Therapies for Psoriatic Enthesopathy. A Systematic Review

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ABSTRACT. Enthesitis is defined as inflammation at sites of tendon, ligament, joint capsule, or fascia insertion sites to bone, and is a hallmark feature of psoriatic arthritis. Several outcome measures have been developed to assess enthesitis, but none have been validated in psoriatic arthritis. In this evidence-based review, we assess the limited data on treatments for enthesitis and make recommendations for further studies in psoriatic enthesitis. (First Release May 15 2006; J Rheumatol 2006;33:1435–8)

Key Indexing Terms:
ENTHESITIS ENTHESOPATHY PSORIATIC ARTHRITIS
ANKYLOSING SPONDYLITIS SPONDYLOARTHROPATHY TREATMENT

INTRODUCTION

Enthesitis (or inflammation at tendon, ligament, joint capsule sites, or fascia insertion sites to bone), although rare in rheumatoid arthritis (RA), is a hallmark feature of psoriatic arthritis (PsA)[1]. The most common clinical syndromes in PsA include plantar fasciitis, epicondylitis, and Achilles tendonitis[2].

Biopsies of bone underlying entheses revealed edema and predominance of CD8+ T lymphocytes[3], while monocytes were the major cell type isolated from the tendon or ligament[4]. Moreover, fat-suppressed magnetic resonance imaging (MRI) studies of knees from patients with spondyloarthritis (SpA) showed marked bone marrow edema adjacent to entheseal insertion sites; this observation raised the possibility of an underlying osteitis[5]. Of interest, treatment of patients with SpA with the anti-tumor necrosis factor (TNF) agent etanercept reversed high intensity MRI signals in axial and peripheral bone adjacent to entheseal insertion sites[6]. This reversal of bone marrow edema on MRI, along with marked improvement in clinical findings, supported the concept that TNF-α is a pivotal cytokine in the bone inflammatory response adjacent to enthesitis.

Outcome Measures

The clinical assessment of enthesitis is challenging because these structures are not often visibly inflamed. They can be located deep within surrounding tissues, and they are often contiguous with synovium. Therefore, a reliable and accurate instrument must not only localize the enthesis anatomically, but also distinguish it from other forms of joint inflammation. Several outcome measures have been developed to assess enthesitis (Table 1). The Mander Enthesitis Index (MEI) grades severity of tenderness (0–4) at 66 sites[7]. This index is generally thought to be too cumbersome for routine use[2]. The modified MEI is an assessment of tenderness (0–4) at 17 axial and peripheral sites[8].

The Maastricht Ankylosing Spondylitis (AS) Enthesitis Score (MASES), like the modified MEI, was designed as a less cumbersome instrument than the MEI. Tenderness and/or swelling are measured at 13 sites without grading pain intensity[9]. Investigators in the Canadian Spondyloarthritis Research Consortium (SPARCC) published a method that assessed enthesitis at 4 paired sites, plantar fasciae, Achilles tendons, tibial tuberosities, and rotator cuff insertions, but observer agreement was moderate to poor[10]. In the IMPACT 1 and IMPACT 2 trials of infliximab, enthesitis was determined by recording the presence or absence of tenderness in the Achilles tendons and the plantar fasciae[11,12].

Ultrasonography also has been used to assess enthesitis. Signs suggestive of entheseal inflammation are altered vascularization, thickened tendon insertions, fusiform swelling of the tendon or ligament, calcific deposits, paratendinitis, erosions or periostitis of adjacent bone, and loss of the normal fibrillar pattern of the enthesis that occurs with edema[13,14]. MRI changes seen in enthesitis include soft tissue swelling, distention of the bursa with fluid, and bone marrow edema near the insertion site[5,15].

Search Strategy

The focused clinical question for this review was: In PsA patients, what therapies are effective for the treatment of enthesitis?

Initial searches identified only 3 studies that included the therapeutic impact of a specific agent on enthesitis in PsA. Therefore, the search was expanded to include AS and other forms of SpA. This decision was a result of discussions of the Group for Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) at the annual meeting of the American College of

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Table 1. Outcome measures for enthesitis.

Study	Instrument	Method	Validation in PsA
Mander[7]	MEI	Tenderness at 66 sites, scored 0–3	No
Clegg[8]	Modified MEI	Tenderness at 22 sites, scored 0–4	No
Heuft-Dorenbosch[9]	MASES	Tenderness at 13 sites	No
Gladman[10]	—	Tenderness at 4 paired sites	No
Antoni[11]	—	Tenderness at 2 paired sites	No
Kane[13]	Ultrasound	Signs of enthesitis	No
D'Agostino[14]			
Grigoryan[15]	MRI	Signs of enthesitis	No
Marzo-Ortega[6]			

MEI: Mander Enthesitis Index; MASES: Maastricht AS Enthesitis Score.

Rheumatology in October 2004. The members of GRAPPA agreed that therapeutic responses in AS could be generalized to PsA until additional data become available.

