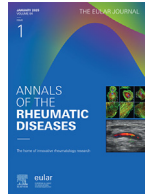




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Axial spondyloarthritis

The Assessment of SpondyloArthritis International Society (ASAS) Consensus-Based Expert Definition of Difficult-to-Manage, including Treatment-Refractory, Axial Spondyloarthritis

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ABSTRACT

Objectives: To develop a consensus-based expert definition of difficult-to-manage (D2M) axial spondyloarthritis (axSpA), incorporating treatment-refractory (TR) disease.

Methods: A literature review was conducted in 2022 to identify potential definitions for D2M/TR axSpA from prior studies, followed by a 2-round Delphi consensus process conducted in 2022 and 2023 to identify components of D2M axSpA. Based on the results of the Delphi process, a draft of the D2M axSpA definition was developed and presented to the expert task force, including patient representation, and, subsequently, to the Assessment of SpondyloArthritis International Society (ASAS) membership for endorsement in January 2024.

Results: Consensus was reached on a D2M definition encapsulating treatment failure (treatment according to the ASAS-European Alliance of Associations for Rheumatology recommendations and failure of ≥ 2 biological or targeted synthetic disease-modifying antirheumatic drugs with different mechanisms of action unless contraindicated), suboptimal disease control, and physician or patient acknowledgement of problematic signs/symptoms in patients diagnosed with axSpA by the rheumatologist. This definition represents a broad concept that includes various reasons that lead to an unsatisfactory treatment outcome. TR axSpA is covered by the D2M definition but requires a history of treatment failure, the presence of objective signs of inflammatory activity, and the exclusion of noninflammatory reasons for nonresponse. The proposed D2M definition incorporating TR disease was endorsed by ASAS at the annual meeting in January 2024, with 89% votes (109/123) in favour of it.

Conclusions: The ASAS D2M axSpA definition, including TR disease, allows for identifying patients with unmet needs, paving the way for further research in this condition and its clinical care improvement.

INTRODUCTION

Axial spondyloarthritis (axSpA) is an immune-mediated inflammatory condition primarily affecting the axial skeleton (spine and sacroiliac joints) [1,2]. Based on the presence or absence of definitive radiographic sacroiliitis according to the radiographic criterion of the modified New York criteria [3],

axSpA can be classified as radiographic, historically known as ankylosing spondylitis (AS) [4], or nonradiographic, respectively.

The first-line therapy for axSpA consists of nonsteroidal anti-inflammatory drugs (NSAIDs) in conjunction with nonpharmacological interventions, including regular exercise and physiotherapy [5]. In patients where first-line therapy is ineffective or

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Despite the availability of several efficacious treatment options, a significant proportion of patients with axial spondyloarthritis (axSpA) do not achieve satisfactory treatment outcomes.
- There has been no consistent or universally accepted definition of ‘difficult-to-manage’ (D2M) or ‘treatment-refractory’ (TR) axSpA, hindering the identification and management of patients with unmet needs.

WHAT THIS STUDY ADDS

- This study presents a consensus-based definition of D2M axSpA incorporating key elements such as treatment failure (defined by failure of at least 2 biological or targeted synthetic disease-modifying antirheumatic drugs), suboptimal disease control, and the perception of problematic signs and symptoms by both rheumatologists and patients.
- The definition includes a specific subset of patients with TR axSpA, characterised by objective signs of inflammatory activity despite optimal treatment, distinguishing them from patients who may have noninflammatory reasons for nonresponse.
- The definition was endorsed by the Assessment of SpondyloArthritis International Society, reflecting a broad consensus among experts in the field.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- The proposed definition provides a standardised framework for identifying patients with D2M and TR axSpA, facilitating targeted research into the underlying mechanisms, epidemiology, and potential interventions for these patient populations.
- This definition may inform policy-making, supporting the development of clinical guidelines and resource allocation for the management of patients with D2M axSpA.

not tolerated, second-line therapy should be considered. This includes biological or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs). The first group of these drugs includes tumour necrosis factor (TNF) inhibitors and interleukin-17 (IL-17) inhibitors. The second group consists of Janus kinase (JAK) inhibitors [5].

The primary treatment target in axSpA is sustained remission, defined as the absence of clinical (signs and symptoms) and laboratory (primarily C-reactive protein [CRP]) indicators of disease activity [5,6]. The Axial Spondyloarthritis Disease Activity Score (ASDAS) is the preferred composite measure of disease activity in axSpA [5,6]; ASDAS < 1.3 is considered an inactive disease state and corresponds to remission, while ASDAS between 1.3 and 2.1 is classified as a low disease activity state and should be used as the alternative treatment target if remission is unachievable [7]. A clinically important improvement in ASDAS (Δ ASDAS \geq 1.1) is used as a criterion for deciding on the continuation of b/tsDMARDs as outlined in the Assessment of SpondyloArthritis International Society (ASAS)-European Alliance of Associations for Rheumatology (EULAR) management recommendations for axSpA [5]. The ASAS 40 and 20 response criteria are frequently used in clinical trials as key outcome parameters [8].

