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Updates on Axial Psoriatic Arthritis From the 2020 GRAPPA Annual Meeting

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ABSTRACT. This article summarizes sessions that dealt with axial psoriatic arthritis (axPsA) at the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2020 virtual meeting. The summary includes the symposium, which comprised a plenary presentation by Dr. Dafna Gladman from Toronto, Canada, as well as a panel discussion with Dr. Philip Helliwell, Dr. Denis Poddubnyy, and Dr. Gladman, moderated by Dr. Philip Mease. In addition, the paper also summarizes Dr. Mease's "Meet the Expert" session, which focused on axPsA.

Key Indexing Terms: GRAPPA, psoriasis, psoriatic arthritis

Clinical Characterization of Axial Psoriatic Arthritis

In her presentation on axial psoriatic arthritis (axPsA), Dr. Dafna Gladman reported on a number of observational studies that have attempted to characterize the genetic, clinical, and imaging characteristics of patients with axPsA. She reviewed how patients with axPsA differ from patients with PsA without axial involvement, and how patients with axial spondyloarthritis (axSpA) differ. A previous systematic review suggested that compared to ankylosing spondylitis (AS), patients with axPsA have a later age at onset, less inflammatory back pain, involvement of the spine without sacroiliitis, and a lower prevalence of HLA-B27.[1] All the studies quoted in the review were cross-sectional. The first study from Toronto in 1993 assessed clinical and radiographic features, as well as the genetics of 40 patients with AS and 66 patients with axPsA.[2] The study found a higher prevalence of inflammatory back pain (IBP), limitation of spinal mobility, grade 4 sacroiliitis, and syndesmophytes among the patients with AS compared to those with axPsA, and worse peripheral arthritis in patients with axPsA. HLA-B27 and HLA-Cw2 were higher and HLA-B17 was lower in patients with AS compared to those with PsA. A study from Leeds in 1998 compared radiographic features and outcome measures in 91 patients with AS, 14 patients with AS and psoriasis, 31 patients with AS and inflammatory bowel disease (IBD), and 7 patients with AS and reactive arthritis.[3] They reported higher asymmetry, as well as less severe changes and fewer distinctive syndesmophytes in patients with AS and psoriasis compared to patients with AS without concomitant disorders. The RESPONDA registry from Spain reported on 1072 patients with AS, 147 patients with PsA, and 45 patients with IBD-associated spondylitis in terms of demographic, clinical, and radiographic measures, as well as outcome measures. They found increased IBP and spinal limitation in patients with AS and increased dactylitis, enthesitis, and peripheral arthritis in patients with PsA; Bath AS Radiographic Index, Bath AS Disease Activity Index (BASDAI), Bath AS Metrology Index (BASMI), and quality of life scores were comparable in the 3 groups.[4] A study from the regional health register of southern Sweden reported in 2016 on 319 patients with AS, 409 patients with PsA, and 282 patients with other forms of SpA in terms of IBP, BASDAI, Bath AS Functional Index, and EQ-5D scores, and found that IBP was substantial in all 3 groups but highest in the AS group.[5] A study from Bath in 2017 compared clinical and radiographic features as well as genetics and outcomes measures in 157 patients with AS without psoriasis, 118 patients with axPsA, and 127 patients with peripheral arthritis.[6] The authors reported that 24% of the patients fulfilled the classification criteria for both AS and PsA. HLA-B27 was more common in patients with axPsA than in patients with peripheral PsA. Disease activity, metrology, and disability were similar in all 3 groups. Of interest, 33% of the patients with axPsA were diagnosed on the basis of syndesmophytes without sacroiliitis and these patients

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less frequently carried HLA-B27. The Psoriatic Arthritis Spinal Radiographic Index scores were worse in AS than in axPsA.

