Effectiveness of Psoriatic Arthritis Therapies

Dafna D. Gladman

Objective: **To review the effectiveness of systemic therapies for psoriatic arthritis (PsA).**

Methods: **Data on the efficacy of PsA therapies from selected literature, including American and international medical journals and recent abstracts from key rheumatology meetings, were reviewed.**

Results: **Most therapeutic agents used to treat PsA are used on the basis of data from patients with rheumatoid arthritis (RA), and have not been adequately assessed in patients with PsA. However, the progressively destructive nature of the disease demands aggressive treatment with agents tested specifically in PsA. Conventional agents used to treat RA, such as methotrexate and sulfasalazine, have adverse effects that often lead to drug discontinuation and may not always be effective in reducing symptoms or radiographic progression in PsA. Newer medications, such as etanercept and infliximab, specifically inhibit the actions of tumor necrosis factor, which plays a major role in joint destruction. The Food and Drug Administration has recently approved etanercept for treatment of PsA. Current data with infliximab are limited to small open-label trials; however, randomized controlled trials are underway.**

Conclusions: **PsA and RA are distinct diseases, and the efficacy and safety of an agent in RA cannot necessarily be equated with efficacy and safety in PsA. For most conventional agents, data from controlled clinical trials in PsA are scant. Etanercept is currently the only therapeutic agent with sufficient data from placebo-controlled, randomized trials to receive a Food and Drug Administration indication for the treatment of PsA.**

Semin Arthritis Rheum 33:29-37. ***© 2003 Elsevier Inc. All rights reserved.***

INDEX WORDS: Psoriatic arthritis; tumor necrosis factor; inhibitor; treatment; etanercept.

FEW AGENTS FOR psoriatic arthritis (PsA) have been stringently proven effective in randomized, controlled clinical trials. On the other hand, a plethora of well-designed clinical trials have accompanied an influx of new agents targeted for rheumatoid arthritis (RA). Because of some clinical similarities between the arthritis of RA and PsA, the treatment of the latter has been based primarily on drug therapy developed for RA. However, despite the fact that both PsA and RA are forms of inflammatory arthritis, these 2 conditions are distinct diseases, and therapies that are effective in RA are not always useful in PsA.

A comparison of the inflammatory features, patterns of inflammation, and clinical laboratory characteristics of PsA and RA shows both differences and similarities (Table 1). In addition to distinct clinical features, PsA and RA also show differences in the inflammatory reaction that accompanies each form of arthritis. For example, studies comparing the synovial joints from patients with these 2 diseases have found differences in the distribution of inflammatory cells. Significantly less lining layer hyperplasia, fewer macrophages, and a greater number of blood vessels in the synovial membrane are found in PsA than in RA

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0049-0172/03/3301-0003$30.00/0

doi:10.1053/sarh.2002.50024

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Table 1: Clinical Features of PsA and RA

Feature	PsA	RA
Rheumatoid factor	Uncommon	Common
Nail lesions	Common	Uncommon
Psoriasis	Common	Uncommon
Pattern of joint involvement	Asymmetric/ symmetric*	Symmetric
Peripheral joint involvement	Common	Common
Distal interphalangeal joint involvement	Common	Uncommon
Spondylitis	Common	Uncommon
Sacroiliitis	Common	Uncommon

*Often initially asymmetric before becoming symmetric as disease progresses.
Adapted from Rahman and Gladman (3).

(1). In addition, synovial fluid from patients with PsA have a greater number of $CD8^+$ T lymphocytes compared with patients with RA, which resulted in a reversal of the CD4 to CD8 ratio in the patients with PsA (2).

PsA and RA also differ with regard to the joints involved and in the patterns of inflammation that develop. In general, involved joints in PsA are tighter, contain less fluid, and are less tender than those in RA (3,4). Inflammation tends to be less symmetric in its distribution in PsA than in RA (3,5). Dactylitis, spondylitis, sacroiliitis, and distal interphalangeal joint involvement are common in PsA but are usually absent or uncommon in RA (6,7).