Despite several efficacious anti-inflammatory treatment options, only about 40% to 50% of patients with axSpA achieve a relevant treatment response, and an even smaller proportion (approximately 10%-20%) reach remission or an inactive disease activity state within 16 to 24 weeks of treatment initiation, according to data from randomised controlled trials with b/

tsDMARDs [9]. After the failure of 1 b/tsDMARD and in the presence of active disease, a switch to another b/tsDMARD is recommended [5]. However, a group of patients with non- or incomplete responses remains despite exposure to multiple advanced therapies. There are several potential reasons for non-response or partial response in axSpA, which may be related to the disease itself or factors other than inflammatory activity (eg, nonnociceptive pain mechanisms [10–12]). A misdiagnosis could also contribute to the observed nonresponse. The mechanisms underpinning nonresponse remain incompletely understood, and there are no evidence-based approaches to address this issue in clinical practice.

In recent years, the concept of ‘difficult-to-treat’ rheumatoid arthritis (RA) has evolved [13], leading to the development of specific recommendations for its management in clinical practice [14].

As part of the ASAS Difficult-to-Manage (D2M) axSpA initiative, which aims to define D2M axSpA and provide management guidance, we sought to develop a consensus-based expert definition of D2M axSpA, incorporating treatment-refractory (TR) disease, which will help facilitate further initiatives to improve the clinical care of these patients and research in this area.

METHODS

The process of developing the D2M definition involved forming a task force and conducting a literature review to inform the task force and a 2-round Delphi survey. Importantly, ASAS intended to develop a consensus-based definition and not classification criteria, which determined the methodology of the process. The first Delphi round was conducted among ASAS members to determine the main elements of the future definition. Following the discussion of the results within the task force and at the ASAS annual meeting, the second Delphi round focused on specific definition elements. Based on the results of this round, a draft of the D2M axSpA definition was developed and presented to the task force and, subsequently, to the ASAS membership for endorsement.

Task force

After the ASAS executive committee approved the project, a task force consisting of 29 rheumatologists and full ASAS members, 2 young ASAS representatives (a rheumatologist and an epidemiologist, full ASAS members), 2 patient representatives, 1 psychologist and behavioural medicine specialist, 1 physiotherapist, and 1 physical medicine specialist (full ASAS member) was convened.

Literature review

A literature review aimed at identifying potential definitions for D2M axSpA from prior studies was conducted in 2022, including a Medline (via PubMed) search using established review methods and the search terms outlined in [Supplementary File S1](#). Following the RA model, the term ‘difficult-to-treat’ was utilised in the first search strategy. Recognising that the terminology in the literature might vary, a second, broader search strategy using terms reflecting treatment nonresponse in axSpA was implemented ([Supplementary File S1](#)). The search was performed for all types of articles published in English and based on studies in humans, with a publication date between 2012 and 2022. After excluding duplicates, titles and abstracts were

screened, followed by a full-text review by MT and DP. From the included publications, information was retrieved on the definition of treatment failure, the definition of active disease, and the terminology used to characterise the concept of ‘difficult-to-manage’ disease.

The first Delphi round

The first Delphi round focused on defining the following main elements of the definition: uncontrolled disease (clinical manifestations, composite outcome measures, objective signs of inflammation, and radiographic progression), treatment failure (types and number of treatment options applied), and other potential factors that might contribute to the D2M situation. At this stage, we used the term ‘difficult-to-treat,’ which was later replaced with ‘difficult-to-manage’ (see Results). The first Delphi round included 9 questions related to the D2M topic, including 1 open question (Supplementary File S2). It was conducted from November to December 2022, with all ASAS members and co-opted members of the D2M initiative—including 2 patient representatives, a psychologist and behavioural medicine specialist, and a physiotherapist, all of whom were non-ASAS members—invited to participate. The survey results were discussed with the members of the task force at a dedicated virtual meeting and subsequently with ASAS members at the annual meeting in January 2023.

