA subpopulations, study their endotypes, and develop effective treatment strategies with the goal of improving outcomes and HRQoL for those affected. Further, by adding a set of quality indicators, the TF aims to continue this initiative by encouraging the research community to test these definitions in interventional and observational studies, and to ultimately produce management recommendations for D2M and TR PsA. This work is of

relevance as it addresses an important unmet need in PsA and complements previous EULAR initiatives, including recommendations for management of PsA with pharmacological therapies [2] and PtCs for the definition of clinical and imaging features suspicious for progression from PsO to PsA [61]. In this way, EULAR effectively provides a framework to support best care and further research across the psoriatic disease continuum, from prevention to treatment of refractory disease.

The result of this project confirms the robustness of the EULAR SOPs process, with the PtCs performing in effect as a road map towards the formulation of the final definitions. By formulating the PtCs as standalone statements, they can be

easily translated into different languages to facilitate research in this area. In addition, they may provide a foundation for clinicians to discerningly approach challenging scenarios of D2M and TR in clinical practice. An important consideration at the start of this work was the anticipated lack of data in the literature to help develop a data-driven process, as shown by the initial surveys [12,13] and scoping literature review [14]. The SC and full TF membership, however, felt strongly that an SLR was the best methodological approach to appraise the level and quality of existing data, as this was also needed to identify gaps and areas of unmet need towards the formulation of a research agenda. Indeed, the evidence was limited, extremely heterogeneous, and generally of low to moderate quality [17], reflecting the need for this exercise to act as a springboard to facilitate further research using standardised definitions. Further, an important aspect of the process was reaching consensus among the expert members and patient research partners contributing to the TF. We took special effort and consideration in carefully choosing wording and terminology that was accurate to avoid misinterpretation. This was essential since the development of definitions is the first step towards facilitating a new avenue of research. In this context, it is important to stress that we are defining not a disease or a permanent condition, but rather a dynamic disease state that may change or fluctuate over time. In this respect, while the threshold of the number of previous DMARDs is not reversible, criteria 2 and 3 of both definitions 'allow' for disease to be defined in and out of D2M and TR PsA states. Unfortunately, the SLR [17] identified a lack of evidence to establish a minimum time threshold to apply to these definitions and consider re-evaluation, which highlights the need for these terms to be applied to the disease rather than the individual, to avoid misclassification or stigmatisation. Nevertheless, anchoring these definitions to the EULAR management recommendations implies that a minimum timeframe is applied to these concepts. Evaluating their performance cross-sectionally and over time is a research priority (Table 3) to understand how these definitions may change for individuals or groups, and establish their real value in the clinical setup.

The resultant definitions reflect 2 core concepts: one that encompasses the wider notion of D2M and which incorporates the second, less frequent, and more specific scenario of TR PsA with ongoing objective inflammation. Together, these terms incorporate the full construct of what is understood by 'difficult to treat'. This is a similar approach to the one adopted by the ASAS (Assessment of Spondyloarthritis International Society) group recently in axSpA [15], a condition closely related to PsA, with both considered part of the wider spondyloarthritis spectrum [62]. A clinical situation where PsA is associated with cardiometabolic disease, depression, and joint pain with no synovitis, enthesitis, or active axial disease, but moderate skin disease, and poor drug tolerability may be classified as D2M PsA, yet it may not represent TR disease. In contrast, all clinical scenarios of TR PsA will fulfil the definition of D2M.

Pharmacological interventions, including novel treatment strategies incorporating combination therapy, need to be developed and tested for TR PsA, with the wider range of nonpharmacologic interventions and holistic approach needed in both scenarios as appropriate. As suggested on the proposed quality indicators, further work now needs to be done applying these definitions to establish the real-world prevalence and incidence of D2M and TR PsA, which is estimated to apply to only a small proportion of PsA.

The lack of evidence highlighted by the SLR was obvious when trying to cover all the possible aspects of D2M/TR PsA, in particular, the long-term outcomes and predictive factors of D2M/TR PsA, which was to be expected due to the newness of the concept. The definitions presented here will help focus research efforts by addressing the wider factors associated with nonresponse in D2M PsA [63,64], including genetically determined disease manifestations (PsO, uveitis, IBD), biologically related inflammatory comorbidities (obesity, cardiometabolic syndrome, dyslipidaemia, and MASLD), pain syndromes, overlapping rheumatological conditions, such as gout, osteoarthritis or fibromyalgia which may also mimic PsA, and psychosocial factors including treatment nonadherence, lifestyle, and others. Exploring the impact of shared decision making and addressing the misalignment between patient and clinician expectations will be key to improving patient engagement, compliance with treatment, and overall satisfaction [65].

In the context of TR PsA, a focus on translational research is needed to understand the genetic, cellular, and molecular factors underpinning nonresponse to the different available MoAs of advanced therapies, and their interplay with the heterogeneity of tissue(s) involved. Skin transcriptomics in patients with PsA denotes greater IL-17 gene signature, chemokine-mediated pathways, and homogenous IL-23 genomic profiling, while the synovium shows more heterogeneous IL-23 expression and balanced TNF and interferon-γ signatures [66−68]. These differences in tissue-specific transcriptomic profiling between the skin and synovium of patients with PsA may potentially inform future therapeutic strategies. In addition, recent studies suggest that the cellular sources of cytokines involved in different affected tissues may vary, and that this, in turn, may explain the apparent lack of response of some targets, such as IL-23 inhibitors in axSpA [69]. This would imply a new concept in TR disease, namely, whether currently used treatment doses are sufficient or whether specific titration should be used [70]. Finally, improving the sensitivity of current imaging modalities to detect subclinical inflammation is needed, with data starting to emerge on the ability of newer techniques, such as PET-CT (Positron Emission Tomography-Computed Tomography) with FAPi tracer, to detect active fibroblasts in inflamed joints and entheses, with good sensitivity to change in PsA [71,72].

In this light, the proposed new definition of TR PsA will facilitate dialogue and collaboration between rheumatologists, dermatologists, basic scientists, radiologists, and others to help personalise treatment to manage and prevent TR scenarios. Understanding why drugs stop working and what treatments offer the most benefit (considering efficacy, tolerability, and safety) for the different body tissues affected in PsA are priority area of research for patients [73].

In conclusion, EULAR developed PtCs and 2 consensus definitions to identify a D2M PsA population, including a subgroup with TR disease. These definitions should now be applied in well-designed observational, interventional clinical trials and basic science research studies, to characterise the phenotypes and underlying endotypes of these 2 populations, test interventions, and guide further research to understand disease pathogenesis and improve the care of people living with PsA.

CONTRIBUTORS

HM-O wrote the first draft of the manuscript with help from SS, PMM, and AS. All authors participated in the work of the task force, contributed to manuscript writing, and read and approved the final version of the manuscript.

PATIENT CONSENT FOR PUBLICATION

Patients and/or the public were involved in the design, or conduct, or reporting or dissemination plans of this research project.

Ethics approval

No ethics committee approval was needed for this study.

Provenance and peer review

Not commissioned; externally peer reviewed.

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Competing interests

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Funding

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