

Safety and Efficacy of Therapies for Skin Symptoms of Psoriasis in Patients with Psoriatic Arthritis: A Systematic Review

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ABSTRACT. Numerous guidelines and recommendations exist for the treatment of psoriasis in various populations. One important population is patients with psoriatic arthritis (PsA) who have symptoms of both joint and skin disease. In patients with both facets of psoriatic disease, skin and joints must be treated separately, but also simultaneously. As several systemic therapies are approved for either one or both, the concept of treating both facets with the same drug is feasible. This review summarizes evidence from studies in patients with PsA on the efficacy of these drugs on psoriatic skin disease in these patients. (*J Rheumatol* 2014;41:2301–5; doi:10.3899/jrheum.140880)

Key Indexing Terms:

PSORIASIS

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Numerous guidelines and recommendations exist for the treatment of psoriasis (PsO), based on a wealth of literature summarizing evidence from multiple clinical trials^{1,2}. Most guidelines focus on chronic plaque-type psoriasis as the most common clinical manifestation; however, in recent years, other phenotypes have been addressed³. In the majority of guidelines, patients are stratified according to disease severity into those suffering from mild versus moderate-to-severe psoriasis. Disease activity and severity as assessed by the Psoriasis Area and Severity Index (PASI), the affected body surface area (BSA), and the burden of disease (often assessed using the Dermatology Life Quality Index questionnaire) usually provide the basis for this stratification, although recent initiatives consider additional criteria often not adequately assessed by the above tools⁴.

An important population with signs and symptoms of PsO are patients with psoriatic arthritis (PsA). To comprehensively treat patients with both PsA and PsO, control of both facets of the disease is essential⁵. Several drugs used to treat PsA also exhibit efficacy in PsO. To decide which treatment to choose in these patients, physicians often evaluate PsO literature (and guidelines) and assume that

observations from PsO trials can be extrapolated for patients with PsA. However, efficacy data from PsA or PsO studies, using the same drug, often show discrepancies. Among expert explanations for this phenomenon is that many patients with PsA have relatively mild PsO. The milder the PsO, the more difficult it is to use the metrics of the PASI and other measures to assess efficacy⁶.

We therefore performed a systematic literature review of the efficacy of drugs studied in PsA clinical trials on the skin symptoms of these patients. The results of this review are intended to provide the basis for updated treatment recommendations for PsA and PsO by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).

MATERIALS AND METHODS

Search strategy/methods. On April 17, 2014, PubMed and Embase were searched for clinical studies, using the following keywords: psoriatic arthritis, therapy, biologics, abatacept, adalimumab, apremilast, brodalumab, cyclosporine, disease-modifying antirheumatic drug (DMARD), etanercept, golimumab, infliximab, ixekizumab, leflunomide, methotrexate, secukinumab, and ustekinumab. PsA studies assessing efficacy on psoriasis lesions using the PASI were included in the analysis. To provide a more complete picture of the drugs that are likely to become available in the near future to treat PsO and/or PsA, we also included data from PsO studies if PsA data were not in the public domain at the time we performed the literature search. Whenever possible, the percentages of patients with 50% or 75% reduction in the PASI (PASI50, PASI75) are indicated.

RESULTS

We identified 11 publications reporting the effects of conventional DMARD (Table 1) and 13 reports addressing biologics (Table 2). Moreover, 1 study on a novel small molecule inhibitor (apremilast) was identified, also included in Table 2.

Conventional DMARD. Seven of 11 studies, including a total of 410 patients, focused on the effects of methotrexate (MTX).

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Table 1. Summary of clinical PsA trials evaluating the efficacy of conventional DMARD therapies on signs and symptoms of PsO.