The evidence in this review was compiled following a comprehensive literature search of Medline, Ovid, and PubMed dating from 1966 to the present. The Cochrane database of systemic reviews online was also searched. Reference lists of trials selected through the electronic search were manually reviewed to identify additional trials. Lastly, the author contacted several experts in the field, including Daniel Clegg, Dennis McGonagle, Dafna Gladman, Philip Mease, Christian Antoni, Arthur Kavanaugh, and Neil McHugh, in order to identify unpublished data.

The search terms used were enthesitis, enthesopathy, psoriatic arthritis, ankylosing spondylitis, spondyloarthropathy, therapy, and treatment. Crossing enthesopathy (111,681 hits) with therapy (621,600 hits) yielded 26 articles. Crossing enthesitis (209 hits) with therapy yielded 14 articles. The following inclusion and exclusion criteria were then applied to these articles:

Inclusion criteria: Peripheral enthesitis in adult SpA patients; clinical trials, randomized or open-label, that specifically determined the treatment efficacy of agents for enthesitis (in almost all trials, enthesitis was not the primary outcome measure); case series also were included since the purpose of this review was to be comprehensive.

Exclusion criteria: Enthesitis in non-SpA patients; axial enthesitis (it is recognized that some SpA patients have enthesitis limited to the spine; however, the purpose of this review was to examine efficacy of therapies in peripheral entheses); and subjects less than 18 years of age.

Ten publications were selected for this review of psoriatic enthesopathy. Details of these trials are outlined in Table 2.

RESULTS

Sulfasalazine (SSZ). Three double-blind, randomized, placebo-controlled trials were performed in patients with SpA; each of these trials examined the effect of SSZ on enthesitis. In the first 2 studies, the outcome measure was the modified MEI; the third trial used findings from ultrasonography.

In the first trial, Clegg, *et al* assessed change in the modified Mander score in 221 PsA patients[16]. A high percentage of these patients (74%) had axial involvement. The modified Mander score decreased in both the SSZ and placebo groups, but the difference in change score was not significant. In the second study, Clegg used the same outcome measure in 264 patients with AS, but did not find a significant decline in the modified MEI between patients taking SSZ and placebo[8]. These studies had several limitations. The number of patients with enthesitis was not stated; presumably, enthesitis scores were averaged over the entire study population, but not all patients had enthesitis. Also, the fact that the modified Mander score has not been validated makes it hard to interpret these results. Last, the rate of axial involvement in the PsA study was 74%, which is much greater than that reported in the PsA population (25%–40%); therefore, the applicability of these findings to PsA patients in the general population is questionable.

In the third study, SSZ therapy did not lessen enthesitis as determined by ultrasound[17]. This is the first and only study that has looked at this measure in PsA. Limitations of this study include the small sample size (type II error) and the fact that ultrasound measures of enthesitis have not been validated in PsA.

Mesalamine. The efficacy of mesalamine (1500 mg/day) was examined in an open-label trial in 30 patients with SpA as defined by the European Spondylarthropathy Study Group[18]. Treatment with mesalamine lowered the Mander score from 5.6 ± 4.03 to 3.7 ± 1.0. The open-label design of this trial precludes any strong conclusions regarding efficacy.

Methotrexate (MTX). Altan, *et al* evaluated the efficacy of MTX plus naproxen versus naproxen alone in a randomized trial where the assessor but not the patient was blinded[19]. The Mander score significantly declined only in the group taking MTX. The significant lowering of the Mander score in the treatment group must be interpreted with caution, because the enthesitis index in the MTX group was almost 50% lower than in the placebo group at baseline. Thus, the 2 groups differed greatly in the degree of enthesitis before treatment, which could have influenced the outcome.

Anti-TNF therapy: infliximab and etanercept. The anti-TNF

Table 2. Summary of clinical trials with enthesitis.

Study	Disease Type	Agent	No. of Patients	Study Type	Outcome Measure	Results	p	Effect Size	Comments
Clegg[8]	PsA	Sulfasalazine	221	DBRPC	Modified Mander	S:0.3 ± 5.9/1.5 ± 4.5 P:4.4 ± 5.6/–0.9 ± 4.1	NS	0.50	74% with axial disease
Clegg[16]	AS	Sulfasalazine	264	RDBCT	Modified Mander	S:4.1 ± 5.3/–1.4 ± 4.0 P:3.8 ± 5.0/1.6 ± 4.6	NS	0.74	
Altan[19]	AS	Naproxen (I) vs MTX + naproxen (II)	51	RCT, assessor blinded	Mander	Group I: 3.78 ± 5.02/1.5 ± 1.95 Group II: 7.21 ± 7.46/3.68 ± 5.27	< 0.05	0.30	Enthesitis Index greater in Group II at baseline
Gorman[21]	AS	Etanercept	40	RDBCT	Modified Mander	E:4.5 ± 8.4/0.0 ± 3.0 P:3.0 ± 7.9/1.5 ± 8.0	< 0.001 < 0.72	0.51	Pts allowed to continue other meds
Lehtinen[17]	ReA-12 AS-8 USpA-1 PsA-3	Sulfasalazine	23	RDBCT	Ultrasound	A:10/12 to 9/12 P:7/11 to 8/11	NS		Ultrasound not validated for enthesitis
Thomson[18]	AS-27 USpA-1 ReA-2	Mesalamine	30	OL	Mander	5.61 ± 4.0/3.70 ± 1.0	< 0.04		Open-label study
Antoni[11]	PsA	Infliximab	77	RDBCT	Tenderness over 4 bilateral entheses	1:13 to 7 points P:13 to 15 points	< 0.05		Outcome measure not validated
Antoni[12]	PsA	Infliximab	200	RDBCT	Tenderness over 4 bilateral entheses	1:40–18–11 at baseline, 14 and 24 wks P:41–30–32	14 wks < 0.016 24 wks < 0.002		Outcome measure not validated
Marzo-Ortega[6]	AS-7 EA-2 USpA-1	Etanercept	10	OL	MRI	38 of 44 lesions resolved completely or improved score –2 or –1			Scoring method not validated
Braun[20]	AS	Infliximab	20	RDBCT	MRI	Absolute changes on MRI 1:112.6/68 at 3 mo P:114/108	< 0.021 < 0.80	0.97	MRI scoring system not validated but results similar to spin-inversion/time-inversion recovery