Examining for the presence of both rheumatoid factor and extra-articular manifestations can help distinguish PsA from RA. Approximately 80% of patients with RA are positive for rheumatoid factor, whereas most patients with PsA (91% to 94%) are seronegative (6,7). Patients with PsA have psoriatic skin lesions, which may occur by chance in 3% of patients with RA (7). In particular, nail lesions, including pits and onycholysis, develop in approximately 84% of patients with PsA, but occur in only 46% of patients with uncomplicated psoriasis (8). Together, the distinct patterns of joint inflammation and the absence of rheumatoid factor and psoriasis should help clinicians distinguish PsA from RA and, therefore, aid in determining the proper course of treatment.

PsA: THE CLINICAL PROBLEM

The exact prevalence of PsA is unknown; it has varied from 0.04% in the Faroe Islands to 1.4% in Sweden. A recent study from the Mayo Clinic calculated the prevalence at 0.1%. However, a recent survey by the National Psoriasis Foundation suggests that this might grossly underestimate the true prevalence (9). The number of adults in the United States who have PsA is approximately 1 million (9). Arthritis occurs in 23% of patients with psoriasis, and it may affect as many as 40% of hospitalized patients who have extensive skin involvement (10,11). PsA may affect as many as 30% of patients with psoriasis (12). Because psoriasis occurs in 1% to 3% of the population, the prevalence of PsA may be as high as 1%, similar to that of RA. Joint damage and decreases in quality of life are comparable between patients with PsA and those with RA (13,14). Compared with RA therapy, PsA treatment is complicated by the effect of agents on the psoriatic skin lesions. Accordingly, therapeutic strategies for treating PsA should involve medications that clear skin lesions, alleviate joint pain, prevent joint damage, and are well tolerated. Most of the drugs that are used to treat PsA have not been adequately examined for efficacy in this disease and are only administered because of their known efficacy in RA.

Although not tested for validity outside of therapeutic trials, the development of the Psoriatic Arthritis Response Criteria (PsARC) (adapted from Clegg et al [15]) should help in the assessment of new therapies in PsA. PsARC is a set of criteria for the study of sulfasalazine in PsA (15). The criteria include a joint pain/tenderness count, a swollen joint count (both of which must decrease by 30% to constitute improvement), a physician global assessment, and a patient global assessment (both of which must decrease by at least 1 unit on the 0 to 5 Likert scale to show improvement). To be considered a responder, a patient must show improvement in at least 2 of the 4 criteria (1 of which must be either joint pain/tenderness or swollen joint count), and none of the criteria may show worsening. In the sulfasalazine study, the placebo response when using the PsARC was high at 45%. The Psoriasis Area and Severity Index (16) and the target lesion evaluation have been used to assess

psoriasis. These measures should help in the assessment of new therapies in PsA.

METHODS

A literature search was conducted by using PubMed (1960 to 2002) to gather information on the efficacy and safety of PsA therapies. Information on agents used to treat PsA also was gathered from recent abstracts presented at recent American College of Rheumatology (ACR) or European League Against Rheumatism (1999 to 2001) meetings. When possible, randomized, placebo-controlled trials were used as the primary source of data. However, for some agents and information discussed, trials of this nature were not available. In these cases, data were derived from open-label studies, retrospective record reviews, and case reports.

THERAPY FOR PsA

PsA should be diagnosed early and treated aggressively with the goal of minimizing or avoiding joint damage (5,6). Joint damage in patients with PsA is comparable with that in patients with RA (13). Not surprisingly, joint erosion caused during PsA significantly reduces patient health-related quality of life and ability to function. Husted et al (17) observed that, compared with patients with RA, patients with PsA experienced more bodily pain and more role limitations because of emotional problems. Overall, the reduction in quality of life owing to arthritis is similar in patients with PsA and RA (14,17). Thus, it is clear that early aggressive therapeutic interventions are necessary in this disease.