Drug	Dosing Regimen	Efficacy (study reference)	Approved for PsA	Approved for PsO	Efficacy in PsO (Nast 2012) ¹
Methotrexate	15 mg/week 10-25 mg/week 15 mg/week 16.2 mg/week 15 mg/week 7.5-15 mg/week 15 mg/week IM	Mean PASI reduced from 3.76 to 2.2 at 6 mo ⁷ After 6 mo: PASI50: 31% PASI75: 24% ⁸ Mean PASI reduced from 2.2 to 1.9 after 12 mo ⁹ PASI50: 57% after 24 mo ¹⁰ PASI75: 54.3% after 4 mo ¹¹ After 12 mo: Reduction of the mean PASI in overweight patients from 13.1 to 3.05, in normal weight patients from 11.98 to 1.04 ¹² Reduction of the mean PASI from 8.2 to 4.3 after 6 mo ¹³	Yes	Yes	PASI75: 30-50%
Leflunomide	100 mg/day for 3 days, then 20 mg/day for 6 mo	After 6 mo: PASI50: 30.4% PASI75: 17.4% ¹⁴	Yes	No	No published data from PsO trials in the public domain
Cyclosporine	2.5-3.75 mg/kg/day for 12 mo 3-5 mg/kg/day for 12 mo 3 mg/kg/day for 24 mo	PASI response after 12 mo: PASI50: 65% PASI75: 27.5% ¹⁵ Mean PASI reduction of 7.6 ¹⁶ Reduction of the mean PASI from 15.1 to 5.2 ¹⁷	No	Yes	PASI75: 50-70%

PsO: psoriasis; DMARD: disease-modifying antirheumatic drug; IM: intramuscularly; PASI: Psoriasis Area and Severity Index.

Table 2. Summary of clinical PsA trials evaluating the efficacy of biologics and apremilast on signs and symptoms of PsO.

Drug	Dosing Regimen	Efficacy (study reference)	Approved for PsA	Approved for PsO	Efficacy in PsO (per Nast 2012) ¹
Adalimumab	40 mg SC every other week for 48 weeks	PASI75: 58% after 48 weeks ¹⁸	Yes	Yes	PASI75: about 70%
Certolizumab pegol	200 mg every 2 weeks or 400 mg every 4 weeks	PASI75 at week 24: 47% ¹⁹	Yes	No	PASI75: 75% (200 mg every other week), 83% (400 mg every other week ²⁹)
Etanercept	25 mg SC twice weekly	PASI75 at week 24: 23% ²⁰	Yes	Yes	30-70%
Golimumab	50 or 100 mg SC every 4 weeks	PASI75 at week 14: 40% (50 mg); 58% (100 mg) ²¹	Yes	No	No published data from PsO trials in the public domain
Infliximab	5 mg/kg IV at weeks 0, 2, 6, 14, and 22	PASI75 at week 14: 64% ²²	Yes	Yes	70-90%
Ustekinumab	45 or 90 mg SC at weeks 0, 4, and 16	PASI75 at week 24: 57.2% (45 mg); 62.4% (90 mg) ²³	Yes	Yes	About 70%
Abatacept	3, 10, or 30 mg/kg IV at days 1, 15, 19 (except 30 mg group), and then every 4 weeks	PASI75 at day 169: 38% (3 mg), 14% (10 mg), 10% (30 mg) ²⁴	No	No	No published data from PsO trials in the public domain
Brodalumab*	70, 140, or 210 mg SC at day 1 and then at weeks 1, 2, 4, 6, 8, and 10; 280 mg at day 1 and at weeks 4 and 8	PASI75 at week 12: 33% (70 mg), 77% (140 mg), 82% (210 mg), 67% (280 mg) ²⁵	No	No	NA
Ixekizumab*	10, 27, 75, and 150 mg every other week	PASI75 at week 12: 29% (10 mg), 77% (27 mg), 83% (75 mg), 82% (150 mg) ²⁷	No	No	NA
Secukinumab*	75 or 150 mg SC at weeks 0, 4, and 8	PASI75 at week 12: 57% (75 mg), 82% (150 mg) ²⁶	No	No	NA
Apremilast	20 or 30 mg orally twice daily for 24 weeks	PASI50 at week 16: 33.8% (20 mg), 50.6% (30 mg) ²⁸	Yes	No	PASI75: 24.4% (20 mg twice daily) ³⁰

*Data for this agent are from PsO clinical trials. PsO: psoriasis; IV: intravenously; PASI: Psoriasis Area and Severity Index; SC: subcutaneously; NA: not applicable.

In Kingsley, *et al*, 109 patients with PsA in a randomized placebo-controlled trial received MTX 15 mg/week. In patients with signs of psoriasis, the mean PASI was reduced from 3.76 to 2.2 after 6 months⁷.

Mease, *et al* reported the effects of alefacept and MTX in PsA. Of 62 patients who received MTX only (between 10 and 25 mg/wk), 31% had a PASI50 response and 24% had a PASI75 response⁸.