A recent study from the University of Toronto compared patients with AS, with and without psoriasis, to patients with PsA, with and without axial disease.[7] These patients were followed according to the same standardized protocol, which includes demographics, clinical features, laboratory tests, and radiographs with regular follow-up at 6- to 12-month intervals. Patients with PsA were older at diagnosis than patients with AS. There were 675 patients with AS, 477 patients with axPsA, and 91 patients with AS and psoriasis. Patients with AS were younger ($P < 0.001$) than patients with axPsA or AS and psoriasis. Patients with AS were more frequently male compared to patients with axPsA or AS and psoriasis (76%, 64%, 72%, respectively; $P < 0.001$), and more frequently HLA-B27–positive (82%, 19%, 75%, respectively; $P = 0.001$). Patients with AS had more back pain at presentation than the other groups (90%, 92%, 21%, respectively; $P = 0.001$). Over time, patients with AS also had higher BASDAI, BASMI, and physician global assessment scores; higher grades of sacroiliitis; and were more likely to be treated with biologics. Patients with AS with or without psoriasis were similar in demographic, clinical, and radiographic features. Multivariate analysis comparing patients with AS and psoriasis to patients with axPsA revealed higher prevalence of HLA-B27, higher BASMI, and higher grades of sacroiliitis in the AS group, and more active arthritis in axPsA. These differences were present at baseline and persisted over time. The authors concluded that patients with AS, with or without psoriasis, seem to be different demographically, genetically, clinically, and radiographically from patients with axPsA, and that axPsA may be a distinct entity.

Defining axPsA

Although these studies suggest that axPsA is different from AS, the definition of axPsA varies. In some studies, the requirement was the New York Criteria for AS; in others, either sacroiliitis, which could be unilateral grade 2, or syndesmophytes; and in others still, either the presence of IBP or radiographic features. Therefore, before the question can be fully answered, a clear definition of what is considered axPsA must be sought and agreed upon. To do that, a steering committee including members from the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and the Assessment of SpA international Society (ASAS) was convened, with the aim of designing a prospective study of patients with PsA not on biologic therapy with disease duration of < 10 years (the AXIS trial). All patients will undergo clinical assessment, imaging (including both radiographs and magnetic resonance imaging [MRI]), and HLA-B27 testing, and will provide blood samples for future biomarker studies. This study will likely start in early 2021.

Panel Discussion

Dr. Philip Mease moderated the panel discussion. He first introduced Dr. Denis Poddubnyy from Berlin, who provided information on the AXIS trial, which he is leading, together with Dr. Gladman from Toronto on behalf of the steering committee. In the past 6 months, together with Dr. Mease, treasurer of GRAPPA, and Dr. Filip Van den Bosch, treasurer of ASAS, funds were secured to embark on the study. Members of GRAPPA and ASAS will receive a feasibility questionnaire to determine eligibility for participation, and approximately 50 centers will be recruited. The study will be limited to patients naïve to biologic therapy, who are within 10 years of disease onset. Dr. Deepak Jadon questioned whether the time should be extended to 15 years since we know that in PsA, many patients develop axial involvement later. Dr. Puddubnyy clarified that these criteria were designed to assure that previous exposure to biologic therapy did not influence the course of disease and that patients who may be more likely to have age effects will not be included. Moreover, patients who have had the disease for more that 10 years and are not being treated with biologics or synthetic disease-modifying antirheumatic drugs may have milder disease and reflect a different population.

Dr. Philip Helliwell presented data from the DISCOVER studies, given at the European League Against Rheumatism, which demonstrated improved axial symptoms in subjects with radiographic sacroiliitis treated with guselkumab, an interleukin (IL)-23 inhibitor specific to the p19 molecule.[8] The question posed to him was whether there are differences between patients with AS and axPsA. He mentioned that there is clinical and radiological heterogeneity in the axPsA population, that there are genetic differences, as outlined in the previous presentation by Dr. Gladman, and that this heterogeneity may be underpinned by biological differences between the 2 conditions.

Dr. Gladman reported that one of her residents will be looking at patients with axPsA that are closer to AS than to other patients with axPsA. She hopes that there will be information within the next year. She also commented that the AXIS study will be most informative since it will include clinical assessments as well as imaging, including both radiographs and MRIs. Blood samples for biomarker analysis will be taken, which will hopefully shed light on any differences from AS. The *IL-23* gene is associated with both AS and PsA but it may not be the exact same single-nucleotide polymorphism.

