


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

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**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

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Enthesitis (inflammation of the entheses) is a key pathological and clinical hallmark of pediatric and adult psoriatic arthritis (PsA).<sup>1</sup> Clinically affecting at least 30% of patients,<sup>2</sup> enthesitis has been associated with higher levels of pain, reduced function and quality of life,<sup>3</sup> and radiographic joint damage.<sup>4</sup> 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.<sup>5</sup> 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,<sup>6</sup> and SPARCC demonstrated better discrimination and responsiveness than LEI in some clinical trials.<sup>7-9</sup> 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 enthesal site, may be influenced by subjective factors such as the level of pressure exerted by the examiner and pain amplification syndromes of the patient.<sup>10</sup> Further, significant discrepancies were noted between clinical and imaging detection of enthesitis,<sup>11,12</sup> 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.<sup>13,14</sup>

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.<sup>15</sup>

## 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.<sup>16</sup> 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.<sup>15</sup> 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.<sup>17</sup> 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.<sup>17</sup> An analysis of pooled results across the Psoriatic Arthritis Long-Term Assessment of Clinical Efficacy (PALACE) 1 to 3 studies showed a significant reduction

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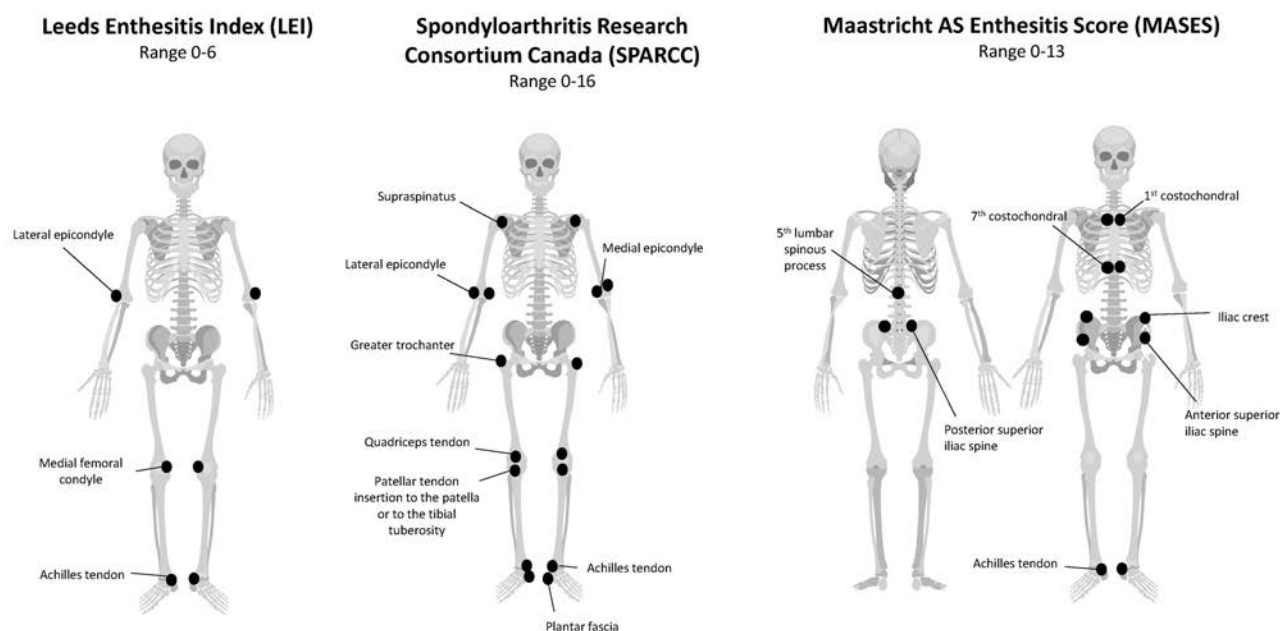


Figure. Commonly used enthesitis scoring systems in psoriatic arthritis clinical trials.

in enthesitis in the APR 30 mg group compared to placebo.<sup>18</sup> 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.<sup>19</sup>

**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.<sup>20</sup> 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.<sup>21</sup> 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.<sup>22</sup> In both SELECT-PsA-1 and SELECT-PsA-2 trials, upadacitinib (15 mg and 30 mg daily) were more effective than placebo in achieving enthesitis resolution.<sup>23,24</sup> Deucravacitinib, a selective tyrosine kinase 2 inhibitor, was assessed in a phase II PsA trial (6 mg and 12 mg doses) vs placebo.<sup>25</sup> 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.<sup>15</sup> 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.<sup>21</sup> The ADA group in SPIRIT-P1 was numerically superior but not

significantly different than placebo in the resolution of enthesitis and reduction in LEI.<sup>26</sup> Limited information about the efficacy of ETN for enthesitis was previously reported.<sup>15</sup> 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.<sup>27</sup> 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.<sup>15</sup> 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.<sup>28</sup> The GO-VIBRANT trial showed that treatment with intravenous GOL (2 mg/kg Q8W) was associated with significantly greater enthesitis improvement than placebo.<sup>29</sup> 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.<sup>30</sup>

**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.<sup>31,32</sup>

**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.<sup>33,34</sup> In the FUTURE 1 study, more patients in the combined SEC (75 mg and 150 mg Q4W) achieved resolution of enthesitis.<sup>33</sup> The FUTURE 2 study showed that more patients treated with SEC (75 mg, 150 mg, or 300 mg Q4W [combined]) achieved enthesitis resolution.<sup>34</sup> 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.<sup>35</sup> In FUTURE 4, resolution of enthesitis was numerically higher with SEC (150 mg Q4W, with and without loading) vs placebo.<sup>36</sup> FUTURE 5 showed that resolution of enthesitis was significantly higher with SEC (150 mg and 300 mg with loading) vs placebo.<sup>37</sup> SPIRIT-P1 showed that ixekizumab (IXE; 80 mg Q2W and Q4W) resulted in significantly more resolution of enthesitis than placebo.<sup>27</sup> 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.<sup>38</sup> 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.<sup>38</sup> 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.<sup>39</sup> 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.<sup>40</sup> 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.<sup>39</sup> 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.<sup>40</sup> Improvements in LEI scores were also significantly higher with GUS administered Q4W.<sup>40</sup>

*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.<sup>41</sup>

*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.<sup>8</sup>

*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.<sup>17</sup> 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.<sup>27</sup> 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.<sup>42</sup>

*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.<sup>9,45</sup> Complete resolution of enthesitis by SPARCC (but not by LEI) was achieved by significantly more patients in the IXE vs ADA group.<sup>9</sup> 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.<sup>43</sup>

*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.<sup>7</sup> 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.<sup>7</sup>

*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.<sup>44</sup>

*Local corticosteroid injections.* No information exists about the efficacy of local corticosteroid injections for enthesitis in PsA.<sup>15</sup>

*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.<sup>45</sup> 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.<sup>46</sup>

*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.<sup>47</sup> 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 enthesal 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.<sup>48</sup> 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.<sup>27</sup> 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 enthesal sites since it may lead to the rupture of tendons.<sup>49</sup> 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.<sup>7</sup> 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 enthesal 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 entheses 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.

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