Fraser, *et al* conducted a randomized, double-blind, placebo-controlled study of the combination of MTX and cyclosporin A (CSA). Thirty-four patients received MTX only (15 mg/wk) and were also assessed using the PASI. After 12 months, the mean PASI was reduced from 2.2 to 1.9⁹. Of note, in patients receiving MTX plus CSA (2.5 mg/kg/day), mean PASI was reduced from 2.0 to 0.8.

In a longitudinal observational study, Chandran, *et al* observed a PASI50 response in 57% of their cohort after 24 weeks (average MTX dose 16.2 mg/week)¹⁰.

In a study by Baranaukaite, *et al* comparing MTX alone versus MTX in combination with infliximab, 53 MTX-naive patients received MTX alone (15 mg/week). After 4 months, 54% of these patients had a PASI75 response¹¹.

Two studies analyzing the effects of tumor necrosis factor- α (TNF- α) blocking therapies on body weight contained information on patients receiving MTX monotherapy: In a study by Saraceno, *et al*, 50 patients received MTX (between 7.5 and 15 mg/week) for 12 months. The mean PASI was reduced from 13.1 to 3.05 in the overweight-to-obese population, and from 12.0 to 1.0 in the underweight-to-normal weight group¹². Comparable results were extracted from a publication by Gisondi, *et al*: 43 patients who received MTX (15 mg/week) for 6 months had a mean reduction of the PASI from 8.2 to 4.3¹³.

The Treatment of Psoriatic Arthritis Study, reporting on the efficacy of leflunomide in PsA, included 92 patients with skin involvement assessed by the PASI. After patients received a 100 mg/day loading dose for 3 days, followed by 20 mg/day for 6 months, 30.4% achieved a PASI50 response and 17.4% achieved a PASI75 response¹⁴.

Three studies were identified on the efficacy of CSA. Karanikolas, *et al* studied adalimumab or CSA alone or in combination. Among 57 PsA patients receiving CSA alone (between 2.5 and 3.75 mg/kg/day), 65% achieved a PASI50 response, 45% a PASI75 response, and 27.5% a PASI90 response after 12 months of therapy¹⁵.

In a small prospective study, Spadaro, *et al* followed 10 patients receiving CSA for 12 months (3 mg/kg/day, which could be increased to 5 mg/kg/day if response was unsatisfactory)¹⁶. Investigators reported a mean PASI reduction of 7.6.

Following a cohort of 60 patients receiving CSA 3 mg/kg/day over 24 months, Sarzi-Puttini, *et al* observed a reduction of the mean PASI from 15.1 to 5.2¹⁷.

Biologics. Among the biologic therapies, TNF- α -inhibiting

drugs adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab, as well as the anti-p40 antibody ustekinumab, are already approved for treating PsA. Relevant data from PsA trials are also available for abatacept, which blocks T cell costimulation; and the phosphodiesterase 4 inhibitor apremilast, recently approved in the USA for treatment of PsA. Finally, efficacy data in PsO are available for brodalumab, ixekizumab, and secukinumab, directed against the interleukin 17 (IL-17) RA receptor or IL-17A, respectively. Because these therapies are in advanced stages of clinical development for PsO and may be approved for this indication soon, data are included here for reasons of comprehensiveness.

The fully human TNF- α -blocking antibody adalimumab was evaluated in the Adalimumab Effectiveness in Psoriatic Arthritis Trial. After patients completed a 24-week double-blind study of adalimumab versus placebo, they could receive open-label adalimumab 40 mg subcutaneously every other week. At week 48, 69 patients were assessed for their skin responses: 67% had a PASI50 response, and 58% a PASI75 response¹⁸.

Data from a phase III PsA study are available for the TNF- α -blocking pegylated antibody certolizumab pegol (200 mg subcutaneously every other week or 400 mg every 4 weeks). At week 12, 46.7% and 47.4%, respectively, achieved a 75% PASI reduction¹⁹.

In a randomized, placebo-controlled trial, 25 mg of etanercept, a fusion protein functioning as soluble receptor for TNF- α , was injected twice weekly for 24 weeks. At week 24, 23% of patients available for skin assessment achieved a PASI75 response, compared to 3% in the placebo group²⁰.

