Systematic Review of Treatment Effectiveness and Outcome Measures for Enthesitis in Psoriatic Arthritis

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ABSTRACT. Enthesitis is a characteristic feature of psoriatic arthritis (PsA) and is important in disease pathogenesis and classification. Use of clinical outcome measures for enthesitis is heterogeneous, and only 1 measure has been specifically developed and validated in PsA. Ultrasound and magnetic resonance imaging assessments of enthesitis may have advantages over clinical examination but are insufficiently studied. As part of an update of treatment recommendations by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), we performed a systematic literature review and identified randomized controlled trials with enthesitis outcomes in PsA. For each treatment agent we calculated treatment effect sizes (where applicable) and graded the level of evidence. (J Rheumatol 2014;41:2290–4; doi:10.3899/jrheum.140878)

Key Indexing Terms:
ENTHESITIS ENTHESOPATHY PSORIATIC ARTHRITIS
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Enthesitis or inflammation at sites where ligaments, tendons, and joint capsules attach to bone (1) is prevalent (25%–78%) in psoriatic arthritis (PsA); (2) may be the initial inflammatory manifestation[1]; and (3) may be centrally involved in disease pathogenesis in PsA[2,3]. While the entheses have become a key outcome in clinical trials[4], a number of enthesitis instruments are available, and 5 different enthesitis outcome measures were used across 12 clinical trials (Table 1). The Leeds Enthesitis Index (LEI)[5] is the only enthesitis measure developed and validated for PsA.

Both power Doppler ultrasound (PDUS) and magnetic resonance imaging (MRI) can identify both inflammatory and chronic changes, with PDUS providing additional information on vascularity, and MRI on osteitis; thus enthesitis can be detected at earlier stages and with greater sensitivity. Sensitivity to change of both imaging modalities for enthesitis has been shown in various studies, supporting their use in clinical trials.

MATERIALS AND METHODS

In a centralized systematic literature search performed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) to support evidence-based updated treatment recommendations for PsA manifestations[6], 32 full-text articles were identified for enthesitis in PsA. Eligibility for inclusion in the enthesitis review was defined as interventional randomized controlled trials (RCT) with enthesitis outcomes performed in PsA. Of these 32 full-text articles, 15 did not correspond regarding study design (open-label, case-control, case report, comment, review); 1 study reported additional results of a trial already included[7]; 7 did not report on PsA; and 2 did not report enthesitis outcomes; therefore, 7 of those initially identified full-text articles remained and are included here[8,9,10,11,12,13,14].

The GRAPPA Enthesitis Working Group also included the first double-blind RCT in PsA with enthesitis outcomes[15], and several additional RCT that were searched by hand after consulting experts in the field. Thus, 5 articles, representing the initial sulfasalazine trial in PsA[15] and trials completed after the date of the initial literature search[16,17,18,19], were added to the initial 7 articles[8,9,10,11,12,13,14], for a total of 12 articles included in this review.

A standardized data collection form was used to extract study information (year, author, journal); study type; participant diagnosis; treatment and comparator drug; dose; number of participants; enthesitis measure(s)

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Table 1. Enthesitis measures used in randomized controlled trials in psoriatic arthritis.

Enthesis Measure	Method (score range)	Trials in PsA	Validation in PsA
Modified Mander Enthesitis Index[25,25a]	Tenderness at 21 sites, scored at each site on 4-point scale: 0 = no pain; 1 = mild tenderness; 2 = moderate tenderness; 3 = wince or withdrawal. 1st cervical spinous process; 2nd cervical spinous process; 7th cervical spinous process; 1st thoracic spinous process; 12th thoracic spinous process; 1st lumbar spinous process; 5th lumbar spinous process; 1st sacral spinal process; symphysis pubis; greater trochanters, left, right (L,R); pelvic abductor origin (L,R); anterior superior border of the iliac crest (L,R); ischial tuberosity (L,R); Achilles tendon insertion (L,R); plantar fascia insertion (L,R)	Clegg 1996[15]	No
IMPACT Index[9]	Tenderness (yes/no) at 4 sites (0–4); Achilles tendon insertion (L,R); Plantar fascia insertion (L,R)	Antoni 2005[8,9]; Mease 2005[10]; Genovese 2007[11]; Gottlieb 2009[13]; Sterry 2010[14]	No
Maastricht AS Enthesitis Score (MASES)[26]	Tenderness (yes/no) at 13 sites (0–13). 1st Costochondral joint (L,R); 7th Costochondral joint (L,R); Posterior superior iliac spine (L,R); Anterior superior iliac spine (L,R); Iliac crest (L,R); 5th Lumbar spinous process; Proximal insertion of Achilles tendon (L,R)	Kavanaugh 2014[18] Ritchlin 2014[19]	No
PsA Modified MASES[12]	Tenderness (yes/no) at 15 sites (0–15). 1st Costochondral joint (L,R); 7th Costochondral joint (L,R); Posterior superior iliac spine (L,R); Anterior superior iliac spine (L,R); Iliac crest (L,R); 5th Lumbar spinous process; Proximal insertion of Achilles tendon (L,R); Plantar fascia insertion (L,R)	Kavanaugh 2009[7,12]; McInnes 2013[16]	No
Leeds Enthesitis Index (LEI)[5]	Tenderness (yes/no) at 6 sites (0–6); lateral epicondyle (L,R); medial femoral condyle (L,R); Achilles tendon insertion (L,R)	Mease 2014[17]	Yes[27], clinical LEI, odds ratio: 2.16 (0.81–5.70) for PsA vs RA

