Systematic Review of Treatments for Psoriatic Arthritis: An Evidence Based Approach and Basis for Treatment Guidelines

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ABSTRACT. Psoriatic arthritis (PsA) is a chronic systemic inflammatory disorder characterized by the association of arthritis and psoriasis. In addition to a heterogeneous and variable clinical course, PsA is complex and multifaceted and may include prominent involvement in the peripheral and axial diarthrodial joints, the skin and nails, and in periarticular structures such as entheses. A central mission of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is to develop guidelines, based upon the best scientific evidence, for the optimal treatment of patients with PsA. We outline the specific methods and procedures used in this evidence-based, systematic review of treatments for PsA, which we hope will provide a basis for future treatment guidelines. (First Release May 15 2006; J Rheumatol 2006;33:1417–21)

Key Indexing Terms:
PSORIATIC ARTHRITIS PSORIASIS DACTYLITIS ENTHESITIS NAIL PSORIASIS

INTRODUCTION

Psoriatic arthritis (PsA), a chronic systemic inflammatory disorder characterized by the association of arthritis and psoriasis, follows a heterogeneous and variable clinical course. While some patients have mild disease that is adequately responsive to mild therapeutic intervention, others have a severe erosive arthropathy that is often refractory to several treatments and may be associated with functional disability and accelerated morbidity. Although research has identified certain characteristics that are associated with poorer outcomes, such as polyarticular involvement, genetic associations, and radiographic damage, additional data are required so that patients can be individually stratified for optimum therapy.

PsA is a complex, multifaceted disease with prominent involvement of peripheral diarthrodial joints, axial joints, periarticular structures (e.g., entheses and other soft tissues, resulting in dactylitis), and the skin and nails. Recognizing this diversity of clinical characteristics, classification criteria for PsA have been developed and updated[1,2]. For a particular patient, treatment decisions may be driven by the extent and severity of involvement in one or more of these areas; however, all sites should be closely monitored for manifestations of active inflammation.

A number of different therapies have been adopted for the treatment of the various manifestations of PsA. Most of these treatments were "borrowed" from conditions that bear pathophysiologic and clinical semblance to individual facets of PsA: for example, peripheral arthritis in patients with rheumatoid arthritis (RA), axial involvement in patients with spondyloarthritis, and the skin and nails from patients with psoriasis. The extent to which therapeutic strategies can be extrapolated from other systemic inflammatory diseases to PsA remains to be fully defined. Similarly, outcome measures have been validated or are in the process of validation for these other conditions. The potential applicability of outcomes initially derived for patients with RA, psoriasis, and spondyloarthropathy in the assessment of patients with PsA is currently under investigation.

Recent progress in the delineation of immunopathophysiologic characteristics of PsA, in conjunction with advances in biotechnology, fostered the development of various novel therapeutic agents for PsA and other conditions. Issues such as cost, toxicities, and other considerations surrounding these newer treatments have stimulated substantial interest in the development of treatment guidelines for PsA. It is widely

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agreed that guidelines should be based upon the best available scientific evidence. For PsA, however, this raises several concerns. On the one hand, because study in this area is dynamic and rapidly progressing, the "state of the art" often exceeds what is published in peer-reviewed medical literature. For example, results of well designed studies may have been publicly presented at scientific meetings and may be widely known for a considerable period of time before they are actually published. On the other hand, guidelines that adhere to strict scientific evidence may not be able to address many of the practical issues necessary for practitioners caring for patients in the clinic. For example, without head-to-head studies or even comparable trials, it is difficult to state that one class of therapy should be selected prior to another class. It also should be recognized that study designs have evolved rapidly with the inclusion of more homogeneous subsets and a greater number of study subjects. Moreover, it is now expected that trials will be adequately powered to assess compounds that are dosed in the therapeutic range of efficacy with properly validated outcome measures. Thus, from a methodologic standpoint, many older studies were much less rigorous; therefore, potential bias against older therapeutic compounds may arise because the study designs are considered inadequate by today's standards. It should be remembered, however, that absence of evidence of an effect is not equivalent to evidence of absence of an effect. Finally, a major limiting factor in all systematic reviews of PsA is the lack of standardized, validated outcome measures for specific manifestations of disease.

