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Management of Axial Disease in Patients With Psoriatic Arthritis: An Updated Literature Review Informing the 2021 GRAPPA Treatment Recommendations

Ennio Lubrano[1], Jon Chan[2], Ruben Queiro-Silva[3], Alberto Cauli[4], Niti Goel[5], Denis Poddubnyy[6], Peter Nash[7], and Dafna D. Gladman[8]

ABSTRACT. ***Objective.*** Axial involvement in patients with psoriatic arthritis (PsA) is a common subset of this condition, but a unanimous definition has yet to be established. It has been defined by using different criteria, ranging from the presence of at least unilateral grade 2 sacroiliitis to those used for ankylosing spondylitis (AS), or simply the presence of inflammatory low back pain (IBP). Our aim was to identify and evaluate the efficacy of therapeutic interventions for treatment of axial disease in PsA.

Methods. This systematic review is an update of the axial PsA (axPsA) domain of the treatment recommendations project by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).

Results. The systematic review of the literature showed that new biologic and targeted synthetic disease-modifying antirheumatic drug classes, namely interleukin (IL)-17A and Janus kinase inhibitors, could be considered for the treatment of axPsA. This would be in addition to previously recommended treatments such as nonsteroidal antiinflammatory drugs, physiotherapy, simple analgesia, and tumor necrosis factor inhibitors. Conflicting evidence still remains regarding the use of IL-12/23 and IL-23 inhibitors.

Conclusion. Further studies are needed for a better understanding of the treatment of axPsA, as well as validated outcome measures.

Key Indexing Terms: axial disease, GRAPPA, psoriasis, psoriatic arthritis

In 2014, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) updated the axial psoriatic arthritis (axPsA) treatment recommendations.[1] In 2020, a steering committee for the axPsA subset of the treatment recommendations identified 4 topics for this update: (1) How do we define axPsA? (2) What should be used as an outcome measure in axPsA, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and/or the Ankylosing Spondylitis Disease Activity Score (ASDAS)? (3) What new information is available regarding the biologic and targeted synthetic disease-modifying drug (bDMARD and tsDMARD, respectively) therapies for axial spondyloarthritis (axSpA)? and (4) What new information is available regarding axPsA treatment? This current review addresses these topics.

METHODS

This systematic review is an update of one published with GRAPPA collaboration[1] in 2014 based on studies published from 2013 to 2020. Research

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[1]E. Lubrano, MD, PhD, Academic Rheumatology Unit, Department of Medicine and Health Sciences, University of Molise, Campobasso, Italy; [2]J. Chan, MD, Division of Rheumatology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; [3]R. Queiro-Silva, MD, PhD, Rheumatology Division, and ISPA Translational Immunology Division, Hospital Universitario Central de Asturias, Oviedo, Spain; [4]A. Cauli, MD, PhD, Rheumatology Unit, Department of Medicine and Public Health, AOU and University of Cagliari, Monserrato, Italy; [5]N. Goel, MD, Division of Rheumatology, Duke University School of Medicine, Durham, North Carolina, USA; [6]D. Poddubnyy, MD, PhD, Department of Gastroenterology, Infectious Diseases and Rheumatology, Charité – Universitätsmedizin Berlin and Epidemiology Unit, German Rheumatism Research Centre, Berlin, Germany; [7]P. Nash, MBBS, School of Medicine, Griffith University, Queensland, Australia; [8]D.D. Gladman, MD, University of Toronto, and Schroeder Arthritis Institute, Krembil Research Institute, Toronto Western Hospital, Toronto, Ontario, Canada.

Address correspondence to Dr. E. Lubrano, Academic Rheumatology Unit, Department of Medicine and Health Sciences, University of Molise, Campobasso, Italy. Email: enniolubrano@hotmail.com.

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methods are summarized in the Supplementary File (available with the online version of this article). PICO (Patient/Population – Intervention – Comparison/Comparator – Outcome) and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendations were adopted for this systematic review.[2] The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow chart was performed for the search strategy on PsA following the PICO questions raised for all 6 domains of PsA and recently published.[3]

Ethics. This paper does not require institutional review board/animal approval.

