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EDITORIAL

Same, same or different? Commonalities and differences between spondyloarthritis and its subsets of axial and peripheral spondyloarthritis with psoriatic arthritis and its diverse phenotypes

Fabian Proft , Henriette Käding

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For numbered affiliations see end of article.

Correspondence to
Dr Fabian Proft;
Fabian.Proft@charite.de

Medicine is constantly changing and evolving, and rheumatology in particular is a specialty in which diseases that were unknown a few decades ago can now be correctly identified and successfully treated with targeted therapies. Furthermore, exactly these advances regularly confront us with the challenging decision of whether similar diseases should be rather 'lumped' together under one umbrella term to group them, or if they should be 'split' into smaller, differentiated, most specific subclasses. This remains a topic of ongoing discussion and debate, with valid arguments for both positions. Regarding spondyloarthritis (SpA), this debate has currently gained momentum again.

Under the umbrella term of SpA different diseases with similar clinical presentations—that can be divided according to the leading clinical symptom into axial spondyloarthritis (axSpA) and peripheral spondyloarthritis (perSpA)—are subsumed.[1] These entities can be further divided according to the radiographic evaluation of the sacroiliac joints into non-radiographic axSpA and radiographic axial SpA (r-axSpA, formerly known as ankylosing spondylitis (AS)) for axSpA. While the (sub-)group of perSpA can be further differentiated according to the clinical presentation and/or extramusculoskeletal manifestations of the SpA into psoriatic arthritis (PsA), reactive arthritis and inflammatory bowel disease-related SpA. It is utterly important to highlight, that between these phenotypes significant overlaps are commonly apparent.[2]

Additionally, the fact that first the clinical diagnosis (of SpA)—that is strongly influenced by the education from peers and local standards of care—needs to be established and only after that classification criteria for specific diseases (to create a as homogenise group of patients as possible) should be applied, is still important to mention. These classification criteria are widely accepted and used in clinical trials for axSpA (Assessment of SpondyloArthritis International Society (ASAS) criteria for axial SpA)[3] and PsA (ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria)[4] with significant overlaps of both criteria with those for perSpA,[5] meaning that a significant number of patients could fulfil both—or even all three—sets of those criteria at the same time.

DEBATE IF AXPSA AND AXSPA WITH CONCOMITANT PSORIASIS ARE THE SAME DISEASES BUT FROM DIFFERENT VIEWPOINTS OR DISTINCT CLINICAL AND PATHOPHYSIOLOGICAL ENTITIES

The current debate in this field is particularly concerned with the overlap between patients with PsA and axial involvement and axSpA with or without skin psoriasis, and whether axial PsA (axPsA) should be considered a separate entity or whether it is axSpA + PsO. In the historic context, it is important to mention, that already in the middle of the last century, Moll and Wright split off PsA, first as a distinct entity from rheumatoid arthritis and subsequently as a separate disease combining both different forms of arthritis/spondylitis with PsO, so that it was no longer considered the presence of two separated diseases coexisting side by side.[6] When digging into the literature, some differences in the clinical presentation were frequently described between axSpA and axPsA,[7 8] showing that inflammatory back pain was less frequent in

patients with axPsA than in patients with axSpA.[9] Another difference between both groups raised early on is the prevalence of HLA-B27 positivity, as it has been repeatedly shown that patients with PsA with axial involvement are less likely to be HLA-B27 positive than patients with axSpA + PsO.[7 8] Patients also differ in age at onset and gender. For example, patients with SpA are more likely to be male and younger at diagnosis.[8 9]