and assessment technique; mean (SD) scores at baseline and followup; mean (SD) change scores; and percentage with enthesitis at baseline and followup. Two independent reviewers extracted data (AO, JW). Where applicable, effect size calculations were based on mean score change and baseline standard deviation in the treatment and placebo groups, respectively. We used Stata statistical software (Stata 13, StataCorp LP) for Cohen's d effect size calculations[20].

RESULTS

Enthesitis measures used across PsA RCT are summarized in Table 1. Effects of various agents on enthesitis in PsA RCT are summarized in Table 2.

Sulfasalazine. In this study, which used the most complex enthesitis index, the modified Mander Enthesitis Index, the change in score was not statistically significant between treatment and placebo[15].

Infliximab. In 2 infliximab trials (IMPACT 1 and 2), the IMPACT Index was used to assess enthesitis. Post-treatment percentages of patients with enthesopathy were statistically significantly smaller for infliximab versus placebo (14% vs 31%, p = 0.021; and 20% vs 37%, p = 0.002, respectively)[8,9]. Mean change scores, required for effect size calculation, were not reported.

Adalimumab. The adalimumab trials assessed the IMPACT Index. Mean scores were not reported in the ADEPT trial (exploratory endpoint)[10], and in the second trial, mean change scores were not statistically different between adalimumab and placebo at 16 weeks (–0.5 vs –0.2, $p > 0.05$)[11].

Golimumab. The PsA modified Maastricht Ankylosing Spondylitis Enthesitis Score (PsA-modified MASES) was used in the GO-REVEAL trial[7,12]. Differences in mean percentage change scores at 24 weeks were significant between each golimumab group (50 mg, 100 mg, and overall) and placebo (not tested between the active arms). Effect sizes were –0.49 (95% CI –0.7, –0.2) for golimumab 50 mg and –0.62 (95% CI –0.9, –0.4) for golimumab 100 mg. Posthoc analysis of MASES change scores similarly favored golimumab (no baseline MASES scores were given to allow effect size calculations)[7].

Etanercept. Enthesitis was not an outcome in the initial etanercept trial in PsA[21]. In the observational PRESTA trial[14], where 2 active arms of etanercept were compared, no differences were observed between the groups in percentages with enthesitis (IMPACT Index); 70% and 80% of patients had improved IMPACT enthesitis scores at 12 and 24 weeks, respectively (no placebo comparison arm).

Certolizumab. In the RAPID-PsA trial[17], differences in the LEI at 24 weeks were statistically significant in favor of certolizumab versus placebo. Participants in this trial included patients previously treated with an anti-tumor necrosis factor (TNF) agent (20%). Effect sizes were –0.4 (95% CI –0.7, –0.2) for certolizumab 400 mg monthly and –0.6 (95% CI –0.8, –0.3) for certolizumab 200 mg every 2 weeks.

Ustekinumab. In the initial ustekinumab trial[13], percentages of patients with enthesitis (IMPACT Index) at 12 weeks were statistically significantly smaller for ustekinumab

Table 2. Treatment effectiveness for enthesitis outcomes in randomized controlled trials in psoriatic arthritis.