The second Delphi round, draft definition, and endorsement

Taking the results of the discussions with task force members and at the ASAS meeting in January 2023 into account, we drafted the second Delphi round, which focused on refining the criteria for the D2M axSpA definition, including precise definitions for insufficient control of signs and symptoms, required treatment history, the number of prior b/tsDMARDs, discontinuations due to intolerability or side effects, and differentiation between primary and secondary treatment failure. This round included 11 questions related to the D2M definition, including an open question (Supplementary File S3). Before completing the survey, participants (the same group as in the first round) were informed about the outcomes of the previous stage. This round was conducted from September to October 2023 and was followed by discussions with the members of the task force and all ASAS members at the annual meeting in January 2024. As an outcome, the ASAS D2M definition was drafted, followed by a vote on endorsement by the full ASAS membership. A majority of votes in favour of the definition was sought for endorsement.

RESULTS

Literature review

A total of 198 publications were identified using both search strategies. After the exclusion of 12 duplicates, 186 publications were screened based on their titles and abstracts. A total of 134 publications were excluded: 128 were not related to the subject of interest, 4 were related to paediatrics, and 2 were not related to axSpA. Of the 52 publications whose full texts were evaluated, 41 were excluded as unrelated to the subject of interest. However, 4 new publications not captured by the original search strategies were included after a cross-reference check. Ultimately, 15 publications were included in the review: 2 case reports, 5 observational studies, 3 open-label clinical trials, 3 randomised controlled trials, and 2 review articles (see the

Supplementary Fig and Supplementary Table). In summary, the literature review revealed only a few relevant works with no consistent definition of D2M axSpA due to the heterogeneity of the criteria used for defining active disease and history of treatment failure. Furthermore, there was no established terminology to characterise the group of interest.

The first Delphi round

A total of 212 ASAS members (both full and associate), along with 4 co-opted members of the D2M initiative, were invited; 123/212 (58%) responded and completed the survey in full. The majority of the respondents (53%) supported using an ASDAS ≥ 2.1 as an indicator of active disease in the context of D2M axSpA (referred to as difficult-to-treat in this round). Additionally, 73% indicated that objective signs of inflammatory activity (elevated CRP and/or active inflammation on magnetic resonance imaging [MRI]) should be incorporated into the definition of active disease. Moreover, 77% of the respondents believed that all manifestations of spondyloarthritis (axial, peripheral, and extra-musculoskeletal) should be considered in the definition. Concerning the definition of treatment failure, the predominant response (46%) was ‘ ≥ 2 NSAIDs in full anti-inflammatory doses and ≥ 2 b/tsDMARDs with different modes of action,’ without differentiating between primary and secondary nonresponse (79%). Regarding the question of whether intolerability or contraindications to NSAIDs or b/tsDMARDs should be considered as an alternative to insufficient efficacy in the definition, 48% of experts responded positively for both NSAIDs and b/tsDMARDs, while 16% supported this consideration for b/tsDMARDs only. According to 53% of the respondents, radiographic progression should be part of the definition, and 51% indicated that symptoms unrelated to the inflammatory activity of axSpA should not be considered.

In subsequent discussions with the task force and the ASAS membership during the ASAS 2024 annual meeting, it was decided to change the nomenclature from ‘difficult-to-treat’ to ‘difficult-to-manage.’ The main reason for this change is that the management of axSpA better incorporates all management aspects, not only drug treatment, and this is also in line with the ASAS-EULAR management recommendations. Furthermore, it was agreed that the D2M axSpA definition should be broad and inclusive, similar to the difficult-to-treat RA framework, as opposed to the TR scenario, which, being part of the D2M (and therefore covered by the D2M definition), relates to cases where inflammatory activity cannot be controlled with currently available treatments.

The second Delphi round

A total of 205 ASAS members (active at the time of invitation, both full and associate), along with 4 co-opted members, were invited, and 186/205 (91%) responded to the survey. In the first part of this round, we sought components for the definition of insufficient control of signs/symptoms of axSpA. The majority of respondents (59%) favoured using ASDAS ≥ 2.1 as the composite outcome measure threshold indicative of insufficient control of signs/symptoms in the context of the D2M axSpA definition. Other selected components included objective signs of inflammation (elevated CRP and active inflammation on MRI of sacroiliac joints or spine), which should be mandatory but only in TR patients (supported by 62% of the respondents), rapid radiographic spinal progression (defined as the development of >2 new syndesmophytes or bony bridges in 2 years [15], 63%),

and the presence of axSpA symptoms that cause a reduction in quality of life, even if axSpA is controlled according to the criteria mentioned above (80%).