However, as TNF-alpha inhibitors (TNFi) and IL-17A inhibitors are mutually approved for both axSpA and PsA in general and also showed positive efficacy in a post-hoc analysis of a randomised controlled trial (RCT) in patients with PsA with back pain[10] or in observational cohorts,[11] no therapeutic consequences would have resulted from the distinction between these two entities. With the introduction of IL-23 inhibitors and the demonstration of efficacy for PsA,[12] but not for axSpA,[13 14] the question of a therapeutic consequence and thus a separation of the entities was raised yet again. However, post-hoc analyses of PsA trials—focusing on active peripheral arthritis (eg, at least three swollen joints mandatory for inclusion)—have now suggested that IL-12/IL-23 inhibitors[15 16] and IL-23 inhibitors[17] improved back pain symptoms thought to be caused by axial inflammation attributed to existing PsA.[15–17] This has led to a heated debate about the outcome measures employed and about how the patient group analysed in this post-hoc analysis was selected from the overall study population.[18–20] In a scientific exchange it was argued that based on the lack of efficacy in axSpA, this effect in axPsA is rather questionable and more likely due to non-specific effects that are not adequately captured by the tools (eg, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Axial Spondyloarthritis Disease Activity Score (ASDAS)) specifically developed and validated to assess inflammation in axSpA and not axPsA.[18] Furthermore, the debate about the selection of patients in these post-hoc analyses, which were either based solely on a 'check box' indicating physician-reported spondylitis with unclear criteria[15 16] or on the assessment of sacroiliitis on previous imaging or on pelvic radiographs performed at screening by the local investigator,[17] highlights the importance of a well-defined and widely accepted definition of axPsA.[21] A major step forward was made with the MAXIMISE study, the first RCT specifically in patients with axPsA. In this study, secukinumab showed a significant improvement according to ASAS2response compared with placebo for patients with PsA fulfilling the CASPAR criteria and the clinical diagnosis of an axial manifestation of their PsA according to the treating rheumatologist and active spinal disease—defined as a BASDAI score ≥4 and spinal pain score ≥40 by visual analogue score (0–100 mm scale)—and an insufficient response to non-steroidal anti-inflammatory drugs.[22] The fact that MRI of the axial skeleton was performed but not included as an entry criterion for the study needs to be discussed as a limitation of the study design. Two other RCTs are currently ongoing in this specific population of patients with axPsA, investigating the effect of guselkumab as an IL-23 inhibitor in the STAR trial[23] and of the Janus-kinase inhibitor tofacitinib in the PASTOR study.[24] Those results are eagerly awaited and expected for 2024/2025.

As emphasised above, clinical, genetic and radiographic differences have been thoroughly investigated,[7–9] whereas robust data are still lacking for both longitudinal observations of these two groups and for differences in MRI findings as an inflammation-sensitive imaging modality between axSpA and axPsA, making this a priority on the current research agenda. Notably, this is of great importance as axial involvement of PsA tends to be overestimated in clinical assessment and underestimated in radiographic imaging by conventional X-rays only.[25]

So from our point of view, the question of whether we should separate axPsA from axSpA is settled, but this now leads to other important questions:

1. How can we distinguish axPsA from axSpA? and
2. How is axPsA to be classified?

Striving for consensus on a single definition of axPsA

Given the status quo of no agreed definition of what axPsA is, how it should be diagnosed and exactly how it can be adequately classified, and the ongoing debate about phenotypes, entities and definitions, we would like to highlight the Axial Involvement in Psoriatic Arthritis cohort (AXIS) study.[21] In this collaborative effort, ASAS and Group for Research and Assessment of Psoriasis and Psoriasis Arthritis (GRAPPA)—as the leading international scientific societies with a focus on SpA and PsA—are striving for the 'holy grail' of the creation of data-driven classification criteria. This project will shed light on how axPsA manifest and how it can be distinguished from mechanical or degenerative causes of back pain in patients with PsA and also to give an idea how to separate it from axSpA. With the help of this prospective, international, multicentric study it should be possible to create a uniform definition and building classification criteria of axPsA in order to use a uniformly valid definition for upcoming observational studies but also randomised controlled treatment trials. Not only does the development of a definition play an important role for studies, but it can also support in driving the important topic of creating disease activity assessments specific to this entity.

Accordingly, in this edition of RMDopen the analysis of the prospective, cross-sectional data from the REGISPONSER registry are presented. REGISPONSER is a national, multicentre Spanish registry that included patients with SpA from 2004 to 2007 who met the criteria of the European Spondyloarthropathy Study Group. In this registry clinical, laboratory and imaging data were systematically collected.[26] In the current manuscript Michelena *et al* present the analysis of similarities and differences between patients with PsA with physician diagnosed axial involvement (=axPsA) and those with r-axSpA/AS and concomitant skin psoriasis (=r-axSpA + PsO).[27] As already explained above, the investigated topic is highly relevant and axPsA currently a 'hot topic' in SpA

research. This study adds to the literature confirming the clinical differences previously described. It is particularly noteworthy that the large sample size of patients included in the analysis and for whom complete sets of radiographs were available. Michelena *et al* showed that patients with r-axSpA + PsO were more likely to be male and to have a longer diagnostic delay, than patients with axPsA, who were more likely to have peripheral involvement and nail disease. Of particular interest is the authors' comparison of the axPsA and r-axSpA groups in terms of their HLA-B27 status, highlighting that HLA-B27 positive axPsA share similar clinical features to r-axSpA + PsO, although lower Bath Ankylosing Spondylitis Radiology Index (BASRI) scores.[27] When interpreting these results, it has to be taken into account that in the present analysis only a specific subgroup (r-axSpA) with the rather severe phenotype from the wider axSpA spectrum was compared with the whole group of axPsA.

