EDITORIAL

Clearing the fog: A closer look at the differences between axial psoriatic arthritis and axial spondyloarthritis

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Psoriatic arthritis (PsA) is a heterogeneous disease, with axial involvement presenting unique challenges that have led to the description of a subtype known as axial PsA (axPsA). Rheumatologists have long debated the relationship between axPsA and axial spondyloarthritis (axSpA), with some considering axPsA a subset of axSpA and others seeing it as a distinct condition. During the last years, it has been highlighted that a unifying definition for axPsA is needed. Thus, as we dive deeper into the intricacies of axial involvement in PsA, several key questions arise such as: *What is axPsA and why is it important to establish this subtype? Does axPsA possess unique characteristics that distinguish it as a separate entity from axSpA? What are the implications of having a clear and unifying definition for axPsA?* These questions will be tackled in this editorial as we aim to shed some light on the ongoing debate surrounding axial involvement in patients with PsA.

The definition of axPsA is still a matter of debate in the rheumatology community. Different criteria have been proposed to define axPsA, including definitions of a solely clinical phenotype with spinal pain, as well as others requiring the presence of sacroiliitis or spinal findings on imaging. However, a consensus on a universally accepted definition for axPsA has yet to be determined. As an example, clinical trials have used definitions for axPsA based on clinical reported axial involvement - as measured by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Visual Analog Scale (VAS)[1] - or investigator-confirmed sacroiliitis on imaging[2]. Post-hoc analyses of both ustekinumab and upadacitibib trials (PSUMMIT1-2, and SELECT-PsA1-2, respectively), defined axPsA as patients with PsA with clinician diagnosed spondylitis[3–5]. Similarly, the definitions of axPsA in cohort studies have been highly varied, ranging from the opinion of a treating rheumatologist to the strict requirement of changes in the radiographs of the sacroiliac joint (SIJ) fulfilling the modified New York criteria (mNYc)[6,7].

AxPsA presents a variety of demographic and clinical characteristics that can be analyzed by assessing real-world studies. Thus, a comprehensive understanding of the features of axPsA is better attained as we establish a comparison with the group of axSpA. A recent cohort study assessing both groups concluded that the presence of skin psoriasis is associated with a higher frequency of an axial disease pattern in patients with PsA[6]. A subsequent study found that patients with radiographic-axSpA (r-axSpA) presented to the clinic at an earlier age, had a higher male predominance, and were more likely to be HLA-B*27 positive, compared to axial PsA patients. Besides, they had more severe axial disease in terms of symptoms, disease activity scores, metrology, and radiology outcomes. Two studies in the last years based the classification of axPsA on the opinion of the rheumatologist[7,8]. Both studies yielded comparable conclusions, indicating that patients with axPsA were older and less likely to be male as compared to axSpA patients. Additionally, patients with axPsA were more likely to have peripheral manifestations and psoriasis, while patients with axSpA had more frequently extra-musculoskeletal manifestations such as inflammatory bowel disease and uveitis, and greater radiographic damage. Another recent study used a combination of axial symptoms and imaging findings to define axPsA[9]. Results were comparable to the previously mentioned studies, adding that comorbidities were comparable between axSpA and axPsA, except for depression which was more common in axPsA. Imaging and genetic studies have also provided valuable information to differentiate between the two diseases[10]. In axSpA, symmetrical sacroiliitis, classical symmetrical and marginal syndesmophytes, and fusion of lumbar facet joints are commonly seen; on the other hand, in axPsA less severe and asymmetrical sacroiliitis, less syndesmophytes in non-marginal locations and fusion of facet joints in cervical spine[10]. Concerning genetics, a high proportion of axSpA patients showed a higher frequency of HLA-B*27-positivity in different studies[6,8,11], while axPsA has been more frequently associated with HLA-B*08 and HLA-B*38; in this regard, less than half of axPsA patients have been reported to be HLA*B27-positive.

