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EDITORIAL

Axial spondyloarthritis and psoriatic arthritis: mostly overlapping or substantially different diseases?

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The concept of spondyloarthritis (SpA) is clearly not new.[1] Ever since 1974, axial inflammation and psoriasis (Pso) with psoriatic arthritis (PsA) have been part of the concept,[2 3] except for the New York (NY) criteria for ankylosing spondylitis (AS) which have concentrated on axial disease.[4] Historically, the term axial SpA (axSpA) has led to the formation of two subgroups based on the presence or absence of structural changes in the sacroiliac joints, which provided the basis for a classification into radiographic (r)-axSpA and non-radiographic (nr)-axSpA.[5] Linked to drug approval processes, many biological disease-modifying antirheumatic drugs (bDMARDs) such as the tumour necrosis factor inhibitors have been approved for both subtypes. However, clinically, it does not make sense to stick to that differentiation[6] but rather consider a spectrum of disease because the cut-off between the two is not reliable,[7] and the severity of symptoms is rather similar between the two.[8]

While the concept of SpA unifies both axSpA and PsA, key differences between these diagnoses are clinically apparent: distal interphalangeal (DIP) joint involvement and dactylitis which rarely appear in axSpA without pso are considered hallmark signs of PsA. There are other potentially important differences between axSpA and PsA such as the age at onset (patients with axSpA are typically younger) and the sex ratio (favouring males in axSpA). While back pain, often but not always inflammatory back pain, is rather pathognomonic in axSpA, predominant peripheral symptoms are more common in PsA. While HLA B27 is clearly associated with axial disease, it is less common in PsA, even in those with documented axial involvement.[9 10] Classification criteria for axSpA[3] and PsA[11] are known to overlap, and axial symptoms are part of the PsA criteria—although present in a much lower frequency than in axSpA. There are also classification criteria for peripheral SpA,[12] which include arthritis and/or enthesitis and/or dactylitis plus pso or other parameters.

However, the discussion whether axial PsA (axPsA) is different from axSpA or AS with pso is long-standing, and there have been many approaches how to compare the two entities.[9 10 13–17] In addition, there are two international organisations active in this research area, Assessment of SpondyloArthritis international Society (ASAS) and Group in Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) which each clearly have a different focus: the former is rather concerned about axSpA and the latter about PsA and pso. However, both groups have recognised that the lack of a proper definition of axPsA is hampering research into pathogenesis, disease impact and treatment. Research to define prevalence, clinical features, impact, similarities and differences with other axSpA, and treatment is an unmet need.[18] Therefore, international experts from both the ASAS and GRAPPA groups have established a study aimed at an evidence-based definition for axPsA, the protocol has been recently published.[19]

What is the magnitude of the problem (of axial involvement in PsA)? In a very recent study with 1576 patients with PsA, only 2% had isolated axial disease with 29% reporting a combination of axial and peripheral disease, and HLA-B27 positivity was associated with isolated axial disease. The comparison with 1688 AS patients who were significantly younger showed that 5% had isolated axial disease with pso.[20] Thus, looking at PsA and axSpA as the main entities, the prevalence of pure axial disease in PsA and of AS with pso was relatively low.

There has been a long-standing discussion about 'lumping' or 'splitting' within the concept of SpA and this extends to the concept of axSpA and PsA. However, recent developments have brought some challenging intensity to the discussion which is based on the fact that bDMARD therapy with anti-IL 23 antibodies has been shown to work in PsA but not in axSpA.[21] Researchers have questioned whether there could be differential evidence of efficacy in subtypes of axSpA, in particular related to the presence of axial symptoms in patients with PsA.[21] Studies of IL-23 inhibitors in PsA have shown improvement in clinical measures of axial symptoms such as with the Bath ankylosing spondylitis (AS) disease activity index (BASDAI) but these are known to be non-specific to axial inflammation.[22] Therefore, these results have raised substantial concerns that this response would be rather seen due to improvements in PsA symptoms even if the drug was not effective in the axial skeleton. A randomised trial of IL-23 inhibition in PsA patients looking specifically at confirmed axial involvement with MRI is currently recruiting.[23]