The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) was founded in 2003 and comprises rheumatologists, dermatologists, and other investigators whose mission is to:

•Elevate awareness and improve communications between experts in PsA and psoriasis, especially rheumatologists and dermatologists, and other interested entities, including patient leagues, regulatory agencies, industry, other physicians, and the public

•Identify and study key domains of inquiry in PsA and psoriasis

•Develop updated classification criteria of PsA [through the Classification of Psoriatic Arthritis (CASPAR) group]

•Validate and standardize outcome assessment tools in PsA and psoriasis for basic clinical and therapeutic studies

•Improve educational efforts about PsA and psoriasis

•Improve conduct and standardization of clinical registries

•Develop treatment guidelines.

The goal of this review is to present the best scientific evidence relating to the treatment of PsA, while recognizing areas that need further research and clarification. It is accepted that the goals of treatment are: to improve the signs and symptoms of disease, prevent damage and disability, optimize functional status and quality of life, and to avoid toxicity.

This review is intended to be a framework from which treatment guidelines can be crafted.

METHODS

In an attempt to provide a review of the highest quality, authors adhered to the Conference on Guideline Standardization recommendations[3].

Review of treatments began with a consideration of the distinct organ involvement and characteristics of PsA (Figure 1). Individual aspects that were considered and are presented in individual reports include: (1) peripheral arthritis, (2) psoriasis, including nail involvement, (3) enthesitis, (4) dactylitis, and (5) axial arthritis.

For each aspect of disease, the best available evidence was collected, with a systematic review of the literature using established principles for such reviews[4]. Details of individual search strategies (databases scanned, terms used, rules for acceptance of articles) and results (articles retrieved, articles included) are presented in the individual reports[5-11].

In certain areas, there was a paucity of high quality data specifically addressing PsA. For example, few articles assess axial arthritis in patients with PsA, as opposed to patients with other spondyloarthropathies. At a GRAPPA meeting, the strong group consensus was that in areas lacking high quality data specific for PsA, articles addressing similar manifestations in related diseases would be reviewed and noted.

Reviewers excerpted data from retrieved articles to answer the following specific questions, focusing on each of the individual facets of disease:

1. What is the clinical effect of a given therapy on signs and symptoms of disease, and where appropriate, on quality of life/functional status and maintenance of structural integrity (e.g., prevention of joint damage assessed radiographically)?
2. What is the clinical effect of a given therapy with regard to toxicity?

Wherever possible, effect sizes were calculated to quantify the extent of efficacy or toxicity. Effect size, also known as standard mean difference, is the mean difference in effect between treatment and control, divided by the standard deviation of the difference. Effect sizes of 0.2 or less are considered small, whereas effect sizes greater than 0.8 are considered large.

Reviewers then graded the evidence as it related to each specific question, in accordance with recommendations from the Agency for Health Care Policy Research (AHCPR). These categories of evidence include:

1a. Evidence from metaanalysis of randomized controlled trials (RCT). b. Evidence from one or more RCT.

2a. Evidence from one or more controlled trials (without randomization). b. Evidence obtained through other well designed studies (quasi-experimental).

3. Evidence from non-experimental studies (descriptive studies such as comparative or correlation studies, or case-control studies).

4. Expert committee opinions, clinical experience.

Preliminary recommendations for treatment of PsA were made using the best available evidence extracted from pub-

