Therapies for psoriatic enthesopathy: a systematic review

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CRD summary
The author appears to conclude that anti-tumour necrosis factor agents may be more effective for enthesitis in patients with spondyloarthritis, but the evidence was limited and findings should be interpreted with caution. Despite some limitations in the conduct of the review and in view of the limited evidence presented, the author's cautious conclusion seems appropriate.

Authors' objectives
To evaluate treatments for peripheral enthesitis in patients with psoriatic arthritis (PsA). Enthesitis is inflammation at tendon, ligaments, joint capsule sites, or fascia insertion sites to bone.

Searching
MEDLINE, PubMed and the Cochrane Database of Systematic Reviews were searched from inception to present using the reported search terms. In addition, reference lists of selected studies were screened and experts were contacted for details of unpublished studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs), open-label trials and case series were eligible for inclusion in the review. The included studies were RCTs and open-label studies.

Specific interventions included in the review
Studies of treatments for enthesitis were eligible for inclusion. The included studies evaluated sulfasalazine (SSZ), mesalamine, methotrexate (MTX) plus naproxen, and anti-tumour necrosis factor (TNF) therapy (infliximab and etanercept).

Participants included in the review
Studies in adults (aged 18 years or older) with peripheral enthesitis in spondyloarthritis were eligible for inclusion. Studies of patients with only axial enthesitis were excluded. The included studies were in patients with PsA, ankylosing spondylitis, reactive arthritis and undifferentiated spondyloarthropathy. In one study a high percentage of patients (74%) had axial involvement and in other studies not all patients had enthesitis.

Outcomes assessed in the review
It was clear that studies that evaluated enthesitis were eligible for inclusion. The included studies measured outcomes using various measures including the Mander Enthesitis Index (MEI; measures tenderness at 66 sites), a modified MEI (measures tenderness at 22 sites), Maastricht Ankylosing Spondylitis Enthesitis Score (measures tenderness at 13 sites), ultrasound, magnetic resonance imaging, and tenderness at two or four paired sites. In most of the included studies enthesitis was not the primary outcome measure.

How were decisions on the relevance of primary studies made?
The author did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The author did not report any formal assessment of validity. However, aspects of methodological quality, such as the validity of outcome measures, the generalisability of the results, sample size, study design and baseline comparability of the treatment groups, were reported in the text.
Data extraction
The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction. For each study, the mean value for the outcome measure (with standard deviation or range of values) was extracted for each treatment group together with the statistical significance of the treatment effect. For some studies an effect size was presented.

Methods of synthesis
How were the studies combined?
The studies were grouped by intervention and combined in a narrative. The level of evidence for each intervention was apparently graded using a hierarchy of evidence, but no details of this hierarchy were reported.

How were differences between studies investigated?
Differences between the studies were apparent from the text and tables.

Results of the review
Ten studies (n=936) were included: 8 RCTs (n=896) and 2 open-label trials (n=40).

None of the included studies assessed outcomes using an instrument that had been validated for use in PsA. The sample size ranged from 10 to 264.

SSZ: 3 double-blind RCTs were identified. Two RCTs (n=221 and 264) measured outcomes using the MEI or a modified MEI and reported no significant difference in scores between SSZ and placebo. The number of patients with enthesitis was not reported. The third RCT (n=23) assessed outcomes using ultrasound and reported no significant difference between SSZ and placebo.

Mesalamine (one open-label study): this study (n=30) reported that mesalamine significantly reduced the MEI from baseline (5.61 to 3.70, p<0.04).

MTX (one RCT with blinded assessor): this RCT (n=51) reported that the MEI was significantly reduced in patients allocated to MTX plus naproxen compared with naproxen alone. Treatment groups differed at baseline (the enthesitis index was almost 50% lower in the MTX group).

Anti-TNF therapy: 3 RCTs evaluated infliximab and one RCT and one open-label study evaluated etanercept. Two double-blind RCTs (n=77 and n=200) reported a significant reduction in the number of tender areas in patients allocated to infliximab compared with placebo. One small double-blind RCT (n=20) reported a significant reduction from baseline in bone marrow oedema using magnetic resonance imaging in patients allocated to infliximab (p<0.021), but no significant reduction in patients allocated to placebo (p<0.80). One double-blind RCT (n=40) reported a significant reduction from baseline in the modified MEI score in patients allocated to etanercept (p<0.001), but no significant reduction in patients allocated to placebo (p<0.72). One open-label study (n=10) reported that 38 of 44 lesions resolved completely or improved.

Authors' conclusions
The author's conclusions appear to be that anti-TNF agents may be more effective for enthesitis than traditional treatments, but the evidence was limited and findings should be interpreted with caution.

CRD commentary
The review question was defined in terms of the participants and study design; inclusion criteria for the interventions were appropriately broad given the nature of the condition. Not all patients in the review had the target condition (enthesitis and PsA). Two relevant databases were searched and some attempts were made to identify unpublished studies. It was unclear whether any language restrictions had been applied, so the potential for language bias could not be assessed. Although validity did not appear to have been formally assessed, some relevant methodological
limitations were discussed. Some details of the included studies were reported but not information about drug doses or treatment duration. The methods used to select studies, assess validity and extract the data for this single-author review were not described, thus it is not known whether any efforts were made to reduce reviewer errors and bias.

In view of the differences between the studies, a narrative synthesis in which attention was drawn to methodological limitations was appropriate. No details were reported of the hierarchy used to grade the level of evidence for each intervention, so these gradings could not be usefully interpreted. The lack of reporting of review methods make it difficult to confidently assess the reliability of the review. The author's conclusion, that review findings should be treated with caution, appear appropriate in view of the limitations in the included studies.

Implications of the review for practice and research
Practice: The author made recommendations. Specifically: mesalamine (level 3, grade C), infliximab (level 1b, grade A) and etanercept (level 1b, grade A) are effective for the treatment of enthesitis in patients with PsA (level 3, grade C) but SSZ is not recommended; there is insufficient evidence about MTX; and non-steroidal anti-inflammatory drugs (NSAIDs), physiotherapy and corticosteroid injections improve symptoms of enthesitis (level 4, grade D). The author advised caution in interpreting these recommendations since the data were generally flawed and/or incomplete. It should be noted that no studies that evaluated (NSAIDs), physiotherapy or corticosteroid injections were included in the review. Research: The author stated the need to evaluate the diagnostic accuracy of magnetic resonance imaging in enthesitis.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.