Dr. Mease used a speculative approach in an editorial for *Arthritis & Rheumatology* using the SKG mouse model. When the mouse was stimulated with tumor necrosis factor (TNF), IL-17, or IL-23, there were differences in what happened in the heel of the mouse compared to the entheses of the spine, in which there was a completely different pathological process, suggesting that the immune cells may be different or there may be a different response to stimuli.[9] Dr. Gladman pointed out that even looking at the clinical measures of enthesitis, while the Mander and Maastricht emphasize spinal sites whereas the Spondyloarthritis Research Consortium of Canada and the Leeds Enthesitis Index are peripheral. The latter two were more reproducible in PsA, whereas the former two were more reproducible in patients with AS.[10] Nigil Haroon from Toronto had shown that macrophage inhibitory factor is related to disease progression in AS, whereas there is no such relationship in PsA.[11,12]

Could both diseases occur in the same person? There is a relationship between axial disease and PsA, which cannot be

explained by just the co-occurrence of 2 conditions. The differences outlined above in demographics, clinical features, imaging, and genetics suggest that these are distinct conditions.

Metabolic factors overlap with diffuse idiopathic skeletal hyperostosis (DISH) in the PsA cohort. Dr. Helliwell commented that diabetes and metabolic syndrome are more common in PsA, and DISH is common in these conditions, so one can certainly see that occurring in PsA.[13,14] Dr. Gladman reported on a study that was done at the University of Toronto in which the 8.3% of 946 patients that had DISH were more likely to have metabolic syndrome.[15]

There was a question regarding whether we should collect stool samples and send them to Jose Scher to define the microbiome in these patients. Although a good idea, it was thought not to be feasible in this study.

Sibel Aydin made the observation that ultrasound imaging in patients with PsA shows more proliferative-appearing bone than in patients with AS. Dr. Helliwell commented that bigger, bulkier syndesmophytes, as well as paravertebral ossification, are features of spinal disease in PsA, and this may reflect those changes seen peripherally.

Several people asked about the biomarkers that are to be assessed. Dr. Mease wondered whether we should be testing samples for a variety of genetic factors upfront. The AXIS study will collect blood samples for DNA and other biomarkers, and HLA-B27 will certainly be an important marker as it is both a severity and a phenotypic marker. Dr. Jadon commented that one can genotype on an Affymetrics platform and impute multiple HLA and non-HLA alleles.

Meet the Expert Session

In a separate "Meet the Expert" session within the GRAPPA annual meeting, Dr. Mease highlighted much of the same material that Dr. Gladman reviewed on the genetic, clinical, and imaging characteristics of axPsA as distinct from axSpA, and also reviewed data about treatment of axPsA. Historically, phase II and III trials of PsA treatments have not, in a detailed way, determined the effectiveness of drugs in the axial component of PsA. There are a number of reasons for this. In any given cohort of patients with PsA, those with an immunologic inflammatory axial component will likely only be a subset of the patient population, perhaps 40% or less, so the study will not be powered to determine a reliable treatment response in this subgroup. Lacking approved classification criteria for axPsA, there has not been agreement about which patients should be included in this subset to study. The added cost of baseline and serial spinal and sacroiliac radiograph and MRI scans, centrally read, to help define the group and assess response to treatment, would be significant, especially in light of the inadequate powering of the subset. Instead, the interested stakeholders—clinicians, pharmaceutical companies, regulators, and payers—have relied on data from axSpA/AS studies as a surrogate for the expected response of axPsA. For example, the axial domain of the GRAPPA treatment recommendations has been based solely on AS studies.[16]

In order to try to address this deficiency in "domain" analysis, numerous PsA treatment studies have incorporated the BASDAI measure and have analyzed it only in those patients who, in the investigator's judgment, have axPsA. However, the BASDAI was designed to assess spine disease severity and change with treatment in axSpA. Once it is used outside of that intended population, BASDAI has been shown to be nonspecific for spinal involvement since it measures items like peripheral arthritis, enthesitis, fatigue, and stiffness; further, it will be elevated and improve with treatment even in patients with no spine disease.[17] In an effort to address this deficiency, some studies have reported responses for both the overall BASDAI and question 2 of the BASDAI, which is specific for spine pain, as well as a modified version of the BASDAI that excludes the peripheral symptoms question. Two recent studies have gone further to provide a more "objective" basis aside from the BASDAI for identifying the presence of axPsA in cohorts of patients with PsA, and more specifically, for assessing axPsA treatment response.