The second part of the survey dealt with the treatment aspects of the D2M axSpA definition. The definition refers to the current version of the ASAS-EULAR management recommendations; therefore, no specific definition of minimal treatment duration was deemed necessary by 58% of the respondents. The leading response regarding the minimal sufficient treatment history (with 50% of the respondents in favour) was ‘At least 2 b/tsDMARDs with different modes of action,’ while 18% favoured ‘At least 2 b/tsDMARDs with the same or different modes of action,’ and 17% preferred ‘At least 3 b/tsDMARDs with the same or different modes of action.’ Treatment discontinuation due to intolerability/side effects was favoured by 75% of the respondents, and 70% favoured the incorporation of contraindications for treatment with b/tsDMARDs into the D2M definition, meaning that a patient could fulfil the definition without a trial of a b/tsDMARD. Furthermore, 51% of the respondents indicated no need for differentiation between primary and secondary nonresponse in the D2M context. Concurrently, 82% of the respondents believed that a lack of access to treatment should not be a part of the definition.

Draft definition and endorsement

The results of the second Delphi round were discussed by the task force. It was agreed to incorporate components of treatment history and insufficient symptom control into the draft definition based on the outcomes of the Delphi process. Specific attention was given to the items that received less than 70% of votes in the Delphi exercise. Additionally, the third component of the definition, which relates to the perception of the current situation as problematic by the rheumatologist and/or the patient, was also included following a discussion involving patient representatives. The decision to use ‘and/or’ instead of ‘and’ was made to ensure an appropriate representation of both patients’ and physicians’ views on the situation and to keep the definition inclusive.

The draft definition followed minor modifications to the proposed wording; consensus was reached. The final version of the ASAS D2M axSpA definition, as shown in [Figure 1](#), was endorsed by ASAS at the annual meeting in January 2024 with 89% of the votes (109 out of 123 full members).

The D2M axSpA should only be applied to patients with a definite diagnosis of axSpA made by a rheumatologist. It consists of 3 main components: (1) treatment according to the ASAS-EULAR recommendations and failure of ≥ 2 b/tsDMARDs with different mechanisms of action (unless contraindicated); (2) insufficient control of signs/symptoms of axSpA; and (3) the present signs/symptoms being perceived as problematic by the rheumatologist and/or the patient (see [Fig 1](#) for details).

TR axSpA, according to the endorsed definition, is considered a subgroup of D2M axSpA. Patients with D2M axSpA (assuming correct diagnosis, which should be the first step in the evaluation and treatment compliance) can be considered TR if ≥ 2 b/tsDMARDs failed, have high or very high disease activity according to ASDAS (ASDAS ≥ 2.1) plus objective signs of inflammatory activity (elevated CRP or active inflammation on MRI of sacroiliac joints or spine), and if other causes, likely responsible for signs and symptoms (concurrent conditions, non-compliance, etc) are excluded before making a decision on the presence of TR axSpA ([Fig 2](#)).

DISCUSSION

The developed expert consensus-based definition of D2M axSpA, including TR disease, is an important first step of the D2M initiative with the ultimate goal of improving treatment outcomes in axSpA. This initiative, led by ASAS, not only aims to define D2M and TR axSpA but also includes the development of management recommendations for D2M axSpA, encompassing TR cases. Here, we report the finalised definitions while the recommendation development process is ongoing. Importantly, patients are involved in the entire development process. Another important aspect is that the development process involved reaching a consensus among the members of an expert organisation; we did not aim to develop classification criteria, which