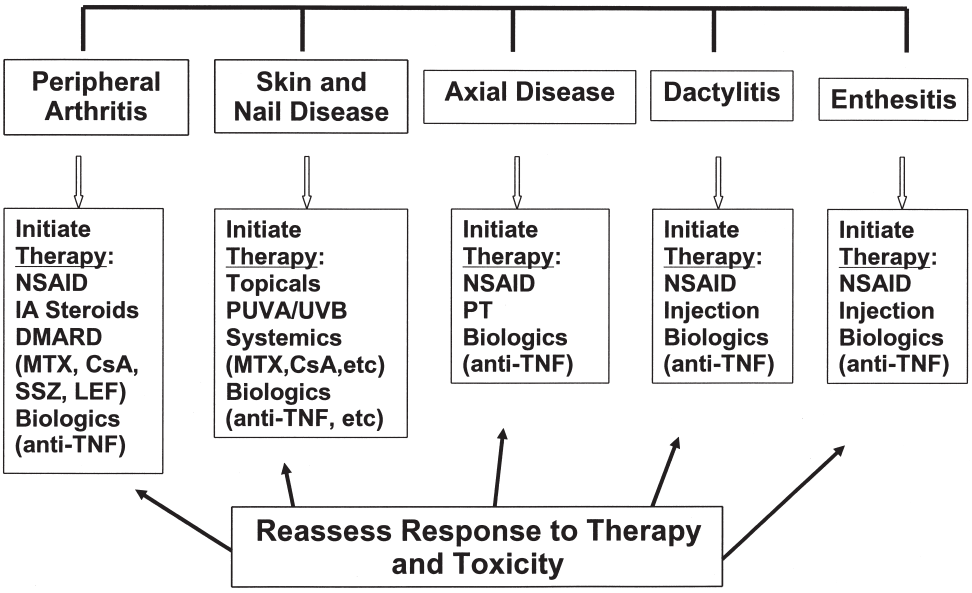

Figure 1. GRAPPA treatment guidelines for psoriatic arthritis, categorized by disease characteristics and distinct organ involvement. Anti-TNF: tumor necrosis factor inhibitor; CsA: cyclosporin A; DMARD: disease modifying antirheumatic drugs; IA: intraarticular; LEF: leflunomide; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drugs; PT: physiotherapy; PUVA: psoralen plus ultraviolet light A; SSZ: sulfasalazine; UVB: ultraviolet light B.

lished literature. The strength of recommendations is graded as follows:
Grade A: Category 1 evidence.
Grade B: Category 2 evidence, or extrapolation from Category 1 evidence.
Grade C: Category 3 evidence, or extrapolation from Category 1 or 2 evidence.
Grade D: Category 4 evidence, or extrapolation from Category 2 or 3 evidence.

In an attempt to bridge the gaps where definitive scientific evidence was lacking, "expert opinion" and consensus (e.g., the community standard) were used to suggest recommendations for key practical issues. However, in determining future treatment guidelines for PsA, factors such as health resource allocations, patient preferences, local issues related to comorbidity, and political and social considerations will be important. Recommendations that appear reasonable according to consensus of experts may well be overly restrictive in certain circumstances or financially untenable in others. Importantly, throughout this systematic review, the reviewers were charged to identify areas lacking sufficient data to support evidence grading or preliminary recommendations, to form an agenda for further research.

SUMMARY OF RESULTS

Because PsA is multifaceted, involvement in distinct aspects of disease must be considered in treatment decisions. Therapeutic choices may be driven predominantly by the aspect of disease considered "worst" or "most severe" at the time of the evaluation. Also, given the need for individually specific outcome measures to assess each type of involvement, it is most straightforward to excerpt data from the medical literature according to individual aspects, as has been done in the accompanying articles[5-11]. Overall treatment decisions, however, should be guided by the interplay of disease manifestations at the different sites for each individual patient.

Peripheral arthritis (*for details, see Soriano, et al*[5])

Factors relevant to the assessment of disease activity and severity of peripheral arthritis in PsA patients include: (1) the extent of synovitis, with polyarticular disease (≥ 4 involved joints) having a more severe course and impaired outcome than oligoarticular disease (< 4 involved joints); (2) the presence of joint damage, indicated by periarticular erosions, which is indicative of disease of greater severity and with a greater propensity for further damage; and (3) impairment of functional status.

Summary. Nonsteroidal antiinflammatory drugs (NSAID) are widely used empirically. The data support the efficacy of various NSAID in peripheral arthritis of PsA patients (level 1b, grade A). NSAID have not been shown to be of benefit for skin disease, and there are anecdotal reports of worsening skin involvement with their use. Data regarding the relative efficacy/toxicity of cyclooxygenase-2 inhibitors in PsA are not available.