Assessing published literature, it can be understood that axSpA and axPsA are two distinct entities that have some similarities, but also many differences. The differences in the phenotype and genetics of axPsA as

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compared to axSpA may have implications in treatment response. For axSpA, non-steroidal anti-inflammatory drugs (NSAIDs), Tumoral Necrosis Factor (TNF) inhibitors, and IL-17 inhibitors are effective treatment options, while IL-23 inhibitors lack efficacy[12]. Nonetheless, besides a well efficacy profile in NSAIDs, TNFis and IL-17 inhibitors, IL-23 inhibitors (guselkumab) and IL-12-23 inhibitors (ustekinumab) have also shown efficacy in axPsA in post hoc analyses[5,13]. The DISCOVER-2 trial was a post-hoc exploratory analyses of guselkumab clinical trials[13]. The trial included patients with active PsA who had investigator-confirmed sacroiliitis on imaging, as determined by the local clinician's judgment, as well as other clinical and laboratory criteria, including at least 5 tender joints, and C-reactive protein (CRP) levels of at least 0.6 mg/dL. The results of the trial showed that patients receiving guselkumab had improvements in various measures of disease activity such as BASDAI, spinal pain, modified BASDAI and Ankylosing Spondylitis Disease Activity Score (ASDAS) compared to placebo. Additionally, a higher proportion of patients receiving guselkumab achieved responses in disease activity measures such as BASDAI50 and ASDAS compared to placebo. Two clinical trials of ustekinumab (PSUMMIT 1 and 2) also found that patients with axPsA who were treated with ustekinumab had significant improvements in their symptoms, including axial pain and inflammation, compared to patients who received a placebo[5]. Around 30% of patients in these trials had physician-reported spondylitis, and ustekinumab was found to improve symptoms of axial pain and inflammation at 24 weeks, measured by the BASDAI, regardless of whether patients had previously received TNF inhibitors. A subsequent post-hoc analysis of these trials involving PsA patients with peripheral arthritis and physician-reported spondylitis found that a greater number of patients treated with ustekinumab achieved BASDAI50 response, improvement in BASDAI question on axial pain, and ASDAS improvements as compared to placebo[5]. Comparable results have not been achieved in axSpA, where trials where discontinued due to primary outcome (ASAS40 and ASAS20)[14]. Nonetheless, it is worth noting that the studies of IL-23 inhibitors and IL-12/23 inhibitors are the result of post-hoc analysis of randomized trials based on patients with PsA having concomitant peripheral and axial involvement defined with different criteria that axial involvement in axSpA, but not conducted specifically to evaluate the effectiveness of the drug in axPsA[15]. The only study with this design has been the MAXIMIZE study, which evaluated the effectiveness of secukinumab in axPsA and involved patients with an inadequate response to NSAIDs. In this study, PsA was classified using the CASPAR criteria, and the study also required scores of at least 4 on the BASDAI and at least 40 on the VAS for spinal pain to be classified as axPsA, but no imaging criteria was used to define axial involvement of the disease[1]. This study found that 63.1% and 66.3% patients with axPsA who had an inadequate response to NSAIDs receiving secukinumab 300 mg and 150 mg respectively, achieved ASAS20 responses at week 12 compared to 31.3% receiving placebo. The study also found that reductions in Berlin Magnetic Resonance Imaging (MRI) scores evaluating bone marrow edema for the entire spine and sacroiliac joints of treatment versus placebo were statistically significant at week 12. Clinical response was maintained through week 52, at which 75.0% and 79.7% of patients receiving secukinumab 300 mg and 150 mg, respectively, achieved ASAS20. To support these findings, there is a need for further studies with appropriately designed protocols to address the question of the efficacy of other treatments in axPsA.

Current studies on axPsA have limitations, the most relevant being a lack of a standardized definition for the disease. Given the overlapping of axPsA and axSpA with psoriasis, it may be argued at this point: Is it relevant for clinical or research purposes to develop a definition of axPsA? There are several reasons why fitting together the puzzle pieces to create an accepted definition is critical for the management of axPsA. First, a broadly accepted definition of axPsA would help rheumatologists to accurately identify patients and distinguish it from other similar conditions, while it would facilitate collection of accurate data. In this regard, it would allow for more appropriate comparisons between studies, ensuring that all included patients have the same condition. This would eventually lead to treatment implications, helping clinicians to choose the most appropriate treatment option for each patient. Eventually, a definition of axPsA would enable rheumatologists, researchers and patients to communicate effectively about the condition. For these reasons, a multinational group including members from the Assessment of SpondyloArthritis international Society (ASAS) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), is working to develop a broadly accepted definition for axPsA in the AXIS study[16]. An evidence-based definition would improve the knowledge of the disease and contribute to homogenize of studies to gain insights in clinical features and treatment response. Besides, some new approaches to investigate axPsA are emerging. As an example, the STAR study will assess efficacy outcomes of guselkumab in patients with PsA with centrally assessed MRI-confirmed axial inflammation, with the primary endpoint being the change in the BASDAI at week 24[17]. Studies such as this one will increase the