The type of treatments prescribed for patients with PsA usually depend on the extent of both skin and joint manifestations. Because the majority of patients with PsA have psoriatic skin lesions in addition to arthropathy, therapy for PsA should target both the skin and the joints. Consequently, a multidisciplinary therapeutic approach involving rheumatologists and dermatologists may be necessary to treat PsA effectively. Mild skin involvement usually is treated with topical medications, including corticosteroid creams, tar shampoos, vitamin D cream, and ultraviolet irradiation, whereas mild arthritis is typically treated with nonsteroidal anti-inflammatory drugs. More severe skin disease is treated with psoralen with ultraviolet A irradiation, cyclosporine, and methotrexate (MTX). In cases in which both skin and joint involvement is severe, systemic therapies are usually prescribed, such as the disease-modifying antirheumatic drugs (DMARDs) MTX and cyclosporine. In addition to sulfasalazine, other systemic therapies that have been used in patients with PsA include chloroquine, gold, and penicillamine (18,19). These drugs have been thoroughly examined for efficacy in RA, but none of them have been approved in the United States for treating patients with PsA. In fact, most DMARDs that are used to treat PsA are administered only because they have been shown to be effective in treating RA (20,21). Few well-designed double-blind, controlled studies have examined the efficacy of conventional DMARDs in PsA (22). Several studies have analyzed small numbers of patients, were uncontrolled, and had poorly characterized patient groups (18,19,23-25). Studies that have looked at the long-term effects of these drugs in preventing progression of damage have not shown their superiority over nonsteroidal anti-inflammatory medications (26-28).

Clinical studies suggest that PsA treatments, in general, are not particularly effective and often not well tolerated. In a recent analysis of patients receiving DMARD treatment for PsA, Marguerie et al (29) found that both lack of efficacy and that adverse effects resulted in high discontinuation rates (Fig 1). Furthermore, studies that have looked at the long-term effect of conventional DMARD therapy for preventing progression of damage in PsA have not found significant differences between treated patients and controls (26-28). For these reasons, new therapies, including biologic agents, are being closely examined for their potential in PsA.

MTX

MTX is one of the most commonly prescribed drugs for the treatment of RA and has been rigorously examined for efficacy in this disease. Several randomized controlled studies involving patients with RA have shown that high-dose MTX can inhibit the radiologic progression of joint disease (30-32). The beneficial effects of MTX are dose dependent: higher doses are more effective in reducing clinical symptoms and in slowing radiographic progression (33,34).

MTX has been used for the treatment of psoriasis since the early 1960s. Although the effectiveness of MTX in RA has been thoroughly evaluated,

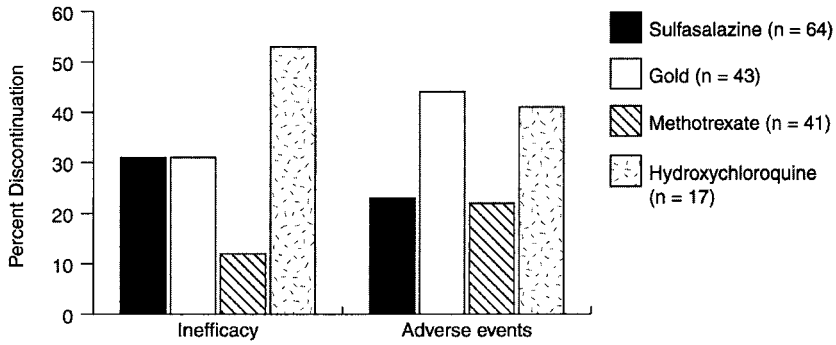

Fig 1. Discontinuations of DMARDs owing to lack of efficacy or to adverse events in patients with PsA. Data from Marguerie et al (29).

few controlled studies have examined its efficacy in PsA. Nevertheless, oral MTX is considered by rheumatologists to be the most effective PsA agent and is the drug of choice for patients with moderate to severe PsA (21). A few placebo-controlled trials in PsA have established that MTX has some efficacy (35,36), although the data are stronger for high-dose MTX than for low-dose regimens (23). An open, prospective study of 40 patients with PsA, MTX dosed at the discretion of the investigator provided good clinical response (24).