The MAXIMISE trial is the first trial dedicated solely to ascertaining effectiveness of a treatment in patients with axPsA.[18] Two different doses of the IL-17A inhibitor secukinumab (150 mg and 300 mg) were tested against a placebo. Enrollment of the 498 subjects was based on investigator judgement that the patient had axPsA (not specifically defined), as well as elevated BASDAI and spine pain. MRI scans of the sacroiliac joints and spine, scored with the Berlin method to assess inflammation, were obtained but were not part of the inclusion criteria. At baseline, the patients were equigender, about 20% fulfilled AS criteria, about a third were HLA-B27–positive, and 60% had abnormal MRI scans of the spine and/or pelvis consistent with spondylitis, leaving 40% who did not have abnormal MRI scans at baseline. As anticipated, secukinumab was effective in treating axPsA symptoms, with over 60% achieving ASAS20 response at Week 12 in both secukinumab treatment arms compared to 31% in the placebo arm. These results were sustained and even improved up to 52 weeks. MRI inflammation scores improved significantly in both spine and sacroiliac joints in those with positive MRI scans. The degree of ASAS20/40 improvement in both the MRI-positive and the overall group was similar. This trial paves the way for future trials dedicated to axPsA, although questions remain about how best to define the study population, especially the subgroup that was MRI-negative; thus, the need for the AXIS study, described above, to develop classification criteria for axPsA.

A second recent study attempted to objectively define a subgroup of patients with axPsA in the pooled population of 2 phase III studies in PsA with the drug guselkumab, a p19/IL-23 inhibitor. The overall positive results of these 2 trials, DISCOVER-1, which enrolled 382 patients with PsA, 30% of whom had previously been treated with a TNF inhibitor, and DISCOVER-2, which enrolled 741 bionaïve patients with PsA, have been reported in *The Lancet*.[19,20] An exploratory substudy of patients pooled from both studies, with investigator-defined axPsA, radiographically defined sacroiliac joint abnormalities consistent with sacroiliitis, and elevated BASDAI and spine pain, was conducted and reported at 24 and 52 weeks.[8,21] Radiographs were read locally by a radiologist and/or investigator and confirmed by the investigator as being consistent with sacroiliitis. Approximately 30% of the subjects from each study were

included (n = 312). Radiographs from DISCOVER-1 patients were historical whereas in DISCOVER-2, they were obtained at baseline. Both guselkumab dose arms demonstrated significant improvements in spine pain, BASDAI, modified BASDAI (excluding the question on peripheral arthritis), BASDAI50, AS Disease Activity Score (ASDAS)-CRP, ASDAS clinically important and major improvement, and ASDAS inactive disease, regardless of HLA-B27 status, with sustained improvement through 52 weeks.[8,21] These results are encouraging because they suggest that symptomatic improvement occurred utilizing a p19/IL-23 inhibitor, whereas there has been doubt about the efficacy of this class of treatment in axSpA.[9] However, the results need to be considered tentative and exploratory given the limitations of the analysis. These limitations include potential unreliability of local rather than central (expert) radiographic reading (with consequent uncertainty about accurate inclusion of the patients as a true axPsA subset), lack of baseline and serial MRI scans of pelvis and spine, and the use of outcome measures that may be influenced by both peripheral (which all these patients had) and axial disease. If a future study of this or a similar p19/IL-23 inhibitor were to show efficacy in a trial dedicated to axPsA, it would illuminate the point that axPsA and axSpA are different entities and that we cannot automatically extrapolate from treatment response in one to the other.

Conclusion

AxPsA is heterogeneous and a proportion of patients appear to have axial disease distinct from axSpA. In addition to genetic, clinical, and imaging differences, axPsA may respond differently to treatment than axSpA. A classification schema will hopefully be defined through an international collaboration such that further studies on both the pathogenesis and treatment of the condition can be performed in a reliable manner. It is hoped that through the AXIS study, several issues regarding axPsA will be addressed and potentially resolved.

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