However, what are the similarities in patients under suspicion of SpA with axial symptoms in nr-axSpA and PsA? Lets first look at the background situation in the population. First, back pain and even chronic back pain are so frequent in all age groups. Inflammatory back was reported to occur in 5%–6% of the US population.[24] The prevalence of HLA B27 is between 6% and 8% of the West European population and 2%–3% have pso. In addition, the frequency of degenerative spinal changes (in the asymptomatic population) exceeds 50% (28%) demonstrating a high 'background noise' found in radiographic findings in these patients. Similarly, the prevalence of MRI findings similar to axSpA was higher than 20% in a population-based study[25] being influenced by age, sex, HLA B27 and a history of pregnancy/delivery[26] Thus, we have a difficult background for diagnosis here, since symptoms and findings are rather prevalent in the general population. We do not repeat the discussion on radiographic axial findings in axSpA and axPsA here because the former specific features of the latter such as unilateral sacroiliitis and the syndesmophyte shape are not seen in the majority of patients and have recently not been confirmed.[9 10] It is interesting that there is no study comparing r-axSpA plus pso versus nr-axSpA plus pso to date. It could well be that there may be more similarities seen between nr-axSpA plus pso and axPsA but given the lack of specific classification criteria for axPsA, these patients are difficult to separate. In research studies, patients classified as nr-axSpA usually have the same degree of back pain and disease activity as those with r-axSpA while most comparative studies report less or even no clinical symptoms in patients considered to have axPsA.[9 10] However, these studies could possibly miss some mild cases of axSpA that may remain undiagnosed in the community.

In this issue of *RMD Open*, Regierer *et al* report results from a cohort study within RABBIT-SpA, the German SpA register.[27] The authors describe differences between axSpA plus pso and axPsA based on clinical findings similar to those cited above,[18] including age at onset, sex, peripheral symptoms and HLA-B27 positivity. The main problem in this approach, however, is that there is no accepted definition for axPsA at present. Patients recruited into the RABBIT-SpA registry are included by their treating physicians either as an axSpA or PsA case. This introduces a circular argument as the study automatically takes the rheumatologist's initial opinion as gold standard, where that clinician's classification is likely to be based on accepted features of PsA such as peripheral arthritis, dactylitis, sex and age and then reports results showing that there is a difference between the two groups based on these clinical features. However, this problem is present in most published analyses covering axPsA,[20 28] as there is no accepted definition of axPsA yet available.

In conclusion, the big question around potential differences between axSpA and axPsA seems to have risen in reaction to the surprising lack of efficacy of IL-23 inhibitors in axSpA. Even though patients who had all been included because of peripheral PsA have reported improvements in back pain and BASDAI scores with these drugs, this is clearly not specific and not convincing at all. Previous cohort studies have demonstrated similar BASDAI scores in PsA, correlated highly with patient global in those patients with and without axial involvement.[29 30] Each individual BASDAI question, including the question on spinal pain, shows similar disease activity and response after effective treatment in those with and without axial disease.[31] We do not believe that these data can ever support the use of IL-23 inhibitors in patients with axPsA given that these agents clearly not work in axSpA.[21]

Thus, coming from a clinical point of view, the existing status quo in most clinical studies in SpA seems favourable at the current time—if patients have back pain, active disease and fulfil the classification criteria for AS they can be included in r-axSpA studies[31]. Patients with PsA and predominant peripheral arthritis should of course be considered for PsA studies. Until further research provides any new alternative evidence-based definitions, our opinion is that patients with pso fulfilling NY criteria can be classified as r-axSpA plus pso and patients with no definite radiographic changes, depending on the clinically leading symptom, as either nr-axSpA plus pso or axPsA. For diagnosis, the rheumatologist should orientate towards the predominant clinical symptom, and if there is more than one domain of active disease, decide on a case-by-case basis on the optimal treatment for that individual.

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