RESULTS

Definition of axPsA. The definition and assessment of axPsA remains controversial. The presence of spinal involvement was originally identified by Moll and Wright in 1973 in their seminal paper as one of the 5 subsets characterizing PsA.[4] Pure axial involvement occurs in approximately 5% of patients with PsA. However, axial involvement may be detected in up to 70% of patients with PsA who also have peripheral involvement/predominant features other than axial involvement.[5,6] There is an open debate on how to define this intriguing subset due to the broad spectrum of criteria used, ranging from the presence of at least unilateral grade 2 sacroiliitis, to those used for ankylosing spondylitis (AS),[7] or simply the presence of inflammatory low back pain (IBP).[8]

In the last few years, an increasing interest in axPsA has been noted in the literature. In 2018, a review compared the main clinical, radiographic, genetic, prognostic characteristics, and treatment options for axPsA to AS and found similarities and differences between the 2 conditions.[9] Feld et al concluded that HLA-B27 occurs less frequently in axPsA than in AS patients but is a genetic risk factor for both diseases.[9] AxPsA is less symptomatic and is associated with distinct radiographic features when compared to AS. The same authors conducted a retrospective analysis of prospectively collected data from 2 longitudinal cohorts: (1) AS with or without psoriasis and (2) PsA with or without axial involvement.[10] The results confirmed patients with AS, with or without psoriasis, were different demographically, genetically, clinically, and radiographically from patients with axPsA.[10] These data are in keeping with 2 other studies evaluating axPsA vs AS, which showed that axPsA seemed to be a distinct entity from classical AS.[11,12] Coates et al, along with an international collaboration, aimed to compare the radiographic phenotype of axial spondyloarthritis (axSpA) according to HLA-B27 status in a cross-sectional study.[11] This study also found fewer patients with axPsA had HLA-B27 present, but emphasized the importance of HLA-B27 status in the severity and the phenotypic expression of disease radiographically. Jadon et al also showed the pattern of axial disease was influenced significantly by the presence of skin psoriasis and HLA-B27.[12] Overall, these studies support the concept that axPsA seems to be a different condition when compared to AS.[13]

Outcome measures for axPsA. Currently, PsA-specific composite indices for assessing axial disease are not available, and specific axSpA instruments (ASDAS or BASDAI) have been used to monitor axPsA. However, it is worth noting the importance of monitoring axial symptoms, which usually overlap with those resulting from peripheral joint involvement. Although axial involvement is less frequent in PsA than in AS, such patients are more likely to have severe psoriasis, higher tender joint counts, worse physical function, and worse health-related quality of life (HRQOL).[14] In addition, axPsA may show some peculiarities not adequately represented in most axial composite measures (Table). In several studies, ASDAS has not been superior to BASDAI in its ability to discriminate between high and low disease activity states in axPsA.[15-17] On the other hand, when patients with PsA simultaneously present with axial and peripheral involvement, as determined by whether inflammatory spinal signs or symptoms were present at their first presentation to clinic, the instruments designed to evaluate the axial component do not discriminate well between both components.[18,19] Thus, in axPsA, BASDAI tends to correlate highly with patient perception of disease activity, but there is no significant effect of the pattern of disease (axial or peripheral) on this relationship.[18,19]

Recently, the MERECES study recommended the use of ASDAS plus the Psoriatic Arthritis Impact of the Disease (PsAID) questionnaire in those patients with prevalent axial involvement because it includes both objective and subjective measures.[20] Moreover, most MERECES participants considered that both composite indices were useful to evaluate the efficacy of bDMARDs in patients with peripheral involvement (89.6% for the Disease Activity for Psoriatic Arthritis [DAPSA] and 91.3% for the minimal disease activity indices) and 90.4% of the patients with axial involvement considered ASDAS useful. PsAID was considered as a useful patient-reported outcome measure to assess the effect of PsA on HRQOL in patients with both peripheral (83.5%) and axial (76.5%) involvement.[20] Queiro et al found a good clinimetric alignment between remission and a low impact of disease (PsAID ≤ 4) in patients with axPsA.[21]

In another recent Delphi exercise, aimed at defining remission and disease activity assessment in PsA, a panel of 77 rheumatologists reached agreement on 62 out of the 86 (72%) proposed items.[22] ASDAS was the preferred index for the assessment of axPsA, whereas BASDAI was accepted as an alternative.[22]

However, in the only randomized controlled trial (RCT) carried out to date specifically designed for axPsA, the instrument used by the authors was the BASDAI, and not the ASDAS.[23] In another recent RCT, a modified version of the BASDAI (excluding question 3 regarding peripheral involvement) was used to evaluate the effects of guselkumab on the axial component of PsA. Like other axial outcome measures, this modified version of the BASDAI showed good sensitivity to change.[24]

Update on bDMARD and tsDMARD therapies for axSpA. Several tsDMARDs have demonstrated efficacy for the treatment of axSpA in patients who have an inadequate response to nonsteroidal antiinflammatory drugs (NSAIDs). While it is still being debated as to whether patients with classic AS should be managed differently than those with nonradiographic axSpA (nr-axSpA), tumor necrosis factor inhibitors (TNFi) and interleukin (IL)-17A inhibitors have been approved for the treatment of both AS and nr-axSpA, as well as PsA.[25] Treatment recommendations for axPsA still are primarily extrapolated from

Table. Areas covered by the different tools to assess axial involvement in psoriatic arthritis.

	ASDAS-ESR	ASDAS-CRP	BASDAI	mBASDAI[a]
Back pain	+	+	+[b]	+[b]
Morning stiffness level	+	+	+	+
Morning stiffness duration	+	+	+	+
Patient global assessment	+	+	-	-
Peripheral pain/swelling	+	+	+	-
Fatigue	-	-	+	+
Neck/back/hip pain	-	-	+	+
Tender areas	-	-	+	+
ESR	+	-	-	-
CRP	-	+	-	-

[a] Excludes question 3, "How would you describe the overall level of pain/swelling in joints other than neck, back, hips you have had?" [b] Includes neck/back/hip. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; mBASDAI: modified Bath Ankylosing Spondylitis Disease Activity Index.

studies for the treatment of AS, axSpA, and nr-axSpA. There are increasing data available specifically for the treatment of axPsA as well, though these data vary in the underlying definition used to define axPsA.

· *TNFi.* TNFi were the first biologics approved for the treatment of axSpA and have been demonstrated to improve multiple measures including Assessment of SpondyloArthritis international Society (ASAS) response criteria (ASAS20/40), pain visual analog scale (VAS), BASDAI, ASDAS, Bath Ankylosing Spondylitis Functional Index (BASFI), high-sensitivity C-reactive protein (hsCRP), Ankylosing Spondylitis Quality of Life (ASQoL), ASAS Health Index (ASAS HI), and partial remission.[26,27] Phase III trials for each TNFi, with the exception of infliximab, have also demonstrated efficacy in patients with nr-axSpA,[26,27] especially in patients with bone marrow edema on magnetic resonance imaging (MRI) and/or elevated CRP.

There is some debate as to whether treatment with TNFi can slow the rate of radiographic progression, as measured by the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). Radiographs from patients treated with adalimumab, etanercept, and infliximab for 2 years were compared to those from a historic cohort and did not show any reduction in mSASSS progression.[28] Further studies comparing a longer duration of TNF therapy have used propensity matching and suggested radiographic progression may be inhibited after at least 4 years of therapy.[29,30] A placebo-controlled RCT demonstrating radiographic progression would be difficult to conduct given the length of treatment required; however, a definitive answer could possibly be obtained from future head-to-head studies between agents.

· *IL-17A inhibitors*. Two IL-17A inhibitors (secukinumab and ixekizumab) have been approved for the treatment of AS and nr-axSpA, and phase II trials for a third IL-17A (netakimab)[31] and a dual IL-17A and IL-17F inhibitor (bimekizumab)[32] have also been published. In each of the phase III clinical trials, patients who received IL-17A inhibitor therapy showed significantly greater improvements in ASAS20/40 response rates compared to placebo.

Among the 4 trials (2 trials of secukinumab and 2 of ixekizumab) focusing on the efficacy of IL-17A inhibitors in AS, 1153 patients received IL-17A inhibitor therapy (777 on secukinumab and 376 on ixekizumab) and 580 patients received a placebo (389 patients were used as comparators for secukinumab and 191 for ixekizumab).[33-36] Pooled analysis demonstrated that at week 16, the primary endpoint of ASAS20 response was significantly higher in patients treated with any dosage and type of IL-17A inhibitor (57.6%) compared to placebo (35.3%; relative risk [RR] 1.63, 95% CI 1.45-1.84, $P < 0.001$). Subgroup analysis suggested similar results for the comparison of both secukinumab (58.4%) vs placebo (35.7%; RR 1.64, 95% CI 1.41-1.89, $P < 0.001$) and ixekizumab (55.9%) vs placebo (34.6%; RR 1.63, 95% CI 1.31-2.01, $P < 0.001$; data not shown). Ixekizumab is the only biologic with an RCT to demonstrate efficacy in patients with AS who have inadequate response to a previous biologic.[37]

After IL-17A inhibitor treatment, the most frequent adverse events (AEs) reported were treatment-emergent AEs (57.2%, 660/1153 vs placebo 51.4%, 297/578; RR 1.11, 95% CI 1.01-1.22, $P = 0.03$) and nonsevere infections (27.4%, 211/770 vs placebo 15.0%, 58/384; RR 1.82, 95% CI 1.40-2.37, $P < 0.001$). The majority of infections were mild or moderate, with the most frequently reported being upper respiratory tract infections and nasopharyngitis. Taken together with respect to the safety profile, more treatment-emergent AEs (RR 1.11, 95% CI 1.01-1.22, $P = 0.03$) and nonsevere infections (RR 1.82, 95% CI 1.40-2.37, $P < 0.001$) were described after treatment with IL-17A inhibitors than after treatment with placebo, whereas no increased risk of death, discontinuation due to AEs, or serious AEs were seen with IL-17A inhibitor therapy (data not shown).

Treatment with IL-17A inhibitors demonstrated reduction in inflammation as measured by MRI using the Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging Index (SPARCC) sacroiliac and spine score system.

· *JAK inhibitors.* Three phase II and II/III studies[38-40] demonstrated efficacy of JAK inhibitors including tofacitinib, upadacitinib, and filgotinib for the treatment of active AS despite

treatment with NSAIDs. Improvements of multiple measures including ASAS20/40 response, pain VAS, BASDAI50, ASDAS, BASFI, and hsCRP, enthesitis, ASQoL, and ASAS HI were seen in these studies. JAK inhibitors are currently not approved for the treatment of axSpA and there have not been any studies looking at their efficacy in patients with nonradiographic disease. Data from the phase III study of tofacitinib for the treatment of AS were presented during the American College of Rheumatology 2020 annual meeting; however, these data have not been published at the time of submission of this manuscript.

Treatment with each JAK inhibitor demonstrated reduction in inflammation as measured by MRI using the SPARCC sacroiliac and spine scoring system. AEs seen in these studies were similar to what has been reported in previous studies for these drugs for other indications.

Treatments that are not effective for axSpA. Biologics that have been effective for the treatment of other rheumatic conditions such as rheumatoid arthritis and/or PsA have been studied in AS but were not found to be effective. The IL-23 inhibitor risankizumab did not show any clinically meaningful improvement compared with placebo in patients with active AS.[41] Three RCTs assessed the efficacy of ustekinumab in both radiographic axSpA and nr-axSpA[42] and this medication was also not found to be effective. Two IL-6 inhibitors sarilumab and tocilizumab[43,44] and the phosphodiesterase-4 (PDE-4) inhibitor apremilast[45] were also studied in patients with AS but did not meet their primary end points.

Finally, head-to-head studies between drugs are currently ongoing and may give some guidance regarding which classes of medication may be more effective. The evidence supporting the use of these medications is from randomized, double-blind, placebo-controlled trials and the risk of bias is felt to be low.

Updates on new treatments of axPsA. Ustekinumab is an anti-IL-12/23 monoclonal antibody with specificity for the p40-subunit shared by IL-12 and IL-23. It has been licensed by the US Food and Drug Administration and the European Medicines Agency for the treatment of skin psoriasis and PsA, but not for AS and nr-axSpA. In order to test ustekinumab efficacy in axPsA, a post hoc analysis of PSUMMIT-1 and 2 trials was conducted in > 200 patients with PsA with physician-reported spondylitis (all with severe peripheral arthritis). In this subset of patients, 54.8%, 29.3%, and 15.3% of patients treated with ustekinumab achieved BASDAI 20, 50, and 70 responses, respectively, vs 32.9%, 11.4%, and 0% of patients treated with placebo, respectively (as assessed at 24 weeks, $P \leq 0.002$).[46] However, the presence of spondylitis at baseline was based solely on the treating physician's assessment and did not require radiographic or imaging evidence.

· *Anti–IL-23.* Guselkumab is a monoclonal antibody that binds to the IL-23p19 subunit inhibiting signaling of IL-23. To evaluate the possible efficacy in the axial subset, a post hoc analysis of DISCOVER 1 and 2 was carried out in > 300 patients with PsA with peripheral joint and imaging-confirmed sacroiliitis (both in bio-naïve and bio-inadequate responders).[24] In patients treated with guselkumab, significant improvements compared to placebo from baseline to week 52 in BASDAI (−2.67 vs −1.35), spinal pain (BASDAI question 2, −2.73 vs −1.30), modified BASDAI (−2.16 vs −1.13), and ASDAS-CRP (1.43 vs −0.71) were reported. Further, most patients treated with guselkumab achieved higher level of improvements in axial scores compared to placebo at week 52: BASDAI 50 (40.5% vs 19.1%), ASDAS responses of inactive disease (17.4% vs 1.7%), major improvement (27.9% vs 8.7%), and clinically important improvement (53.5% vs 28.7%), all of which were statistically significant.[24]

· *Anti-IL-17A.* Secukinumab was evaluated for the management of axial manifestations of PsA, defined as active spinal disease with a BASDAI score ≥ 4, spinal pain score ≥ 40 by VAS (0-100 mm scale), and inadequate response to at least 2 NSAIDs over a 4-week period.[22] This phase IIIb, double-blind, placebo-controlled, multicenter 52-week trial showed that secukinumab 300 mg and 150 mg significantly improved ASAS20 response vs placebo at week 12 (63% and 66%, respectively, vs 31%).

Overall, secukinumab at dosages of 300 mg and 150 mg both provided significant improvement in signs and symptoms of axial disease compared with placebo in patients with PsA and axial manifestations with inadequate response to NSAIDs.[23]

Finally, a treatment difference in the group using secukinumab vs placebo was observed in the change from baseline in total Berlin MRI score for the entire spine at week 12 (−0.4 vs 0.1; secukinumab 300 mg; $P < 0.01$ and −0.4 vs 0.1; secukinumab 150 mg; $P < 0.05$). Similar treatment difference vs placebo was observed in change from baseline in total Berlin MRI score for the sacroiliac joints at week 12 (−0.5 vs 0.2; secukinumab 300 mg; $P < 0.01$ and 0.5 vs 0.2; secukinumab 150 mg; $P < 0.01$).

· *Ixekizumab.* Limited data is available on the effect of ixekizumab on axial manifestations of PsA. In a sub-analysis from the SPIRIT P1/2 trial, patients with PsA with self-reported axial pain starting before the age of 45 years showed significant improvement on ixekizumab compared to placebo in total BASDAI scores and BASDAI questions 2, 5, and 6 at weeks 16 and 24.[47]

· *Anti-JAK1.* JAK inhibitors are small molecules that target JAK family members (JAK1, JAK2, JAK3, and TYK2) and block intracellular cytokine pathways by inhibiting their heterodimer. Upadacitinib is a selective JAK1 inhibitor. In a published abstract of a post hoc analysis of SELECT PsA1 and 2, which considered about 400 PsA patients with physician-diagnosed axial involvement, upadacitinib (15 mg and 30 mg) resulted in significant greater clinical efficacy from baseline as measured by the overall BASDAI, BASDAI question 2 (neck/back/hip pain) and question 3 (joint swelling/pain), and ASDAS-CRP endpoints at weeks 12 and 24 compared to placebo.[48] Similarly, significantly higher percentages of patients on upadacitinib 15 mg and 30 mg achieved BASDAI 50, ASDAS inactive disease, ASDAS low disease activity, ASDAS major improvement, and ASDAS clinically important improvement at weeks 12 and 24 vs placebo.[48]

In conclusion, the present systematic review is an update of the axPsA section of the treatment recommendations by

GRAPPA previously published[1] in 2014. It confirms that axPsA could be considered a different entity from classical AS and in general, from axSpA. Based on the recent literature, NSAIDs, physiotherapy, simple analgesia, TNFis, IL-17 inhibitors, and JAK inhibitors are strongly recommended for the treatment of axPsA, while there is still insufficient evidence for the use of IL-12/23 and IL-23. However, the possibility to achieve a state of remission or low disease activity is now available for axPsA.[49] These recommendations are valid either for biologic-naïve patients, partially based on the axSpA literature, or for patients with an inadequate response to biologics, partially based on the AS literature. Further studies are needed for a better understanding of this intriguing subset, as well as validated outcome measures. Specific radiological indices have been developed for axPsA for the assessment of the spine such as the Psoriatic Arthritis Spondylitis Radiology Index,[50] but further studies are needed for the role of MRI. Indeed, further data coming from RCTs and real-world evidence studies will provide more insights for the best management of axPsA.

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ONLINE SUPPLEMENT

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