In a randomized study, placebo or 50 or 100 mg of golimumab, another TNF- α -blocking antibody, was injected every 4 weeks in 405 patients with PsA. At week 24, the PASI75 responses were 3%, 40%, and 58%, respectively²¹.

In the Infliximab in PsA study (IMPACT 2), 200 PsA patients received either placebo or infusions with the chimeric TNF- α -blocking antibody infliximab (5 mg/kg) at weeks 0, 2, 6, 14, and 22. At week 14, the PASI75 response rates were 2% and 64%, respectively²².

Ustekinumab is an antibody targeting the common subunit of IL-12 and IL-23, which may interfere with the development of TH17 lymphocytes; it is already used to treat moderate-to-severe plaque-type psoriasis. In a phase III study in PsA, placebo or ustekinumab (45 or 90 mg) were injected at weeks 0, 4, and 16. At week 24, PASI75 responses were 57.2% and 62.4%, respectively, compared to 11% in the placebo group²³.

In a phase II PsA study, abatacept, which targets the costimulatory molecule cytotoxic T lymphocyte antigen 4 (CTLA4), patients were randomized to receive intravenous placebo; abatacept 3 or 10 mg/kg on days 1, 15, and 19; or abatacept 30 mg/kg on days 1 and 15; infusions continued

every 4 weeks thereafter. At day 169, PASI75 responses were 38%, 14%, and 10%, respectively, in abatacept groups, compared to 5% in the placebo group²⁴.

The antibody brodalumab targets the IL-17 RA receptor, potentially blocking the biologic effects of several isoforms of IL-17 on its target cells. In a phase II study in PsO, 70, 140, or 210 mg of brodalumab were injected at day 1 and then at weeks 1, 2, 4, 6, 8, and 10; or 280 mg at day 1 and weeks 4 and 8. At week 12, PASI75 responses were 33%, 77%, 82%, and 67%, compared to 0% in the placebo group²⁵.

Data from phase II PsO trials of 2 subcutaneously administered anti-IL-17A antibodies — secukinumab and ixekizumab — have been published. Ixekizumab was administered at 10, 25, 75, and 150 mg every 2 weeks; at week 12, the respective PASI75 responses were 29%, 77%, 83%, and 82%, with 8% in the placebo group²⁶. Secukinumab, administered at 75 or 150 mg at weeks 0, 4, and 8, yielded, respectively, PASI75 responses at week 12 of 57% and 82%, compared to 9% in the placebo group²⁷.

Apremilast, an oral phosphodiesterase 4 inhibitor, was evaluated in a placebo-controlled PsA trial (20 or 30 mg twice daily for 24 weeks) in 504 patients. At week 16, PASI50 responses were 33.8% and 50.6% in the apremilast groups, respectively, compared with 18.5% in the placebo group. The PASI75 responses were 17.6%, 21%, and 4.6%, respectively²⁸.

DISCUSSION

To date, of the numerous DMARD available for treating PsA — both nonbiologic and biologic, with different modes of action — there is evidence that all of them also exhibit at least some efficacy as therapy for PsO.

However, although a wealth of literature exists for treating PsO and a substantial body of evidence exists for treating PsA, few studies assess the efficacy of a systemic therapy initiated with the intention of simultaneously controlling PsA and PsO. That said, treating both facets of the psoriatic disease is essential in any individual patient⁵. It is therefore of utmost importance to be aware of the currently available evidence for simultaneous treatment.

A general trend may be detected from the data summarized here: The efficacy of drugs approved in PsO is seemingly lower in PsA studies with regard to reducing the PASI¹. Experts agree that this phenomenon is largely explained by the metrics of the PASI, which are not linear. Achieving a similar percentage of improvement is more difficult in patients with mild versus moderate-to-severe PsO, which may introduce a systematic bias to the studies analyzed here, as they often include patients with relatively mild PsO⁶. Thus, of all the drugs in this analysis, the efficacy on PsO in PsA patients is most likely underestimated.

With this limitation in mind, the results reported here reflect what has been observed in pure PsO studies, namely a

trend toward better efficacy of biologics in the reduction of the PASI, compared to conventional systemic drugs. The scope of this review was not to provide treatment recommendations, but rather it is intended that GRAPPA members will use the results of this analysis to develop recommendations.

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