Study	Agent	No.	Enthesitis Measure	Results (p value vs placebo, at followup)	Effect Size [95%CI]
Clegg 1996[15]	Sulfasalazine, 2 g qd	221	Modified Mander Enthesitis Index	Mean at baseline (± SD)/ mean change (± SD) 36 wks. S: 4.3 ± 5.9/–1.5 ± 4.5; P: 4.4 ± 5.6/–0.9 ± 4.1; NS	–0.1 [–0.4, 0.1]
Antoni 2005[8]	Infliximab, 5 mg/kg q8w	104	IMPACT Index	% at baseline/16 wks. I: 25/14. P: 25/31 (p = 0.021)	NA
Antoni 2005[9]	Infliximab, 5 mg/kg q8w	200	IMPACT Index	% at baseline/14 wks/24 wks. I: 42/22/20; P: 35/34/37; (p = 0.016/p = 0.002)	NA
Mease 2005[10]	Adalimumab, 40 mg q2w	313	IMPACT Index	NR/NS	NA
Genovese 2007[11]	Adalimumab, 40 mg q2w	100	IMPACT Index	Mean (± SD) at baseline/mean change 16 wks. Ad: 0.9 ± 1.2/–0.5; P: 1.0 ± 1.3/–0.2; NS	–0.24 [–0.6, 0.2]
Kavanaugh 2009[7,12]	Golimumab, 50 mg q4w; 100 mg q4w	406	PsA modified MASES	% at baseline/14 wks/24 wks. G100: 79/61/50 (NS/p = 0.003); G50: 75/55/49 (p = 0.008/p = 0.002); P:78/71/69	
				Mean (± SD) at baseline/mean % change 24 wks. G100: 6.1 ± 4.1/–52.4 (p < 0.001)	**–0.62 [–0.9, –0.4]**
				G50: 5.7 ± 4.0 /–46.1 (p < 0.001)	**–0.49 [–0.7, –0.2]**
				Gtot: 5.9 ± 4.1/–49.4 (p < 0.001); P: 5.0 ± 4.1/–12.9	**–0.55 [–0.8, –0.3]**
Gottlieb 2009[13]	Ustekinumab, 90 mg or 63 mg qw for 4 wks	146	IMPACT Index	% at baseline/12 wks. U: 45/23; P: 46/42; p = 0.0163	NA
Sterry* 2010[14]	Etanercept, 50 mg biw/qw; 50 mg qw/qw	752	IMPACT Index	% at baseline/improved** 12 wk/24 wk. E (biw/qw): 40.4/73.7/80.9; E (qw/qw): 35.9/70.0 /81.3; (NR)	NA
McInnes 2013[16]	Ustekinumab, 45 mg q12w; 90 mg q12w	615	PsA modified MASES	% at baseline/24 wks. U90: 75.5/60.8 (p = 0.0002); U45: 69.3/68.6 (p = 0.0179); P: 70.4/81.0	
				Mean (± SD) at baseline/mean change 24 wks	
				U90: 5.7 ± 3.8/–2.5 (p = 0.002)^	**–0.31 [–0.5, –0.1]**
				U45: 5.0 ± 3.6/–2.0 (p = 0.057)^	–0.19 [–0.4, 0.0]
				Utot: 5.4 ± 3.7/–2.2 (p = 0.003)^; P: 5.4 ± 3.9/–1.3	**–0.25 [–0.4, –0.1]**
Ritchlin 2014[19]	Ustekinumab, 45 mg q12w; 90 mg q12w	312	PsA modified MASES	% at baseline/24 wks U90: 72.4/70.0 (p = 0.01) U45: 69.9/75.7 (p < 0.05); P: 70.2/88.2	
				Mean (± SD) at baseline/mean change 24 wks. U90: 5.7 ± 3.9/–2.1 (p = 0.08)^	–0.24 [–0.5, 0.3]
				U45: 6.5 ± 3.9/–1.9 (p = 0.16) ^	–0.19 [–0.5, 0.1]
				Utotal: 6.1 ± 3.9/–2.0 (p = 0.07); P: 5.5 ± 4.3/–1.1	–0.22 [–0.5, 0.1]
Mease 2014[17]	Certolizumab, 400 mg q4wk; 200 mg q2wk	409	LEI	Mean(± SD) at baseline/change (± SD) 24 wks. C400: 2.9 ± 1.6/ –1.8 ± 1.9 (p = 0.003)	**–0.44 [–0.7, –0.2]**
				C200: 3.1 ± 1.7/–2.0 ± 1.8 (p < 0.001); P: 2.9 ± 1.6/–1.1 ± 1.8	**–0.55 [–0.8, –0.3]**
Kavanaugh 2014[18]	Apremilast, 20 mg bid, 30 mg bid	504	MASES	Mean(± SD)at baseline/change (± SE) 24 wks	
				Ap30: 4.4 ± 3.1/–1.7 ± 0.3 (p = 0.03)	**–0.27 [–0.5, –0.1]**
				Ap20: 5.0 ± 3.3/–1.6 ± 0.3 (NS); P: 5.4 ± 3.5/–0.8 ± 0.3	–0.24 [–0.5, –0.2]

*All studies are double-blind randomized controlled trials (DBRCT) except for Sterry 2010 (2 active arms). **% with improvement in ≥ 1 site. ^p values for comparison of means calculated using the t test. NA: not applicable; NR: not reported; NS: not significant; Ad: adalimumab; Ap: apremilast; C: certolizumab; E: etanercept; G: golimumab; I: infliximab; P: placebo; S: sulfasalazine; U: ustekinumab; bid: twice daily; biw: twice weekly; qd: daily; qw: weekly. Values in bold face are statistically significant.