Compared with sulfasalazine, gold, and hydroxychloroquine, MTX has the best risk to benefit ratio, and the majority of patients remain on therapy for more than 2 years (29). However, the effect of MTX on long-term joint damage is less clear. Abu-Shakra et al (28) investigated the clinical and radiologic outcome of long-term (24 months) MTX therapy in a clinic population of patients with PsA. Analysis of prospective data showed that MTX was ineffective in retarding radiographic progression compared with nested-matched controls at 24 months; damage scores increased in 63% of the patients treated with MTX. However, dosing was at the discretion of physicians, and the mean dose of MTX was only 10.6 mg/week (28).

Efficacy aside, MTX is fairly well tolerated. Compared with other antiarthritic medications, such as cyclosporine and intramuscular gold, MTX has a lower frequency of discontinuation because of adverse effects (29,37,38). Nevertheless, MTX is associated with toxic effects. In clinical studies of PsA, approximately 10% to 30% of the patients treated with MTX discontinued therapy because of drug toxicity (28,29,37). Liver toxicity is the primary concern and occurs in as many as 28% of patients taking MTX (39). Interestingly, patients with psoriasis and PsA are approximately 3 times more likely than patients with RA to experience histologic hepatic abnormalities with MTX treatment (39). Therefore, periodic liver biopsies should be considered to monitor for liver damage. Another potential adverse effect of MTX treatment is pneumonitis, especially in patients with preexisting lung disease (40). The development of pneumonitis after low-dose MTX therapy has been described in patients with RA and PsA (40).

Sulfasalazine

Sulfasalazine is another DMARD that reduces the symptoms of joint inflammation in patients with RA (41,42). However, in North America, this drug is used less widely for RA than MTX, has worse patient compliance, and does not to inhibit the radiologic progression of RA more than placebo (30,41,42). In patients with PsA, conflicting observations regarding tolerability and efficacy have been reported with sulfasalazine. Recently, Jones et al (23) conducted a literature analysis of randomized trials involving the use of conventional DMARDs in the treatment of PsA. Sulfasalazine and high-dose parenteral MTX were the only medications with well-shown published efficacy in PsA (23). Clegg et al (22) found a trend toward improvement in PsA symptoms with sulfasalazine 2 g/day compared with placebo. Significant improvement in the symptoms of PsA also has been observed with the administration of sulfasalazine at a dose of 3 g/day (43,44). However, cutaneous response does not necessarily correspond with improvement in joint manifestations in individual patients (43). Rahman et al (45) found that nearly 50% of the patients with PsA who were taking sulfasalazine discontinued therapy because of adverse effects. For those patients able to toler-

ate the drug, no evidence of joint improvement over placebo was observed.

Cyclosporine

Cyclosporine reduces joint erosion in patients with RA and improves both joint inflammation and skin lesions in PsA (37,46). This drug also clears cutaneous lesions in patients with severe psoriasis (involving more than 25% of body surface area) (47). However, cyclosporine is not frequently used in either RA or PsA because of problems with toxicity, which have led to discontinuation rates as high as 46% in patients with PsA (37).

Gold

Antiarthritic therapy with gold compounds is moderately effective in reducing the symptoms of RA but is not frequently used because of its high potential for renal side effects (48-50). In patients with PsA, therapy with gold does not appear to prevent joint damage and may actually aggravate psoriasis. Although positive trends above placebo have been observed with oral gold, no significant reductions in the number or severity of joints affected with arthritis have been found (51). Intramuscular gold is more effective than placebo or oral gold in a randomized, controlled trial (52). However, in clinical experience, intramuscular gold is not more effective than MTX in preventing joint damage in patients with PsA (27,38). The lack of significant positive effects on joint inflammation with gold therapy is compounded by the fact that this agent is recognized for its adverse effects on skin. Both oral and intramuscular gold worsen psoriasis and cause dermatitis, which has led to high discontinuation rates in several clinical studies (38,51). Therefore, gold therapy is not considered an effective second-line agent for the treatment of PsA and is rarely used (21).