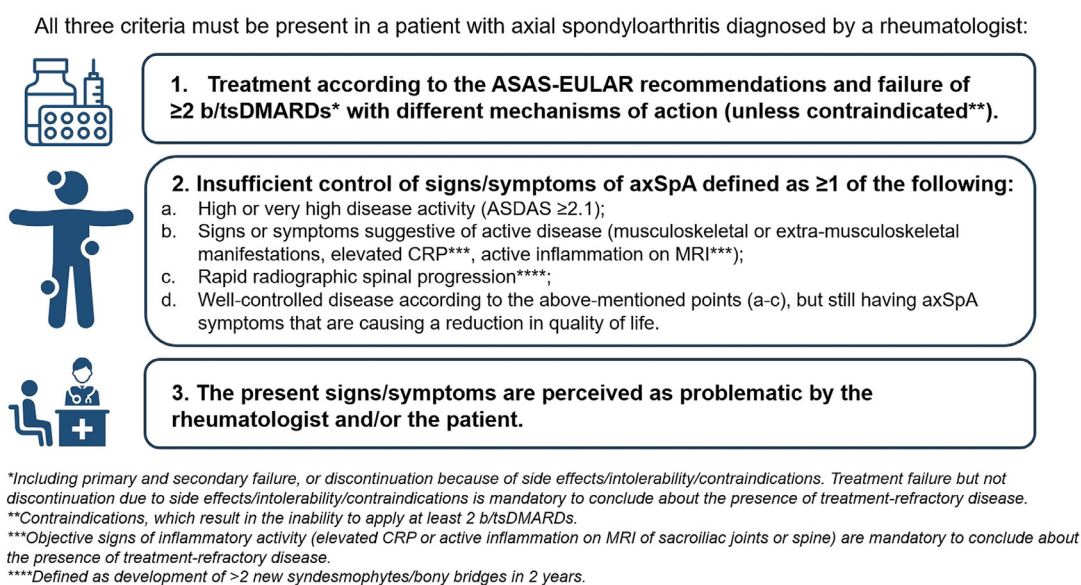


Figure 1. The Assessment of SpondyloArthritis International Society (ASAS) difficult-to-manage axial spondyloarthritis (axSpA) definition. ASDAS, Axial Spondyloarthritis Disease Activity Score; bDMARD, biologic disease-modifying antirheumatic drug; CRP, C-reactive protein; EULAR, European Alliance of Associations for Rheumatology; MRI, magnetic resonance imaging; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

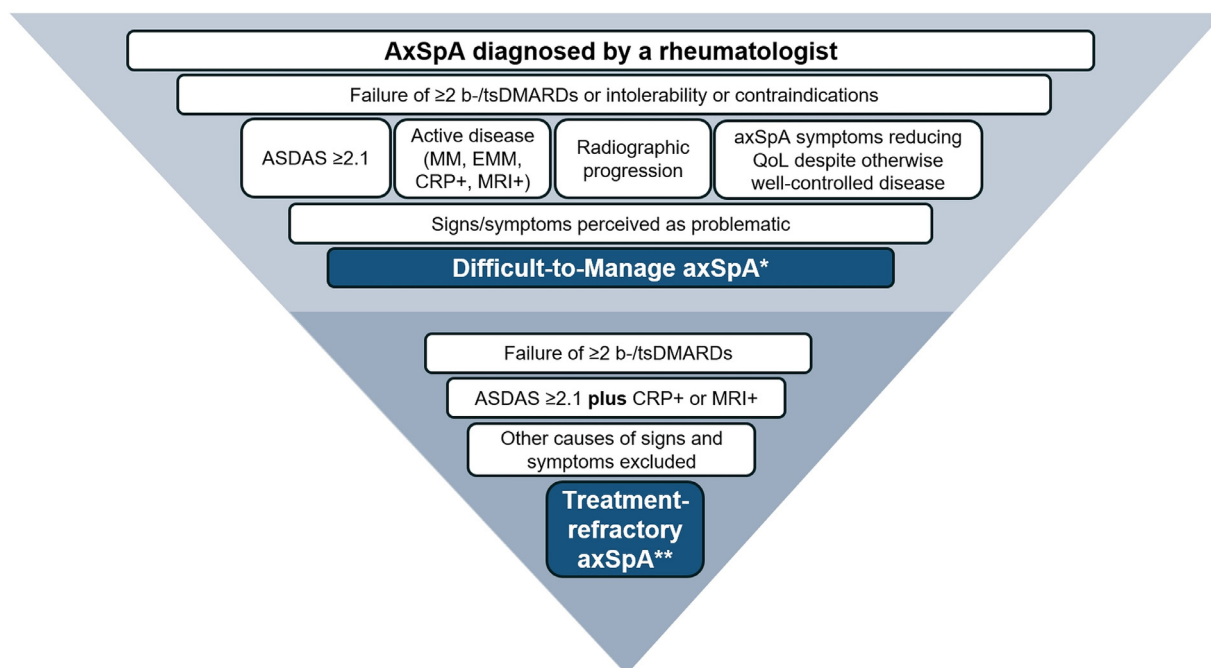


Figure 2. The difficult-to-manage axial spondyloarthritis (axSpA) construct. The starting point in this construct, which applies to both difficult-to-manage and treatment-refractory axSpA, is the diagnosis of axSpA by a rheumatologist. A difficult-to-manage situation (*) is present in cases of treatment failure (or intolerance/contraindications), indicators of uncontrolled signs/symptoms related to spondyloarthritis, and the perception of a problematic situation. A treatment-refractory situation (**) is present in patients meeting the definition of difficult-to-manage axSpA if there is evidence of treatment failure (assuming appropriate compliance, tolerance of the drugs, and sufficient treatment duration), high or very high disease activity according to the Axial Spondyloarthritis Disease Activity Score (ASDAS), and objective signs of uncontrolled inflammatory activity (as reflected by elevated C-reactive protein [CRP]: CRP + or inflammation on magnetic resonance imaging [MRI] of sacroiliac joints or spine: MRI +). It is assumed that other causes, likely responsible for signs and symptoms (including incorrect diagnosis, concurrent conditions, noncompliance, etc), are excluded before deciding on the presence of treatment-refractory axSpA. bDMARD, biologic disease-modifying antirheumatic drug; EMM, extramusculoskeletal manifestations; MM, musculoskeletal manifestations; QoL, quality of life; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