E: etanercept; I: infliximab; P: placebo; S: sulfasalazine; AS: ankylosing spondylitis; MTX: methotrexate; NS: nonsignificant; OL: open-label; PsA: psoriatic arthritis; RCT: randomized control trial; RDBCT: randomized, double-blind, controlled trial; ReA: reactive arthritis; USpA: undifferentiated spondyloarthropathy.

antibody infliximab was compared with placebo for enthesitis outcomes in PsA patients in 2 separate double-blind randomized controlled trials (RCT), IMPACT 1 and IMPACT 2[11,12]. In these trials, tenderness was assessed over 2 bilateral entheseal areas (4 sites) in the lower extremities. These sites were chosen because they are frequently involved in PsA patients (C.E. Antoni, personal communication). In IMPACT 1, 26 of 77 patients had enthesitis, and in IMPACT 2, 35 and 42 of the 100 patients in each group, respectively, had enthesitis. In both trials, a significant decline in the number of tender areas was noted. These trials certainly provide compelling evidence for a treatment effect in PsA specifically, but the results are diluted by the fact that the validity of this outcome measure is unknown, and this approach to entheseal assessment has never been applied in a previous clinical trial. Additionally, in a small double-blind RCT of 20 patients with AS, infliximab lessened bone marrow edema (a marker of acute inflammation) in the spine of patients taking drug but not those taking placebo[20].

The efficacy of etanercept, a soluble TNF receptor molecule, was examined by Gorman, *et al* in a phase IIb double-blind RCT of enthesitis in 40 patients, using the modified Mander scale[21]. The mean Mander score dropped from 4.5 ± 8.4 to 0.0 ± 3.0 in the treatment group and from 3.0 ± 7.9 to 1.5 ± 8.0 in the placebo group, a significant difference in favor of patients taking drug. The large standard deviations, however, illustrate the wide range of entheseal involvement in these patients. Also, validation for this outcome measure has not been performed. Nevertheless, the striking observation that the mean score in the treatment group reached 0 supports the presence of a true treatment effect.

Nonsteroidal inflammatory medications, physiotherapy, and intratendinous steroid injections. Despite the almost universal recommendation in textbooks and review articles regarding the potential effectiveness of these interventions, controlled trials or case series that reported outcomes in SpA patients treated with any of these modalities could not be identified.

Treatment Recommendations

- Sulfasalazine is not effective for treatment of enthesitis in PsA (level 1b, grade A)

- Mesalamine is effective for the treatment of enthesitis in SpA (level 3, grade C).
- Methotrexate has not been analyzed for treatment of enthesitis in PsA
- Infliximab is effective for the treatment of enthesitis in PsA (level 1b, grade A)
- Etanercept is effective for the treatment of enthesitis in SpA (level 1b, grade A)
- NSAID, physiotherapy, and corticosteroid injections improve entheseal symptoms (level 4, grade D)

DISCUSSION

The evidence-based treatment recommendations outlined above suggest that anti-TNF agents (infliximab and etanercept) are more effective for the treatment of enthesitis than traditional agents. These recommendations should be viewed with caution, however, because the data underlying them are incomplete and in many cases severely flawed. First, several different outcome measures were used in the studies examined in this review, and none of them have been validated in PsA. Second, with the exception of SSZ, large controlled trials examining the effect of traditional disease modifying antirheumatic drugs on enthesitis have not been done. Third, most of the studies did not state how many patients in the total population actually had enthesitis, and thus effect size may be overestimated.

The use of imaging modalities to assess entheseal inflammation is particularly appealing because this approach provides an opportunity to visualize the anatomy of the enthesis, thus avoiding the confounding issues that arise from physical examination. But the anatomy of the enthesis may be complex, and discrimination of one domain from another (synovitis from enthesitis or tendonitis) may not be possible even with highly sophisticated imaging modalities. The specificity of MRI must also be addressed, especially because studies have shown that bone marrow edema adjacent to entheseal insertion sites can also be observed in osteoarthritis or following trauma[22,23].

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