Etretinate

Etretinate is a vitamin A analog that is widely used for the treatment of psoriasis vulgaris. Etretinate inhibits the progression of psoriasis by reducing skin inflammation and by promoting keratinocyte differentiation (53). Because etretinate primarily targets the skin, it is not used for the treatment of RA. Although no large placebo-controlled trials with etretinate have been conducted in patients with PsA, pilot studies have shown etretinate to be effective in reducing the severity of skin lesions associated with this disease (54,55). These small studies also concluded that etretinate can reduce joint inflammation; however, these claims are questionable because anti-inflammatory drugs were coadministered (54,55). Etretinate is unlikely to become a useful drug in the treatment of PsA because of its significant adverse effects.

Other Drugs

Chloroquine and hydroxychloroquine are used effectively in early RA (56,57). Gladman et al (26) found that chloroquine was effective in PsA in controlling joint inflammation and did not precipitate skin flares, but was no better than placebo when the primary outcome measure (>30% reduction in joint count) was considered. A randomized controlled trial was recommended, but it was calculated that 200 patients would be necessary to detect a significant effect. Gastrointestinal complications are the major adverse effects caused by hydroxychloroquine and are experienced by approximately 30% of patients with RA who are treated with this drug (56).

Leflunomide, a newer antipyrimidine drug, diminishes symptoms of joint inflammation and inhibits the radiologic progression of RA (58,59). The common adverse effects observed with leflunomide are diarrhea, nausea, rash, and alopecia, which occur in 8% to 17% of treated patients (59). Preliminary studies with leflunomide suggest that this drug may improve skin and joint manifestations in PsA; however, 30% of the patients examined discontinued treatment because of adverse effects (19,60). A multicenter, randomized, controlled trial is currently underway.

Tumor Necrosis Factor (TNF)-Blocking Agents

The latest advances in the development of antiarthritic therapies are biologic agents that block the actions of TNF. Blocking the activity of TNF is a logical approach to treating PsA because high levels of TNF and its receptors have been observed in skin lesions and synovial fluids of patients with this disease (61-63). As in RA, TNF likely functions as a proinflammatory cytokine in PsA and plays a major role in maintaining joint and skin disease (64). Two drugs that block TNF function, etanercept and infliximab, have shown great promise in treating PsA. The Food and Drug Administration (FDA) has recently approved etanercept for this indication.

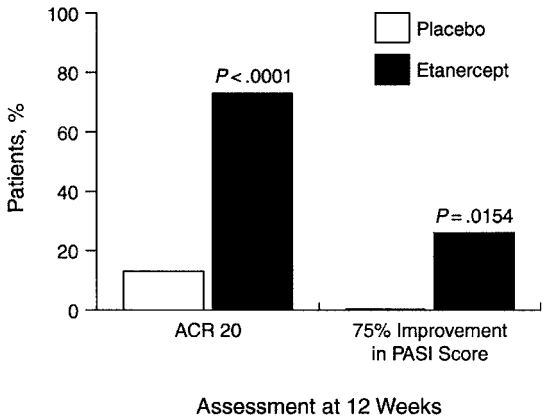

Fig 2. Etanercept improves the symptoms of psoriatic arthritis (PsA). ACR-20 and 75% improvement in Psoriasis and Severity Index score were assessed at 12 weeks after treatment. ACR-20 is the ACR's preliminary criteria for improvement. Data from Mease et al (68).