Although commonly used in the clinic, the utility of oral or parenteral corticosteroids for peripheral arthritis in PsA has not been examined.

While the breadth and depth of studies are modest, some data support the utility of disease modifying antirheumatic drugs (DMARD), including sulfasalazine (level 1a, grade A), leflunomide (level 1b, grade A), methotrexate (level 1b-3, grade B), cyclosporine (level 1b-3, grade B), and azathioprine (level 2b, grade B) in PsA. The evidence was negative (level 1a) for oral and injectable gold. Based on considerations of effect size and quality of the data, all DMARD may have a small to medium effect on improvement of clinical signs and symptoms of PsA. The evidence either refutes or does not strongly support any effect of DMARD on joint damage. Toxicity issues are known and manageable.

Inhibitors of tumor necrosis factor (TNF; etanercept, infliximab, and adalimumab) substantially improve the signs and symptoms of peripheral arthritis in PsA (level 1b, grade A). In addition, all agents improve functional status and quality of life. Moreover, these agents attenuate the progression of joint damage as assessed radiographically. Toxicity issues are known and manageable.

Data are not available to support the necessity or desirability of any specific sequence of treatments for the peripheral arthritis of PsA.

Psoriasis (*for details see Strober, et al and Boehncke, et al*[6,7])

In a recent publication, Mason, *et al*[12] provide a systematic review of the spectrum of topical anti-psoriatic therapies. Similarly, although systematic reviews of phototherapies are scarce, important information can be obtained from Berneburg, *et al*[13] or Zanolli[14]. Although topical therapies do not improve the signs and symptoms of PsA, some data indicate that intensive phototherapy (such as that encountered at the Dead Sea Psoriasis Treatment Spas[15]) improves the signs and symptoms of PsA[16,17]; these reports, however, were not RCT and did not use validated standardized assessment tools. Neither topical therapies nor phototherapies, however, have the potential to improve signs and symptoms of both psoriasis and psoriatic arthritis in patients with PsA. Therefore, the focus of this review was on systemic therapies currently used for treating the cutaneous manifestations of PsA.

Factors relevant to the assessment of disease activity and severity of psoriasis in PsA patients include: (1) body surface area (BSA) of involvement (with ≥ 10% BSA involvement considered moderate to severe, and < 10% considered mild, according to some sources); (2) significant involvement of the face or hands; (3) the presence of other types of involvement, such as pustular or erythrodermic psoriasis; and (4) effect of skin symptoms on quality of life. Recently, a few studies have assessed the efficacy of therapies on psoriasis in patients with PsA; however, more data are available from trials performed in patients with psoriasis, regardless of the presence or absence of arthritis.

Summary. Few well designed, randomized, placebo-controlled studies of an adequate size have been performed on the older systemic agents used to treat psoriasis. Both cyclosporine and methotrexate were equally effective in a recent comparative trial of the 2 agents that did not include a placebo group (level 1b, grade A). The hepatic toxicity of longterm methotrexate in patients with psoriasis is still unresolved, although data from a metaanalysis demonstrated progressive fibrosis without cirrhosis in some patients who had sequential liver biopsies[18]. Cyclosporine is the faster-acting of the 2 medications, but dose-related nephrotoxicity and hypertension have been reported.

Acetretin is less effective when used as monotherapy for plaque psoriasis, and mucocutaneous side effects and alopecia are often observed (level 1b, grade A). Sulfasalazine and leflunomide have level 1b, grade A evidence substantiating their use as monotherapy in plaque psoriasis, but both were minimally effective. No controlled trial data are available for hydroxyurea or 6-thioguanine (level 3, grade C).

Inhibitors of TNF (etanercept, infliximab, and adalimumab) substantially improve the signs and symptoms of psoriasis (level 1b, grade A). Toxicity issues are generally known and manageable. Experience with longterm use is available from observations in other indications (e.g., RA).