would have required a different methodological approach. We believe that a consensus-based expert approach is appropriate in this case, as there was no unified definition or terminology for the clinical situation described by the definition at the start of the initiative. Furthermore, we are defining not a disease or a permanent condition but rather a disease state that may change over time. Moreover, we followed a similar methodology that was used to develop the EULAR difficult-to-treat definition for RA [13].

The developed definition consists of 3 criteria, which must be present in a patient with axSpA diagnosed by a rheumatologist:

1. Treatment according to the ASAS-EULAR recommendations and failure of ≥ 2 b/tsDMARDs with different mechanisms of action (unless contraindicated).

This criterion defines the minimal requirement for treatment history and implies a lack of response to the standard treatment approach, including at least 2 b/tsDMARDs with different mechanisms of action. It implies the failure of b/tsDMARDs with proven efficacy in axSpA, which are incorporated in the ASAS-EULAR recommendations, currently TNF, IL-17, and JAK inhibitors. It is assumed that other treatment options, including NSAIDs and nonpharmacological measures, have been exhausted as well, either before or in parallel with b/tsDMARDs. In axSpA, only 3 classes of b/tsDMARDs are effective and approved for treatment; therefore, experts decided that at least 2 out of 3 classes should be tried before making a conclusion about the presence of D2M axSpA. Treatment failure includes both primary and secondary nonresponses since both may be associated with treatment challenges and a D2M situation. This

criterion does not imply any specific time aspect: neither the duration of treatment, which must be in accordance with current recommendations, nor the timing of the treatment failure. However, this criterion should be considered in the context of other criteria; for instance, the definition of D2M axSpA will not be fulfilled in a patient with a history of b/tsDMARD secondary failure in the past if there are treatment options available or if the current treatment line is associated with a good clinical response. The same applies to the discontinuation of b/tsDMARDs due to intolerability or side effects (which are defined broadly in the D2M context as any event that results in the discontinuation of a drug). Patients with contraindications to 1 or several classes of b/tsDMARDs represent a particular group, which might be considered D2M despite the lack of formal evidence of b/tsDMARD failure. This means that this criterion may be fulfilled in a patient who failed 1 bDMARD and has contraindications to the use of others. When defining TR axSpA, which is a subgroup of D2M axSpA, evidence of treatment failure (at least 2 b/tsDMARDs belonging to different classes with proven efficacy in axSpA) and no discontinuation due to intolerability, side effects, or contraindications is required. This distinction is deemed necessary to differentiate between axSpA patients not responding to currently available treatment options and those who could have responded to the therapy but cannot receive it due to tolerability or safety issues.

2. Insufficient control of signs and symptoms of axSpA.

At least 1 of the following 4 indicators of insufficient control should be present: (i) high or very high disease activity according to the validated outcome measure ASDAS; (ii) presence of

active spondyloarthritis manifestations (musculoskeletal or extramusculoskeletal), including objective signs of inflammatory activity; (iii) rapid radiographic spinal progression, as defined by published data-driven criteria [15]; and (iv) other axSpA symptoms that are attributable to axSpA and cause a reduction in quality of life, even if points i to iv are not met. The criteria are broad and inclusive, aiming to capture the majority of clinical situations where axSpA might be considered insufficiently controlled. It is assumed that the mentioned signs and symptoms are present at, or are closely related temporally to, the time of the D2M status evaluation. The criterion of radiographic spinal progression specifically refers to the past 2 years. However, this must be contextualised with other parameters and the timing of treatment initiation since the effects of anti-inflammatory treatment, such as those shown for TNF inhibitors, typically become evident between years 2 and 4 of treatment [16]. There was significant discussion regarding the necessity of point iv. This point was retained in the final definition to ensure the inclusivity of the D2M definition, aiming to cover a broad range of clinical situations (eg, a patient with prominent fatigue or substantial functional limitations related to structural damage without significant pain or inflammatory activity). Although the mechanisms contributing may vary, inclusivity is vital for capturing these diverse scenarios. For defining TR disease, we propose that objective signs of inflammatory activity (elevated CRP that is attributable to axSpA and not to other causes, or active inflammation on MRI of sacroiliac joints or spine) be mandatory, in addition to the presence of high/very high disease activity according to ASDAS. Of note, patients experiencing rapid radiographic spinal progression would not be classified as TR if active inflammation is otherwise controlled. Radiographic progression in the spine can still be observed in the initial years following the introduction of effective anti-inflammatory treatment, often slowing over time [17]. Therefore, we do not classify patients with structural damage progression as TR if disease activity has been controlled by effective anti-inflammatory treatment, as there is a reasonable likelihood that progression will decelerate over time due to a time-shifted effect [16].