versus placebo (23% vs 42%, p = 0.016). In the P-SUMMIT 1 and 2 trials [16,19], using the PsA-modified MASES score, differences between mean enthesitis scores at 24 weeks were statistically significant only in the P-SUMMIT 1 trial for the ustekinumab 90-mg group and for the combined ustekinumab group versus placebo, respectively. In the P-SUMMIT 1 trial, effect size was –0.3 (95% CI –0.5, –0.1) for ustekinumab 90 mg, not significant for 45 mg [–0.19 (95% CI –0.4, 0)], and –0.25 (95% CI –0.4, –0.1) for the ustekinumab arms combined. In the P-SUMMIT 2 trial, which mainly included participants previously treated with anti-TNF agents (> 60%), effect size was not different than 0 [–0.24 (95% CI –0.5, 0.3) for ustekinumab 90 mg; –0.19 (95% CI –0.5, 0.1) for ustekinumab 45 mg; and –0.22 (95% CI –0.5, 0.1) for the ustekinumab arms combined].

At 24 weeks, percentages of patients with enthesitis as determined by PsA-modified MASES were statistically significantly smaller for ustekinumab versus placebo in both P-SUMMIT trials (percentage of patients with enthesitis in P-SUMMIT1: ustekinumab 90 mg: 61%; ustekinumab 45 mg: 69%; placebo: 81%, p values: ustekinumab vs placebo 0.0002 and 0.0179, respectively; in P-SUMMIT2: ustekinumab 90 mg: 70%; ustekinumab 45 mg: 76%; placebo: 88%, p values ustekinumab vs placebo < 0.01 and < 0.05, respectively).

Apremilast. In the apremilast trial[18], mean enthesitis change score on the MASES index at 24 weeks was statistically significantly in favor of apremilast 30 mg (twice daily) versus placebo [effect size –0.3 (95% CI –0.5, –0.1)]. Mean change score was not significant versus placebo in the apremilast 20 mg arm.

Glucocorticoid injections. A recent systematic review and metaanalysis of controlled studies of local glucocorticoid injections in tendinopathy (not limited to enthesitis) found impaired tendon healing (necrosis, collagen fiber disorganization) and decreased mechanical properties[22]. Limitations of the metaanalysis included heterogeneity of glucocorticoid substances used across studies (dexamethasone, triamcinolone, methylprednisolone, hydrocortisone, and various combinations of these); heterogeneity in sites injected across studies (Achilles/shoulder/forearm/peroneal/patellar tendons); and no information was collected on the exact injection techniques.

Effectiveness of Various Agents for Enthesitis in PsA (level of evidence).

- Effective (1b): Infliximab; golimumab; certolizumab; ustekinumab; apremilast (30 mg twice daily).
- Not effective (1b): Sulfasalazine (2 g daily).
- Not adequately studied: Adalimumab; other disease-modifying antirheumatic drugs (including methotrexate); nonsteroidal antiinflammatory drugs; physiotherapy.
- Not studied in PsA enthesitis: Local glucocorticoid injections.
- Associated with worse outcomes: Glucocorticoid injections in tendinopathy (2a).

DISCUSSION

Although the LEI, the PsA-modified MASES, and the MASES showed responsiveness to change in clinical trials, establishing a minimal clinically important difference and selecting a single enthesitis instrument are the next critical steps required to consistently measure enthesitis outcomes. Additionally, understanding efficacy of various agents is challenging in the absence of head-to-head randomized clinical trials.

Individual anti-TNF agents have shown effectiveness for enthesitis, with moderate treatment effect size for golimumab and certolizumab[23] and significant percentage improvement for infliximab; the exceptions are etanercept and adalimumab, for which evidence is inconclusive due to limitations of study design: no placebo arm and inadequate sample size (exploratory endpoint), respectively; and severe limitations of the scoring measure used (poor responsiveness and inter-rater reliability of the IMPACT Index)[5,24]. We can conclude based on high quality clinical trial data available for infliximab, golimumab, and certolizumab that anti-TNF agents are effective for enthesitis as a class, which is expected based on the pathophysiology of enthesial inflammation where TNF plays a central role[2].

In addition to anti-TNF agents, ustekinumab and apremilast are also effective for enthesitis in PsA, based on limited high quality clinical trial data. These findings underscore a potential role for interleukin 12 (IL-12), IL-23, and IL-17, as well as for other upstream key molecules such as anti-phosphodiesterase 4, suggesting these pathways may be involved in the pathogenesis of enthesitis.

In conclusion, high quality data from clinical trials are now available to support efficacy of anti-TNF agents, ustekinumab, and apremilast for enthesitis in PsA.

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