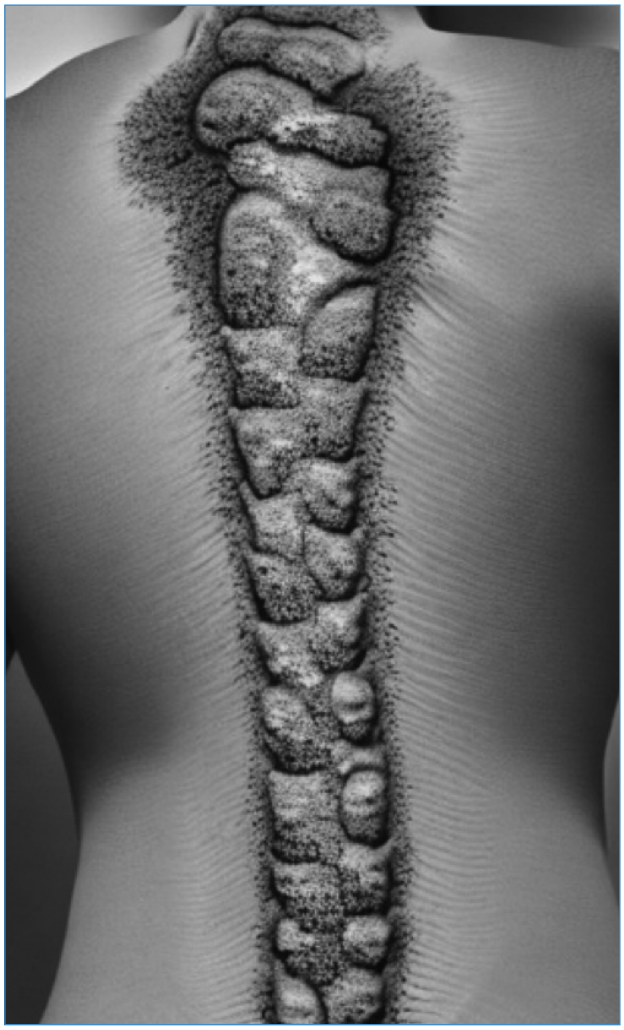

Figure 1. Psoriatic arthritis in the spine
The image was generated using a deep generative neural network called "Stable Diffusion" developed by the CompVis group at LMU Munich. This model is a type of latent diffusion model, which is a variation of generative adversarial networks. The Stable Diffusion model was trained on a large dataset of images and can generate new, synthetic images based on a low-dimensional latent space representation. The prompt "Psoriatic arthritis in the spine" was used to generate this image.

evidence on the treatment axial symptoms and inflammation in patients with active axPsA.

The subtlety of differentiating between axPsA, other phenotypes of PsA and axSpA is similar to trying to discern between strains of a virus; while all may potentially cause harm, the management and treatment may be different. The challenge at this point is to disentangle which are the levers to pull in each case. Despite the promising new therapies under development for the treatment of PsA, it is important to note that the most effective treatment plan for an individual patient with PsA should be tailored to their specific needs under a shared-decision strategy, considering their specific domains of disease, particularly the axial involvement. The advent of innovative research methods, such as leveraging large data sets and implementing artificial intelligence techniques, has the potential to provide a more comprehensive lens through which to examine diseases (Figure 1). These new methodologies of research can help us by improving our understanding of axPsA, specifically in identifying the subtleties of this phenotype, which may eventually lead to more effective treatment for the disease.

