Systematic Review of Treatments for Psoriatic Arthritis: 2014 Update

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ABSTRACT. Psoriatic arthritis (PsA) is a chronic systemic inflammatory disorder characterized by the association of arthritis and periarticular inflammation in patients with 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. Simultaneous inflammation in the skin and musculoskeletal structures in a single patient, a relatively common scenario, often leads to marked decrease in function and quality of life. