The Journal of Rheumatology 2022;xx:xxxx
doi:10.3899/jrheum.220312
First Release November 1 2022

The Journal of Rheumatology

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

Lihi Eder[1], Ashish J. Mathew[2], Philippe Carron[3], Heidi Bertheussen[4], Juan D. Cañete[5], May Azem[6], Andrea Delle Sedie[7], Carlo Salvarani[8], Roberto Ranza[9], Ashley Elliott[10], Anthony Turkiewicz[11], Ricardo Acayaba de Toledo[12], Hulya Bukulmez[13], Maria S. Stoenoiu[14], Arthur M. Mandelin II[15], Michaela Koehm[16], Chris A. Lindsay[17], Evan Siegel[18], and Philip J. Mease[19]

ABSTRACT. ***Objective.*** Enthesitis is a key pathological and clinical feature of psoriatic arthritis (PsA) in children and adults. Enthesitis is typically assessed clinically using several validated enthesitis scoring systems that have been used in clinical trials. Enthesitis treatment response has been reported as change in the total enthesitis score or the proportion of patients who achieved complete resolution. The majority of trials in PsA did not require patients to have enthesitis at study entry since enthesitis was evaluated only as a secondary outcome. Despite the inherent limitations of the clinical assessment of enthesitis, imaging of the entheses using ultrasound or magnetic resonance imaging has rarely been used in clinical trials to assess response to treatment of enthesitis. This systematic review summarizes existing evidence regarding pharmaceutical and nonpharmaceutical interventions for enthesitis in patients with PsA to facilitate an evidence-based update of the Group for Research and Assessment in Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations for PsA.

Methods. We performed a systematic literature review to identify 41 randomized clinical trials that reported enthesitis treatment response in patients with PsA. For each intervention, the response effect size was summarized and the quality of evidence was graded. Recommendations were then formulated for the various pharmacological and nonpharmacological therapies.

Results. We included 41 randomized clinical trials in our review and graded each intervention.

Conclusion. Several classes of systemic conventional and advanced therapies and local measures were recommended for active enthesitis in patients with PsA.

Key Indexing terms: GRAPPA, psoriasis, psoriatic arthritis

LE received educational and research grants and consulting fees from Janssen, AbbVie, Pfizer, Novartis, Eli Lily, UCB, and Sandoz. AJM received research grants from Ipca Laboratories and speaker fees from Novartis and Ipca Laboratories. PC received educational and research grants and consulting fees from Janssen, AbbVie, Novartis, Eli Lily, Sandoz, and Galapagos. H. Bertheussen received consulting fees from Pfizer. CS received consulting fees, research or institutional support, and educational grants from AbbVie, Lilly, Novartis, Pfizer, Roche, and MSD. RR has been a speaker and consultant for Pfizer, Novartis, Janssen, and AbbVie. AE received honoraria for speaking from Novartis and Lilly. AT received research grants from AbbVie, Lilly, Pfizer, Novartis, and Janssen, and consulting/advising/speaking honoraria from AbbVie, Lilly, Pfizer, Novartis, Janssen, UCB, and AstraZeneca. RAT received educational and research grants and consulting fees from Janssen, AbbVie, Pfizer, Novartis, UCB, and GSK. MSS received educational and research grants and consulting fees from AbbVie, Pfizer, Roche, and UCB. AMM is on the speakers' bureau for AbbVie, BMS, Lilly, Pfizer, and Sanofi-Genzyme/Regeneron, and is a consultant for CVS Caremark. MK received educational and research grants and consulting fees from Janssen, Pfizer, GSK, BMS, Amgen, Novartis, Eli Lilly, UCB, and AbbVie. CL has stock in Amgen, and is employed by Aurinia Pharma US, Inc. ES has received research grants, consulting fees, and/or speaker fees from AbbVie, BMS, Eli Lilly, Novartis, Janssen, and UCB. PJM has received research grants, consulting fees, and/or speaker fees from AbbVie, Amgen, BI, BMS, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Novartis, Pfizer, Sun, and UCB. The remaining authors declare no conflicts of interest relevant to this article.

[1]L. Eder, MD, PhD, Women's College Research Institute, University of Toronto, Toronto, Ontario, Canada; [2]A.J. Mathew, MBBS, DNB, DM, The Copenhagen Center for Arthritis Research (COPECARE), Center for Rheumatology and Spine Diseases, Rigshospitalet Glostrup, University of Copenhagen, Copenhagen, Denmark, and Department of Clinical Immunology and Rheumatology, Christian Medical College, Vellore, India; [3]P. Carron, MD, PhD, Department of Internal Medicine and Pediatrics, Ghent University, Ghent University Hospital, and VIB Center for Inflammation Research, Ghent, Belgium; [4]H. Bertheussen, Patient Research Partner, Oslo, Norway; [5]J.D. Cañete, DMD, PhD, Department of Rheumatology, Hospital Clinic and IDIBAPS, Barcelona, Spain; [6]M. Azem, MD, Solo Private Practice, and Department of Internal Medicine, Lake Hospital, University Hospital Systems, Cleveland, Ohio, USA; [7]A. Delle Sedie, MD, Rheumatology Unit, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; [8]C. Salvarani, MD, Dipartimento Specialità Mediche, Azienda Unità Sanitaria Locale-IRCCS di Reggio Emilia, Reggio Emilia and Dipartimento Chirurgico, Medico, Odontoiatrico e di Scienze Morfologiche con interesse Trapiantologico, Oncologico e di Medicina Rigenerativa, Università di Modena e Reggio Emilia, Modena, Italy; [9]R. Ranza, MD, PhD, Rheumatology Unit, Hospital de Clinicas, EBSERH, Universidade Federal de Uberlandia, Uberlandia, Minas Gerais, Brazil;

Enthesitis (inflammation of the etheses) is a key pathological and clinical hallmark of pediatric and adult psoriatic arthritis (PsA).[1] Clinically affecting at least 30% of patients,[2] enthesitis has been associated with higher levels of pain, reduced function and quality of life,[3] and radiographic joint damage.[4] Enthesitis is included in the inner core outcome set (as part of musculoskeletal disease activity) by the Group for Research and Assessment in Psoriasis and Psoriatic Arthritis (GRAPPA) and Outcome Measures in Rheumatology (OMERACT) to be assessed in all clinical trials in PsA.[5] To date, enthesitis has been evaluated only as a secondary outcome in the majority of clinical trials.

Several clinical enthesitis scoring systems have been used in clinical randomized controlled trials (RCTs) in PsA. The most used ones are the Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES; Figure). The LEI and SPARCC have been validated in PsA and have better discriminative ability and responsiveness in patients with peripheral spondyloarthritis than MASES,[6] and SPARCC demonstrated better discrimination and responsiveness than LEI in some clinical trials.[7-9] There is no consensus regarding the optimal enthesitis scoring system for RCTs, what represents a clinically meaningful change in enthesitis score, or what should be the treatment goal.

It is important to note the diagnosis of clinical enthesitis, which relies on eliciting tenderness by pressure at the entheseal site, may be influenced by subjective factors such as the level of pressure exerted by the examiner and pain amplification syndromes of the patient.[10] Further, significant discrepancies were noted between clinical and imaging detection of enthesitis,[11,12] highlighting inaccuracies associated with physical examination of the entheses. To date, imaging has rarely been used in RCTs to assess response to treatment of enthesitis. Two recent studies have used imaging to evaluate the effect of secukinumab (SEC) on enthesitis.[13,14]

This systematic review summarizes existing evidence regarding pharmaceutical and nonpharmaceutical interventions for clinically detected enthesitis in patients with PsA to facilitate an evidence-based update of the GRAPPA treatment recommendations for PsA. This review is an update of one published by the GRAPPA enthesitis working group in 2014.[15]

METHODS

A centralized systematic literature search and data extraction were conducted by GRAPPA for RCTs evaluating the efficacy of various interventions in PsA. A search was performed in MEDLINE, Embase and the Cochrane library from February 2013 to August 2020 for RCTs in patients with PsA. A total of 116 were screened and 55 studies underwent data extraction and assessment of risk of bias using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[16] In addition, abstracts were extracted from rheumatology conference archives. Standardized forms were used to extract study information and enthesitis outcomes.

Ethics. This paper does not require IRB/animal approval.

RESULTS

A total of 41 studies (39 full text publications and 2 abstracts) were included in this review. In the following sections, we review the updated evidence regarding the efficacy of pharmaceutical and nonpharmaceutical interventions for the management of active clinical enthesitis in PsA. Detailed information about the studies and their outcomes is summarized in Supplementary Tables S1 to S4 (available with the online version of this article).

Conventional synthetic disease-modifying antirheumatic drugs. No new studies have been published since the 2014 GRAPPA update on sulfasalazine (SSZ) and leflunomide (LEF) for enthesitis in PsA. The previous update reported a single negative study for SSZ vs placebo and no studies for LEF.[15] Limited information also exists about the efficacy of methotrexate (MTX). However, although no new comparative studies with placebo were found, information from a comparator arm of the Subjects with Psoriatic Arthritis (SEAM-PsA) trial supports a possible efficacy of MTX for enthesitis in PsA.[17] A total of 43.1% and 51% patients achieved complete resolution of enthesitis with MTX at 24 weeks and 48 weeks, respectively, which was similar to etanercept (ETN) combined with MTX, and inferior to ETN monotherapy only at 48 weeks. Although lack of a placebo comparator precludes reaching firm conclusions about MTX efficacy for enthesitis, the significant proportion of responders and the similar effect observed for ETN support the potential use of MTX for enthesitis in PsA.

Phosphodiesterase 4 inhibitors (PDE4i): Apremilast. The Assessing Apremilast Monotherapy in a Clinical Trial of Biologic-Naive Patients With Psoriatic Arthritis (ACTIVE) study showed a significant reduction in enthesitis scores with apremilast (APR) vs placebo.[17] An analysis of pooled results across the Psoriatic Arthritis Long-Term Assessment of Clinical Efficacy (PALACE) 1 to 3 studies showed a significant reduction

[10]A. Elliott, MB Bch BAO, MSc, MRCP, Centre for Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Belfast, UK; [11]A. Turkiewicz, MD, Rheumatology Associates, Birmingham, Alabama, USA; [12]R.A. de Toledo, MD, MSc, Regional School of Medicine Foundation of São José do Rio Preto, São José do Rio Preto, São Paulo, Brazil; [13]H. Bukulmez, MD, Department of Pediatrics, Division of Pediatric Rheumatology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio, USA; [14]M.S. Stoenoiu, MD, PhD, Department of Rheumatology, Cliniques Universitaires Saint-Luc, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, Brussels, Belgium; [15]A.M. Mandelin II, MD, PhD, Northwestern University, Department of Medicine, Feinberg School of Medicine, Chicago, Illinois, USA; [16]M. Koehm, MD, Rheumatology Division, University Hospital Frankfurt and Fraunhofer-Institute for Translational Medicine and Pharmacology ITMP, Frankfurt, Germany; [17]C.A. Lindsay, PharmD, GRAPPA Patient Research Partner, Aurinia Pharmaceuticals Inc., Rockville, Maryland, USA; [18]E. Siegel, MD, Arthritis and Rheumatism Associates, Rockville, Maryland, and Georgetown University School of Medicine, Washington, DC, USA; [19]P.J. Mease MD, MACR, Rheumatology Research, Swedish Medical Center/Providence St. Joseph Health and University of Washington School of Medicine, Seattle, Washington, USA.

Address correspondence to Dr. L. Eder, Women's College Research Institute, 76 Grenville Street, Toronto, Ontario, Canada, M5S 1B2.
Email: Lihi.EDER@wchospital.ca.

Accepted for publication August 5, 2022.

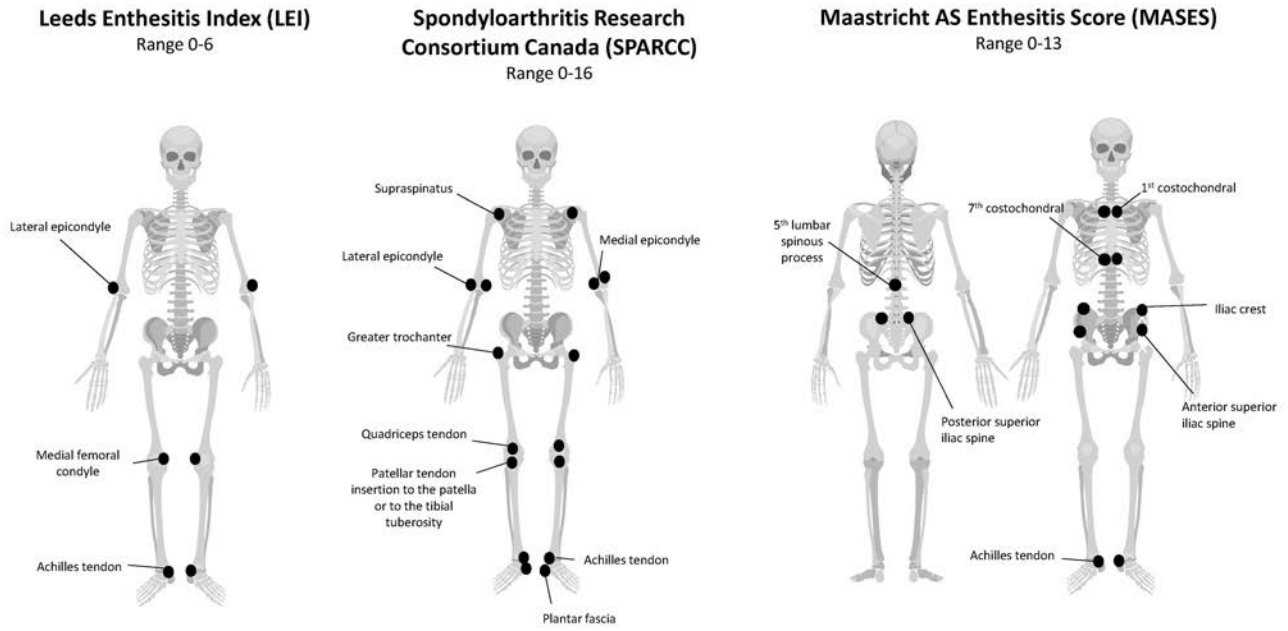

Figure. Commonly used enthesitis scoring systems in psoriatic arthritis clinical trials.

in enthesitis in the APR 30 mg group compared to placebo.[18] In the PALACE 4 study, significantly more patients achieved resolution of enthesitis with APR 30 mg BID vs placebo. No significant differences were observed between APR 20 mg and placebo with regard to enthesitis outcomes in any of the PALACE 1 to 4 studies.[19]

Janus kinase inhibitors (JAKi). In the Oral Psoriatic Arthritis Trial (OPAL) Beyond study, significantly more patients achieved complete resolution of enthesitis with tofacitinib (TOF; 5 mg BID) vs placebo.[20] OPAL Broaden did not find any significant differences in enthesitis score reduction or enthesitis resolution between TOF 5 mg and placebo. An improvement in enthesitis outcomes was found only for TOF 10 mg.[21] However, this dose has not been approved for treatment in PsA. The EQUATOR trial showed that filgotinib (200 mg daily) resulted in significantly greater reductions in enthesitis scores and enthesitis resolution vs placebo.[22] In both SELECT-PsA-1 and SELECT-PsA-2 trials, upadicitinib (15 mg and 30 mg daily) were more effective than placebo in achieving enthesitis resolution.[23,24] Deucravacitinib, a selective tyrosine kinase 2 inhibitor, was assessed in a phase II PsA trial (6 mg and 12 mg doses) vs placebo.[25] Rates of complete enthesitis resolution were significantly higher in both doses compared with placebo.

Tumor necrosis factor inhibitors (TNFi). No new studies have been published since the 2014 GRAPPA update on infliximab. The Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT) did not find a significant change in enthesitis scores between adalimumab (ADA) and placebo.[15] Data from the active control arm that included ADA from 2 trials allowed further evaluation of the efficacy of ADA vs placebo for enthesitis. The ADA arm in OPAL Broaden was superior to placebo in the resolution of enthesitis and reduction in LEI.[21] The ADA group in SPIRIT-P1 was numerically superior but not significantly different than placebo in the resolution of enthesitis and reduction in LEI.[26] Limited information about the efficacy of ETN for enthesitis was previously reported.[15] Although no randomized placebo-controlled data have been published, the SEAM-PsA study showed resolution of enthesitis in 66.3% and 62% with ETN monotherapy and ETN-MTX combination, respectively.[27] The high level of response to ETN demonstrated in the SEAM-PsA trial is consistent with a beneficial treatment effect. Golimumab (GOL) has been previously shown to be more effective than placebo for enthesitis.[15] In the Clinical Remission in Peripheral Spondyloarthritis (CRESPA) trial that enrolled patients with early peripheral spondyloarthritis (41.6% had PsA), subcutaneous GOL (50 mg every 4 weeks [Q4W]) was more effective than placebo in the resolution of enthesitis.[28] The GO-VIBRANT trial showed that treatment with intravenous GOL (2 mg/kg Q8W) was associated with significantly greater enthesitis improvement than placebo.[29] Certolizumab pegol (200 mg Q2W and 400 mg Q4W) was associated with a significantly greater reduction in LEI than placebo in the RAPID-PsA study.[30]

Interleukin (IL)-12/23 inhibitor. PSUMMIT 1 and PSUMMIT 2 trials showed treatment with ustekinumab (UST; 45 mg and 90 mg Q12W) was associated with less active enthesitis than placebo.[31,32]

IL-17 inhibitors. FUTURE 1 to 5 trials evaluated varying doses, routes, and modes of administration of SEC vs placebo in patients with active PsA. Overall, these studies showed favorable response of enthesitis to SEC vs placebo.[33,34] In the FUTURE 1 study, more patients in the combined SEC (75 mg and 150 mg Q4W) achieved resolution of enthesitis.[33] The FUTURE 2 study showed that more patients treated with SEC (75 mg, 150 mg, or 300 mg Q4W [combined]) achieved enthesitis resolution.[34] The FUTURE 3 study showed SEC administered by autoinjector

(150 mg or 300 mg Q4W) vs placebo, was associated with a higher proportion of enthesitis resolution.[35] In FUTURE 4, resolution of enthesitis was numerically higher with SEC (150 mg Q4W, with and without loading) vs placebo.[36] FUTURE 5 showed that resolution of enthesitis was significantly higher with SEC (150 mg and 300 mg with loading) vs placebo.[37] SPIRIT-P1 showed that ixekizumab (IXE; 80 mg Q2W and Q4W) resulted in significantly more resolution of enthesitis than placebo.[27] The reduction in LEI was numerically higher in the IXE arms, but only reached statistical significance for the 80 mg Q2W at 12 weeks but not at 24 weeks. In SPIRIT-P2, the proportion of patients achieving enthesitis resolution was not significantly different between either IXE Q4W or Q2W and placebo. Reduction in LEI was greater than placebo only for Q2W at 12 weeks but not at 24 weeks; the Q4W regimen was not significantly different than placebo.[38] Overall, for IXE 80 mg Q4W, which is the dose approved for PsA, only a single study showed efficacy in the resolution of enthesitis at 1 timepoint.[38] AMVISION-1 and -2, which evaluated the efficacy of brodalumab (BRO; 140 mg and 210 mg Q2W) for active PsA, were terminated early by the sponsor.[39] The pooled results showed that enthesitis resolution was achieved by a significantly higher proportion in both BRO groups vs placebo. Post hoc analysis showed that resolution of enthesitis was achieved by a greater proportion of patients using bimekizumab (160 mg and 320 mg) than placebo; however, significance testing was not performed.[40] Similarly, reduction in MASES was numerically higher for all the doses vs placebo.

IL-23 (p19 subunit) inhibitor. In a phase II trial of guselkumab (GUS; 100 mg Q8W) vs placebo, more patients achieved resolution of enthesitis with GUS.[39] A pooled analysis of DISCOVER-1 and DISCOVER-2 studies showed that patients using GUS (100 mg Q4W and Q8W) were more likely to achieve enthesitis resolution than placebo.[40] Improvements in LEI scores were also significantly higher with GUS administered Q4W.[40]

T cell modulation (cytotoxic T lymphocyte associated antigen-4 immunoglobulin [CTLA4-Ig]). In the Active Psoriatic Arthritis Randomized Trial (ASTREA) study, the proportion of patients in the abatacept (125 mg QW) group that achieved complete resolution of enthesitis was numerically higher, but not statistically different than the placebo group.[41]

IL-6 inhibitor. A phase IIb study that evaluated several doses of clazakizumab (CLAZ) vs placebo showed numerically greater reduction in enthesitis scores in the CLAZ groups, however these changes were not significantly different.[8]

Head-to-head studies: MTX vs TNFi. SEAM-PsA compared the efficacy of MTX oral monotherapy (up to 20 mg weekly) vs ETN (50 mg weekly) monotherapy or combined with MTX.[17] No significant differences in the complete resolution of enthesitis were found, and changes in SPARCC score were similar in both ETN containing arms and MTX monotherapy.[27] The smaller GO-DACT study that assessed GOL (50 mg Q4W) plus MTX vs MTX monotherapy did not find any differences between the groups in changes in enthesitis scores and in the proportion of complete enthesitis resolution. However, the study was likely underpowered to assess these outcomes.[42]

Head-to-head studies: IL-17Ai vs TNFi. Two head-to-head studies compared IL-17Ai and TNFi efficacy. The SPIRIT-H2H study compared IXE (80 mg Q4W) vs ADA (40 mg Q2W) in patients who were biologic-naïve.[9,45] Complete resolution of enthesitis by SPARCC (but not by LEI) was achieved by significantly more patients in the IXE vs ADA group.[9] The EXCEED study evaluated SEC (300 mg Q4W) vs ADA (40 mg Q2W) in patients with PsA. No significant difference was found between SEC and ADA in rates of complete resolution of enthesitis.[43]

Head-to-head studies: IL-12/23i vs TNFi. The only head-to-head study comparing the efficacy of IL-12/23 inhibition and tumor necrosis factor (TNF) inhibition was the Enthesial Clearance in Psoriatic Arthritis (ECLIPSA) study.[7] ECLIPSA is the first and unique study in which enthesitis response was the primary outcome (unlike other clinical trials) and all patients were required to have clinical enthesitis at study entry. This randomized open-label study compared UST vs a TNFi. The type of TNFi was selected based on patient preference. Significantly more patients achieved complete resolution of enthesitis with UST compared with a TNFi. The primary limitation of the study is that it was not blinded, which may have resulted in bias in the assessment of enthesitis.[7]

Tight control vs standard of care. The Tight Control of Psoriatic Arthritis (TICOPA) study evaluated the efficacy of tight control regimen vs standard of care in patients with active PsA who were naïve to disease-modifying antirheumatic drugs (DMARDs). The reduction in enthesitis score was numerically higher in the tight control group than the standard of care group; however no formal comparison was reported.[44]

Local corticosteroid injections. No information exists about the efficacy of local corticosteroid injections for enthesitis in PsA.[15]

Nonpharmacologic interventions. A study among patients with active PsA did not find a difference between polyunsaturated fatty acids (3 g daily) vs olive oil (3 g daily) in change in enthesitis scores.[45] In another study that assessed supervised, high-intensity interval training vs standard of care, no difference was found in SPARCC score change between the groups.[46]

Summary of the treatment recommendations. The GRAPPA treatment recommendations for the management of enthesitis in PsA were given for classes of medications rather than for individual drugs and are based on existing evidence from the literature and expert opinion. The recommendations were given after a structured process that is described in the main GRAPPA treatment recommendations.[47] Treatments with a strong recommendation for use included: TNFi, IL-17i, IL-12/23i, IL-23p19i, PDE4i, and JAKi. Treatments with a conditional recommendation for use included: MTX, nonsteroidal antiinflammatory drugs (NSAIDs), CTLA4-Ig, local corticosteroid injection (with extreme caution since injecting in weight-bearing entheseal sites can lead to the rupture of tendons), and physiotherapy. Other conventional synthetic DMARDs were not recommended because of a lack of evidence.

DISCUSSION

In this review, we summarized current evidence from 41 RCTs regarding the effectiveness of various pharmacologic and nonpharmacologic interventions for enthesitis in PsA and provided recommendations for the treatment of enthesitis in these patients.

Since the last GRAPPA update in 2014, 11 novel targeted medications belonging to 5 different classes of medications (inhibition of IL-17, IL-23, JAK, and IL-6 pathways and T cell modulation) have been evaluated in PsA and many of these medications are now approved for the treatment of PsA. In addition, older drugs have been included in trials as comparator groups, providing novel information about their efficacy for enthesitis. Another change since the previous update is the availability of data from head-to-head studies, which provide novel insights regarding the relative efficacy of different biologic therapies for the different PsA domains.

Overall, this review identified 6 classes of targeted DMARDs as effective treatment options for patients with PsA who present with active enthesitis, including PDE4i, TNFi, IL-17i, IL-12/23i, IL-23p19 inhibitors, and JAKi. Despite novel information about their comparative efficacy emerging from head-to-head studies, no clear and consistent superiority was found for any of the evaluated classes of medications over the others. Therefore, no prioritization was given for any class of medication that was strongly recommended for the management of enthesitis. However, the selection of medications should consider disease activity in other domains of PsA, particularly the skin and nail domains, where superiority of several classes has been demonstrated.[48] In addition, comorbidities, patient preferences, and cost could also influence the selection of medications for active enthesitis.

A conditional recommendation for use was given for MTX, which was not included in the recommendations in the previous guidelines because of a lack of evidence. Data emerging from SEAM-PsA suggest a potential efficacy of MTX that was similar to that observed in ETN.[27] MTX remains a first-line agent for many patients with PsA, required by many funding agencies to get access to advanced therapies, and it remains a mainstay treatment in many low-income countries. The use of NSAIDs, local corticosteroid injections, and physiotherapy have not been specifically investigated for enthesitis; however, these modes of treatment are commonly used as first-line therapies for active enthesitis. They provide relatively safe and affordable options, especially for localized enthesitis. Based on studies that assessed corticosteroid injections for tendinopathies (not limited to enthesitis) that found impaired tendon healing and decreased mechanical properties, caution is recommended when injecting corticosteroids in weight-bearing entheseal sites since it may lead to the rupture of tendons.[49] Additional research is needed regarding efficacy and safety of these commonly used treatment modalities for enthesitis.

Some limitations are notable when interpreting the existing data. First, all studies, apart from one, did not require patients to have enthesitis at study entry since enthesitis was evaluated only as a secondary outcome. Despite the fact most patients enrolled in these trials had clinical enthesitis (~60%), it is possible that some of the trials were underpowered to detect an effect. The ECLIPSA study was unique since it required patients to have enthesitis for inclusion and considered it as its primary outcome.[7] The study found that UST, targeting IL-23/12 pathways, was more effective than TNF blockade in patients with PsA. However, the open-label design of this study, as well as the small number of patients, precludes drawing firm conclusions about the comparative efficacy of these medications. Another limitation is the lack of agreement regarding the preferred tool to evaluate enthesitis in RCTs, which complicates the comparison of effectiveness across studies. Different studies used various entheseal scoring systems and treatment outcomes, and many studies only reported the proportion of resolution of enthesitis without reporting the extent of change in enthesitis score. Further, it remains unclear what is the clinically meaningful change in enthesitis score. Last, none of the studies included in this review used imaging modalities of the enthesis for patient selection or for evaluation of treatment efficacy. Given the inherent limitation in assessing clinical enthesitis, further research is needed to assess the utility of imaging of the entheses in clinical trials.

In summary, this systematic review summarizes existing evidence regarding pharmaceutical and nonpharmaceutical interventions for enthesitis in patients with PsA to inform the evidence-based update of the GRAPPA treatment recommendations for PsA. Several classes of systemic conventional and advanced therapies and local measures were recommended for active enthesitis in patients with PsA.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

REFERENCES

1. Schett G, Lories RJ, D'Agostino MA, et al. Enthesitis: from pathophysiology to treatment. Nat Rev Rheumatol 2017;13:731-41.
2. Polachek A, Li S, Chandran V, Gladman DD. Clinical enthesitis in a prospective longitudinal psoriatic arthritis cohort: incidence, prevalence, characteristics, and outcome. Arthritis Care Res 2017;69:1685-91.
3. Mease PJ, Karki C, Palmer JB, et al. Clinical characteristics, disease activity, and patient-reported outcomes in psoriatic arthritis patients with dactylitis or enthesitis: results from the Corrona Psoriatic Arthritis/Spondyloarthritis Registry. Arthritis Care Res 2017;69:1692-9.
4. Polachek A, Cook R, Chandran V, Gladman DD, Eder L. The association between sonographic enthesitis and radiographic damage in psoriatic arthritis. Arthritis Res Ther 2017;19:189.
5. Orbai AM, de Wit M, Mease P, et al. International patient and physician consensus on a psoriatic arthritis core outcome set for clinical trials. Ann Rheum Dis 2017;76:673-80.
6. Mease PJ, Van den Bosch F, Sieper J, et al. Performance of 3 enthesitis indices in patients with peripheral spondyloarthritis during treatment with adalimumab. J Rheumatol 2017;44:599-608.
7. Araujo EG, Englbrecht M, Hoepken S, et al. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: results from the enthesial clearance in psoriatic arthritis (ECLIPSA) study. Semin Arthritis Rheum 2019;48:632-7.
8. Mease P, Gottlieb A, Berman A, et al. The efficacy and safety of clazakizumab, an anti-interleukin-6 monoclonal antibody, in a

phase IIb study of adults with active psoriatic arthritis. Arthritis Rheumatol 2016;68:2163-73.
9. Mease PJ, Smolen JS, Behrens F, et al. A head-to-head comparison of the efficacy and safety of ixekizumab and adalimumab in biological-naïve patients with active psoriatic arthritis: 24-week results of a randomised, open-label, blinded-assessor trial. Ann Rheum Dis 2020;79:123-31.
10. Højgaard P, Ellegaard K, Nielsen SM, et al. Pain mechanisms and ultrasonic inflammatory activity as prognostic factors in patients with psoriatic arthritis: a prospective cohort study. Arthritis Care Res 2019;71:798-810.
11. Michelsen B, Diamantopoulos AP, Soldal DM, Hammer HB, Kavanaugh A, Haugeberg G. Achilles enthesitis defined by ultrasound is not associated with clinical enthesitis in patients with psoriatic arthritis. RMD Open 2017;3:e000486.
12. Husic R, Gretler J, Felber A, et al. Disparity between ultrasound and clinical findings in psoriatic arthritis. Ann Rheum Dis 2014;73:1529-36.
13. D'Agostino M, Schett G, López-Rdz A, et al. Secukinumab significantly decreased joint synovitis measured by power doppler ultrasonography in biologic-naïve patients with active psoriatic arthritis: primary (12-week) results from a randomized, placebo-controlled phase III study [abstract]. Arthritis Rheumatol 2020;72 (suppl 10).
14. Behrens F, Sewerin P, De Miguel E, et al. Efficacy and safety of secukinumab in patients with spondyloarthritis and enthesitis at the achilles tendon: 52-weeks results from a randomized, placebo-controlled phase 3b trial [abstract]. Arthritis Rheumatol 2020;72 (suppl 10).
15. Orbai AM, Weitz J, Siegel EL, et al. Systematic review of treatment effectiveness and outcome measures for enthesitis in psoriatic arthritis. J Rheumatol 2014;41:2290-4.
16. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-6.
17. Nash P, Ohson K, Walsh J, et al. Early and sustained efficacy with apremilast monotherapy in biological-naïve patients with psoriatic arthritis: a phase IIIB, randomised controlled trial (ACTIVE). Ann Rheum Dis 2018;77:690-8.
18. Gladman DD, Kavanaugh A, Gómez-Reino JJ, et al. Therapeutic benefit of apremilast on enthesitis and dactylitis in patients with psoriatic arthritis: a pooled analysis of the PALACE 1-3 studies. RMD Open 2018;4:e000669.
19. Wells AF, Edwards CJ, Kivitz AJ, et al. Apremilast monotherapy in DMARD-naive psoriatic arthritis patients: results of the randomized, placebo-controlled PALACE 4 trial. Rheumatology 2018;57:1253-63.
20. Gladman D, Rigby W, Azevedo VF, et al. Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. N Engl J Med 2017;377:1525-36.
21. Mease P, Hall S, FitzGerald O, et al. Tofacitinib or adalimumab versus placebo for psoriatic arthritis. N Engl J Med 2017; 377:1537-50.
22. Mease P, Coates LC, Helliwell PS, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. Lancet 2018;392:2367-77.
23. McInnes I, Anderson J, Magrey M, et al. Efficacy and safety of upadacitinib versus placebo and adalimumab in patients with active psoriatic arthritis and inadequate response to non-biologic disease-modifying anti-rheumatic drugs (SELECT-PsA1): a double blind, randomized controlled phase 3 trial. Ann Rheum Dis 2020;79:16-7.
24. Mease PJ, Lertratanakul A, Anderson JK, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Ann Rheum Dis 2021;80:312-20.
25. Mease P, Deodhar A, van der Heijde D, et al. Efficacy and safety of deucravacitinib (BMS-986165), an oral, selective tyrosine kinase 2 inhibitor, in patients with active psoriatic arthritis: results from a phase 2, randomized, double-blind, placebo-controlled trial [abstract]. Arthritis Rheumatol 2020;72 (suppl 10).
26. Mease PJ, van der Heijde D, Ritchlin CT, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017;76:79-87.
27. Mease PJ, Gladman DD, Collier DH, et al. Etanercept and methotrexate as monotherapy or in combination for psoriatic arthritis: primary results from a randomized, controlled phase III trial. Arthritis Rheumatol 2019;71:1112-24.
28. Carron P, Varkas G, Cypers H, et al. Anti-TNF-induced remission in very early peripheral spondyloarthritis: the CRESPA study. Ann Rheum Dis 2017;76:1389-95.
29. Kavanaugh A, Husni ME, Harrison DD, et al. Safety and efficacy of intravenous golimumab in patients with active psoriatic arthritis: results through week twenty-four of the GO-VIBRANT Study. Arthritis Rheumatol 2017;69:2151-61.
30. Mease PJ, Fleischmann R, Deodhar AA, et al. Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). Ann Rheum Dis 2014;73:48-55.
31. McInnes IB, Kavanaugh A, Gottlieb AB, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet 2013;382:780-9.
32. Ritchlin C, Rahman P, Kavanaugh A, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis 2014;73:990-9.
33. Mease PJ, McInnes IB, Kirkham B, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med 2015;373:1329-39.
34. McInnes IB, Mease PJ, Kirkham B, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;386:1137-46.
35. Nash P, Mease PJ, McInnes IB, et al. Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3). Arthritis Res Ther 2018;20:47.
36. Kivitz AJ, Nash P, Tahir H, et al. Efficacy and safety of subcutaneous secukinumab 150 mg with or without loading regimen in psoriatic arthritis: results from the FUTURE 4 study. Rheumatol Ther 2019;6:393-407.
37. Mease P, van der Heijde D, Landewé R, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. Ann Rheum Dis 2018;77:890-7.
38. Nash P, Kirkham B, Okada M, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet 2017;389:2317-27.

39. Deodhar A, Gottlieb AB, Boehncke WH, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet 2018;391:2213-24.
40. Mease PJ, Rahman P, Gottlieb AB, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1126-36.
41. Mease PJ, Gottlieb AB, van der Heijde D, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. Ann Rheum Dis 2017;76:1550-8.
42. Vieira-Sousa E, Alves P, Rodrigues AM, et al. GO-DACT: a phase 3b randomised, double-blind, placebo-controlled trial of GOlimumab plus methotrexate (MTX) versus placebo plus MTX in improving DACTylitis in MTX-naive patients with psoriatic arthritis. Ann Rheum Dis 2020;79:490-8.
43. McInnes IB, Behrens F, Mease PJ, et al. Secukinumab versus adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet 2020;395:1496-505.
44. Coates LC, Moverley AR, McParland L, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet 2015;386:2489-98.
45. Kristensen S, Schmidt EB, Schlemmer A, Rasmussen C, Johansen MB, Christensen JH. Beneficial effect of n-3 polyunsaturated fatty acids on inflammation and analgesic use in psoriatic arthritis: a randomized, double blind, placebo-controlled trial. Scand J Rheumatol 2018;47:27-36.
46. Thomsen RS, Nilsen TIL, Haugeberg G, Bye A, Kavanaugh A, Hoff M. Impact of high-intensity interval training on disease activity and disease in patients with psoriatic arthritis: a randomized controlled trial. Arthritis Care Res 2019;71:530-7.
47. Coates LC, Soriano ER, Corp N, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nat Rev Rheumatol 2022;18:465-79.
48. Armstrong AW, Soliman AM, Betts KA, et al. Comparative efficacy and relative ranking of biologics and oral therapies for moderate-to-severe plaque psoriasis: a network meta-analysis. Dermatol Ther 2021;11:885-905.
49. Dean BJ, Lostis E, Oakley T, et al. The risks and benefits of glucocorticoid treatment for tendinopathy: a systematic review of the effects of local glucocorticoid on tendon. Semin Arthritis Rheum 2014;43:570-6.