REFERENCES

1. Baraliakos X, Gossec L, Pournara E, Jeka S, Mera-Varela A, D'Angelo S, et al. Secukinumab in patients with psoriatic arthritis and axial manifestations: results from the double-blind, randomised, phase 3 MAXIMISE trial. Ann Rheum Dis [Internet]. 2021 May 1;80(5):582–90.
2. Mease PJ, Helliwell PS, Gladman DD, Poddubnyy D, Baraliakos X, Chakravarty SD, et al. Efficacy of guselkumab on axial involvement in patients with active psoriatic arthritis and sacroiliitis: a post-hoc analysis of the phase 3 DISCOVER-1 and DISCOVER-2 studies. Lancet Rheumatol. 2021 Oct 1;3(10):e715–23.
3. Mease PJ, Lertratanakul A, Anderson JK, Papp K, van den Bosch F, Tsuji S, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Ann Rheum Dis. 2021 Mar 1;80(3):312–20.
4. McInnes IB, Kato K, Magrey M, Merola JF, Kishimoto M, Haaland D, et al. Efficacy and Safety of Upadacitinib in Patients with Psoriatic Arthritis: 2-Year Results from the Phase 3 SELECT-PsA 1 Study. Rheumatol Ther [Internet]. 2022
5. Kavanaugh A, Puig L, Gottlieb AB, Ritchlin C, You Y, Li S, et al. Efficacy and safety of ustekinumab in psoriatic arthritis patients with peripheral arthritis and physician-reported spondylitis: post-hoc analyses from two phase III, multicentre, double-blind, placebo-controlled studies (PSUMMIT-1/PSUMMIT-2). Ann Rheum Dis [Internet]. 2016 Nov 1;75(11):1984–8.
6. Jadon DR, Sengupta R, Nightingale A, Lindsay M, Korendowych E, Robinson G, et al. Axial Disease in Psoriatic Arthritis study: Defining the clinical and radiographic phenotype of psoriatic spondyloarthritis. Ann Rheum Dis. 2017;76(4):701–7.
7. Michelena X, López-Medina C, Erra A, Juanola X, Font-Ugalde P, Collantes E, et al. Characterising the axial phenotype of psoriatic arthritis: a study comparing axial psoriatic arthritis and ankylosing spondylitis with psoriasis from the REGISPONSER registry. RMD Open [Internet]. 2022 Dec 1;8(2):e002513
8. Benavent D, Plasencia C, Poddubnyy D, Kishimoto M, Proft F, Sawada H, et al. Unveiling axial involvement in psoriatic arthritis: An ancillary analysis of the ASAS-perSpA study. Semin Arthritis Rheum [Internet]. 2021 Aug 1;51(4):766–74.
9. Fragoulis GE, Pappa M, Evangelatos G, Iliopoulos A, Sfikakis PP, Tektonidou MG. Axial psoriatic arthritis and ankylosing spondylitis: same or different? A real-world study with emphasis on comorbidities. Clin Exp Rheumatol [Internet]. 2022 Jul 1;40(7):1267–72.
10. Poddubnyy D, Jadon DR, van den Bosch F, Mease PJ, Gladman DD. Axial involvement in psoriatic arthritis: An update for rheumatologists. Semin Arthritis Rheum [Internet]. 2021 Aug ;51(4):880–7.
11. Benavent D, Plasencia-Rodríguez C, Franco-Gómez K, Nieto R, Monjo-Henry I, Peiteado D, et al. Axial spondyloarthritis and

axial psoriatic arthritis: similar or different disease spectrum? Ther Adv Musculoskelet Dis. 2020;12:1759720X20971889.
12. 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 Jan 1 ;82(1):19–34.
13. Mease PJ, Rahman P, Gottlieb AB, Kollmeier AP, Hsia EC, Xu XL, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet [Internet]. 2020 Apr ;395(10230):1126–36.
14. Deodhar A, Gensler LS, Sieper J, Clark M, Calderon C, Wang Y, et al. Three Multicenter, Randomized, Double-Blind, Placebo-Controlled Studies Evaluating the Efficacy and Safety of Ustekinumab in Axial Spondyloarthritis. Arthritis Rheumatol [Internet]. 2019 Feb 1;71(2):258–70.
15. Braun J, Landewé RB. No efficacy of anti-IL-23 therapy for axial spondyloarthritis in randomised controlled trials but in post-hoc analyses of psoriatic arthritis-related "physician-reported spondylitis"? Ann Rheum Dis [Internet]. 2022 Apr 1;81(4):466–8.
16. Poddubnyy D, Baraliakos X, van den Bosch F, Braun J, Coates LC, Chandran V, et al. Axial Involvement in Psoriatic Arthritis cohort (AXIS): the protocol of a joint project of the Assessment of SpondyloArthritis international Society (ASAS) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Ther Adv Musculoskelet Dis [Internet]. 2021 Dec 1;13.
17. Gladman DD, Mease PJ, Bird P, Soriano ER, Chakravarty SD, Shawi M, et al. Efficacy and safety of guselkumab in biologic-naïve patients with active axial psoriatic arthritis: study protocol for STAR, a phase 4, randomized, double-blinded, placebo-controlled trial. Trials [Internet]. 2022 Dec 1;23(1):1–14.