Given the lack of a unified definition of axPsA, this work by Michelena *et al* contributes an important puzzle to the ongoing discussion and helps to better shape the 'Gestalt' of axPsA. Nevertheless, the sole use of conventional radiographs of the axial skeleton, which can only visualise chronic changes—indicating inflammatory activity in the past—and the current state of inflammation remains a blind spot, must be mentioned as a shortcoming of the presented results.

This highlights the current unmet needs in axPsA, which should drive the research agenda in the near future:

1. The requirement for a consensual and data-driven set of classification criteria for axPsA.
2. The need for data-driven definitions of MRI findings (active and structural changes) indicative of axPsA
3. Longitudinal cohort studies of axPsA taking 1 and 2 into account.
4. The necessity of a phenotype-specific disease activity score.

DIFFERENCES AND OVERLAPS BETWEEN PERSPA AND PSA SINE PSORIASIS

In the narrative review by Ziade *et al* in this edition of RMDopen, the authors discuss how similar or different perSpA is to PsA sine psoriasis and whether only semantic or also clinically important differences exist.[28] This illustrative review provides a delightful overview of various aspects regarding epidemiology, pathophysiology, classification criteria, therapeutic recommendations and different disease phenotypes and the associated burden of the diseases and thus touches on a very important clinical topic in the field of SpA.

Classification criteria for perSpA were published by ASAS in 2011.[5] However, only a small number of studies investigated the epidemiology and clinical characteristics of perSpA,[29 30] and—in contrast to PsA[31]—still no specific treatment recommendations for perSpA exist and even more important no advanced therapies are approved for the use in perSpA by the regulatory authorities. This gap still exists despite evidence of effectiveness for golimumab[32] or adalimumab[33] as TNFi. This means that patients with perSpA and no evidence of axial involvement or skin psoriasis (at least in the family history) or a PsA-like clinical pattern can only be treated off-label in clinical practice. As this place the treating rheumatologist in a delicate position and is a major barrier in the treatment of those patients, this remains one of the major unmet needs in SpA and potentially leads to 'alternative ways' of coding these patients as PsA sine psoriasis or even axSpA in order to have approved and effective treatment modalities at hand. This is important because the scenario described above could also lead to a selection bias in the literature discussed in the review by Ziade *et al* and must be taken into account in the interpretation of those data. Furthermore, it is also important to note that this could influence and even slow down the approval process of certain drugs, as the actual use of drugs for perSpA and the relevant unmet need is not accurately reflected. Therefore, the work of Ziade *et al* makes an important contribution to the topic of perSpA, again clarifying the difference to PsA sine psoriasis and also highlighting the remaining unmet need for the approval of effective treatment modalities for patients with perSpA, calling for dedicated RCTs in this indication, ultimately leading to the approval of advanced therapies for perSpA.

Provocatively, from our point of view, it should also be challenged whether it is really 'correct' to make a clinical diagnosis of PsA (namely *psoriatic* arthritis!) in a patient without psoriatic skin lesions and without psoriasis in first-degree or second-degree relatives. In our humble opinion, these patients would fall in the clinical category of perSpA and could also be classified as perSpA in accordance with the ASAS perSpA classification criteria.

In summary, the understanding of diseases is evolving, particularly in the field of rheumatology. The further differentiation of individual diseases into separate entities ('splitting') therefore brings benefits, but also challenges and, above all, tasks. In particular, widely accepted definitions need to be formulated and meaningful epidemiological studies and dedicated therapeutic trials—even for infrequent entities—need to be carried out to generate scientific knowledge and evidence to further improve (early and correct) diagnosis and the availability of effective treatment options.

The discussion about axPsA and how it overlaps and differs from the well-accepted axSpA phenotype, and the issue of perSpA as opposed to PsA sine psoriasis, is one of the hot topics now and will continue to occupy us in the forthcoming. We believe that in the future we will only be able to treat our patients in a more targeted way if we drive research into the most specific entities. This is why we are enthusiastically joining the team of 'splitters'!

Author affiliations
Department of Gastroenterology, Infectiology and Rheumatology (including Nutrition Medicine), Charite Universitatsmedizin Berlin, Berlin, Germany

Twitter Fabian Proft @ProftDr

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ORCID iD
Fabian Proft http://orcid.org/0000-0003-4306-033X

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