3. The present signs/symptoms are perceived as problematic by the rheumatologist and/or the patient.

This aspect is crucial as it brings together the physician's and patient's perspectives into the definition. It ensures that the evaluation of the D2M status is not merely based on formalised criteria relating to the number of previous treatment lines and composite outcome measures but also considers the global evaluation of the current situation in the context of the D2M concept. As mentioned above, in the broad and inclusive D2M definition, the opinion of the patient is as important as the opinion of the physician. No specific instruments are proposed to capture the perception of the disease as problematic from either the physician's or the patient's perspective.

What are the potential implications of the developed definition? We expect that it will stimulate research focusing on identifying reasons for D2M and would draw attention to D2M patients in daily clinical practice. We encourage investigators to prospectively collect information related to the elements of this definition in both interventional and observational studies on axSpA. The reasons for D2M may vary from setting to setting but most likely will belong to 1 of 2 main groups, which are important in both daily clinical practice and research contexts:

1. The true nonresponse to anti-inflammatory treatment resulted in a TR case. The exact frequency of this phenomenon, as well as the underlying mechanisms, warrant

investigation, including the generation of epidemiological data, exploration of pathophysiology, and conduction of interventional studies.

2. Signs and symptoms not caused by inflammation but rather by nonnociceptive pain mechanisms (ie, nociplastic or neuropathic pain), concurrent conditions (which might be present even if the diagnosis of axSpA is correct), and other factors—including but not limited to socio-psychological aspects, work, beliefs about the condition, and coping mechanisms—should be further investigated. The list is not exhaustive and should be defined in subsequent steps, as the relevance of these factors may vary across settings. This group of patients also requires further investigations, including identifying the underlying reasons and developing strategies incorporating a multidisciplinary approach to address various aspects of the D2M situation in clinical practice.

Importantly, the criteria presented above assume the correctness of the diagnosis and patient compliance with the prescribed treatment. These are relevant aspects to consider as the first steps when dealing with D2M axSpA patients and defining TR patients. In the next step of the D2M initiative, we plan to develop recommendations on how to approach D2M and TR patients.

Our work has several limitations, which should be acknowledged. First, the approach we used was based on expert and patient opinions rather than being data-driven. While this approach is certainly less rigorous than a data-driven approach (such as that used for classification criteria), we believe that, in the absence of unified definitions and terminology at the outset of the project, this was the only feasible way to progress. A unified definition was necessary as a starting point to stimulate research and develop management recommendations for this patient group. Second, the literature review was conducted as a scoping review rather than a systematic review. However, we believe this did not compromise the work, as the goal of the review was to provide a foundation for expert consensus rather than an exhaustive synthesis of evidence. As previously mentioned, evidence synthesis would not have been possible without a unified definition and nomenclature. Third, even within the expert organisation, there was some heterogeneity of views on certain aspects of the definition, as reflected in the results of the Delphi exercises. Nonetheless, through discussion and refinement, a broad consensus was achieved, with 89% of the members endorsing the final definition.

The D2M axSpA initiative aligns well with similar efforts in other inflammatory rheumatic conditions, such as RA (termed 'difficult-to-treat') [13] and psoriatic arthritis [18,19]. In these conditions, both rheumatologists and patients often encounter challenges in achieving complete control of disease signs and symptoms, even with state-of-the-art treatments. It is anticipated that common mechanisms, such as central sensitisation, along with disease-specific factors, contribute to the development of D2M/difficult-to-treat situations. This understanding likely extends to TR disease as well, thereby stimulating research into these mechanisms across different rheumatic diseases.

In conclusion, the ASAS D2M axSpA definition allows for clear identification of patients with unmet medical needs, indicating the way forward for improved clinical management and further research.

Competing interests

DP has received research support from AbbVie, Eli Lilly, MSD, Novartis, Pfizer, consulting fees from AbbVie, Biocad,

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Contributors

Members of the steering committee (DP, DvdH, VN-C, and XB) initiated and conducted the project, supervised the literature review, developed the surveys, and analysed their results. They also drafted the definition and the manuscript. MT conducted the literature review and supported the project's conduction and manuscript development. All authors contributed to the project's development, interpretation of survey results, drafting of the definition, and revising the manuscript for important intellectual content. All authors have approved the final version of the manuscript. DP acts as the guarantor author of this manuscript.