Alefacept, a T cell-depleting agent that also inhibits T cell costimulation, modestly improves the signs and symptoms of psoriasis; however, efficacy in PsA is limited to one 12-week study where results were modest. The vast majority of data are from studies of psoriasis patients without PsA (level 1b, grade A). Toxicity issues are generally known and manageable. Currently, few data are available on longterm use.

Efalizumab, an inhibitor of the adhesion molecule CD11, modestly improves the signs and symptoms of psoriasis; however, efficacy in PsA is poor. All available data are from studies of psoriasis patients without PsA (level 1b, grade A). Toxicity issues are generally known and manageable. Currently, few data are available on longterm use.

Nail involvement (*for details, see Cassell, et al*[8])

Nail involvement is very common in patients with psoriasis and PsA. Most available data were obtained from studies of psoriasis without PsA. In addition to a paucity of high quality research studies, the lack of validated outcome measures severely affects data in this area.

Summary. Several therapies with modest efficacy have been studied in nail psoriasis. Among available agents, higher quality data are available to support the efficacy of cyclosporine and infliximab, a TNF antagonist.

Axial disease (*for details, see Nash*[9])

Axial involvement is common in PsA, although prevalence rates vary from 40% to 74% depending upon criteria for diagnosis. Currently, very little evidence is available to assess efficacy and safety of therapy for axial involvement in PsA. Despite a number of differences between axial involvement in PsA and axial manifestations of AS, the consensus of GRAP-

PA was to borrow outcome measures and therapies used for AS in this systematic search of the literature.

Summary. Based on studies in AS, the results suggest that infliximab, etanercept, and adalimumab have the potential to reduce the signs and symptoms of moderate to severely active axial involvement in PsA in patients who have had an inadequate response to NSAID (level 1a, grade A). Current evidence supports their use as monotherapy for at least one year.

Enthesitis (*for details, see Ritchlin*[10])

Enthesitis is defined as inflammation at sites of tendon, ligament, joint capsule, or fascia insertion to bone, and is a hallmark feature of PsA. Several outcome measures have been developed to assess enthesitis, including the Mander Enthesitis Index and the Maastricht Ankylosing Spondylitis Enthesitis Score; however, no instrument has been validated in PsA.

Summary. The anti-TNF agents (infliximab and etanercept; level 1b, grade A) are more effective for the treatment of enthesitis than traditional agents. Level 3, grade C evidence suggests the efficacy of mesalamine, and level 4, grade D evidence suggests the efficacy of NSAID, physiotherapy, and corticosteroid injections on entheseal symptoms. Sulfasalazine is not effective (level 1b, grade A), and methotrexate has not been analyzed for treatment of enthesitis in PsA.

It should be noted, however, that several different outcome measures were used in the studies reviewed. Large controlled trials examining the effect of traditional DMARD on enthesitis have not been done.

Dactylitis (*for details, see Helliwell*[11])

Dactylitis occurs in up to one-half of all patients with PsA at some time during their disease course. Imaging studies support the view that dactylitis arises from inflammation in the flexor tendons, although adjacent synovitis and enthesitis are commonly observed. Acute dactylitis appears to be a severity marker for PsA and psoriasis.

Summary. Traditionally, clinicians have used NSAID and local corticosteroid injections to treat dactylitis, although conventional DMARD also are recommended. Valid, reliable, and responsive clinical outcome measures have not yet been developed.

Results suggest that infliximab is effective for the treatment of dactylitis in PsA (level 1b, grade B); however, dactylitis was a secondary outcome measure, and improvement was modest. Data from other studies were too limited to warrant summary.

CONCLUSION

The reviews summarized here and presented in the referenced articles are based upon the best currently available scientific evidence. The decision to choose a particular treatment, however, should be based on a variety of factors: the diagnosis, disease activity, prognosis, comorbid conditions, and individual preferences of each patient; the anticipated benefit and risk of treatment; quality of life issues; and political and social considerations. GRAPPA will continue to encourage research to validate outcome measures and to develop specific treatment guidelines for patients with PsA.

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