Etanercept is a human dimeric fusion protein consisting of the extracellular portion of 2 TNF receptors (p75) linked to the Fc portion of type 1 human immunoglobulin (65). This human TNF receptor fusion protein binds to and inactivates soluble TNF and lymphotoxin-α (66). Etanercept is the only drug proven efficacious in PsA in randomized placebo-controlled trials (67). Etanercept was significantly more effective than placebo in controlling symptoms: 73% of the patients treated with etanercept met the ACR-20 criteria for improvement at 3 months compared with only 13% of the patients treated with placebo (Fig 2) (68), whereas PsARC were met by 83% of the treated patients compared with 13% of the controls. In addition, 26% of a subset of patients with psoriatic lesions ($\geq$3% of body surface area) who were treated with etanercept achieved a 75% improvement in the Psoriasis Area and Severity Index, a composite measure of the extent and severity of skin involvement, whereas none of the patients treated with placebo had skin improvement. Improvement in both arthritis and psoriasis was sustained in these patients during a 24-week, open-label extension study, suggesting that etanercept remains effective with long-term administration (69). A large multicenter, double-blind, placebo-controlled phase 3 trial of 205 patients showed that etanercept is both efficacious and well tolerated in the treatment of psoriasis and PsA. The PsARC were met by 72% of the etanercept-treated patients compared with 31% of the placebo-treated patients at 3 months, and were maintained at 6 months. At 12 weeks, the ACR-20 was met by 59% of the etanercept-treated group compared with 15% of the placebo group ($P < .001$); target lesions were significantly improved with etanercept versus placebo (67). Importantly, etanercept was well tolerated—patterns of adverse effects in patients treated with etanercept were similar to those treated with placebo (67,68,70). Therefore, etanercept is an effective alternative to the more commonly used second-line drugs that are associated with toxic adverse effects and low efficacy.

Infliximab is a chimeric monoclonal antibody that binds specifically to human TNF and is composed of human constant and murine variable regions (71). Infliximab is efficacious in RA when coadministered with MTX (72). Several open-label studies examining small numbers ($N < 25$) of patients with PsA or spondyloarthropathy have observed improvement in both skin and joint manifestations with infliximab 3 to 5 mg/kg (73-80). Furthermore, many of the patients in these studies had PsA that was resistant to prior treatment with prednisone and with common DMARDs, including MTX and sulfasalazine (73,78-80). However, adverse effects in this patient population are of concern, particularly with regard to infections (80). Infliximab has been used successfully to treat recalcitrant psoriasis (81), and a multicenter trial of its use in PsA is underway.

DISCUSSION

PsA is recognized as a progressively destructive disease that can inflict severe damage. Therefore, the goal of the rheumatologist is to diagnose PsA early by using the known clinical features that distinguish PsA from RA. Also, closely monitoring patients with psoriasis for signs of PsA is important because cutaneous involvement usually precedes arthropathy. Given the progressive nature of the disease, PsA should be treated aggressively to avoid or to reduce joint damage. Ideally, therapeutic strategies should target both the psoriatic and arthritic aspects of the disease and should be well tolerated.

The older, more commonly prescribed DMARDs have typically been used to treat PsA because of their known activity in RA. However, there are distinct

differences between these 2 arthropathies, and agents that are safe and effective in the treatment of 1 disease may not necessarily show the same profile in the other. A case in point is the significantly higher incidence of hepatic abnormalities in patients with PsA treated with MTX compared with patients with RA who received this agent (39). Overall, DMARDs have not been well studied in patients with PsA, but available data suggest limited efficacy and tolerability issues.

The need for improved options for the treatment of PsA has led to the development of medications that are effective and tolerable. Preliminary data from small, open-label studies of infliximab and leflunomide suggest that these drugs may be useful; other investigational agents also are being pursued. Of the antiarthritic medications currently available, the TNF-blocking agent etanercept, which recently received FDA approval for this indication, is the only drug determined in randomized, controlled trials to be efficacious in PsA for both joint and skin symptoms. Rheumatologists and dermatologists need to reevaluate information regarding the efficacy of conventional DMARDs and consider TNF-blocking agents when choosing therapeutic strategies for the treatment of PsA.

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