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Patient consent for publication

This project actively involved patients with axial spondyloarthritis (axSpA) throughout the study design, consensus-building process, and the development of the final definition of difficult-to-manage axSpA. Two patient representatives were included as coauthors and contributed significantly to all stages of the project.

Ethics approval

No ethics committee approval was required for this study.

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Supplementary materials

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REFERENCES

- [1] Sieper J, Poddubnyy D. Axial spondyloarthritis. *Lancet* 2017;390(10089):73–84.
- [2] Navarro-Compán V, Sepriano A, El-Zorkany B, van der Heijde D. Axial spondyloarthritis. *Ann Rheum Dis* 2021;80(12):1511–21.
- [3] van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27(4):361–8.
- [4] van der Heijde D, Molto A, Ramiro S, Braun J, Dougados M, van Gaalen FA, et al. Goodbye to the term ‘ankylosing spondylitis’, hello ‘axial spondyloarthritis’: time to embrace the ASAS-defined nomenclature. *Ann Rheum Dis* 2024;83(5):547–9.
- [5] Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis* 2023;82(1):19–34.
- [6] Smolen JS, Braun J, Dougados M, Emery P, Fitzgerald O, Helliwell P, et al. Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann Rheum Dis* 2014;73(1):6–16.
- [7] Machado PM, Landewé R, Heijde DV, Assessment of SpondyloArthritis international Society (ASAS). Ankylosing Spondylitis Disease Activity Score (ASDAS): 2018 update of the nomenclature for disease activity states. *Ann Rheum Dis*. 2018;77(10):1539–40.
- [8] Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. *Ann Rheum Dis* 2009;68(suppl 2) ii1–44.
- [9] Webers C, Ortolan A, Sepriano A, Falzon L, Baraliakos X, Landewé RBM, et al. Efficacy and safety of biological DMARDs: a systematic literature review informing the 2022 update of the ASAS-EULAR recommendations for the management of axial spondyloarthritis. *Ann Rheum Dis* 2023;82(1):130–41.
- [10] Al Mohamad F, Rios Rodriguez V, Haibel H, Protopopov M, Rademacher J, Sieper J, et al. Association of nociplastic and neuropathic pain components with the presence of residual symptoms in patients with axial spondyloarthritis receiving biological disease-modifying antirheumatic drugs. *RMD Open* 2024;10(1):e004009.
- [11] Kieskamp SC, Paap D, Carbo MJG, Wink F, Bos R, Bootsma H, et al. Central sensitization, illness perception and obesity should be considered when interpreting disease activity in axial spondyloarthritis. *Rheumatology (Oxford)* 2021;60(10):4476–85.
- [12] Kieskamp SC, Paap D, Carbo MJG, Wink F, Bos R, Bootsma H, et al. Central sensitization has major impact on quality of life in patients with axial spondyloarthritis. *Semin Arthritis Rheum* 2022;52:151933.
- [13] Nagy G, Roodenrijs NMT, Welsing PM, Kedves M, Hamar A, van der Goes MC, et al. EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2021;80(1):31–5.
- [14] Nagy G, Roodenrijs NMT, Welsing PM, Kedves M, Hamar A, van der Goes MC, et al. EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2022;81(1):20–33.
- [15] Baraliakos X, Listing J, von der Recke A, Braun J. The natural course of radiographic progression in ankylosing spondylitis—evidence for major individual variations in a large proportion of patients. *J Rheumatol* 2009;36(5):997–1002.
- [16] Torgutalp M, Rios Rodriguez V, Dilbaryan A, Proft F, Protopopov M, Verba M, et al. Treatment with tumour necrosis factor inhibitors is associated with a time-shifted retardation of radiographic spinal progression in patients with axial spondyloarthritis. *Ann Rheum Dis* 2022;81(9):1252–9.
- [17] Poddubnyy D, Sieper J. Mechanism of new bone formation in axial spondyloarthritis. *Curr Rheumatol Rep* 2017;19(9):55.
- [18] Marzo-Ortega H, Harrison SR, Nagy G, Machado PM, McGonagle DG, Aydin SZ, et al. Time to address the challenge of difficult to treat psoriatic arthritis: results from an international survey. *Ann Rheum Dis* 2024;83(3):403–4.
- [19] Ribeiro AL, Singla S, Chandran V, Chronis N, Liao W, Lindsay C, et al. Deciphering difficult-to-treat psoriatic arthritis (D2T-PsA): a GRAPPA perspective from an international survey of healthcare professionals. *Rheumatol Adv Pract* 2024;8(3):rkae074.