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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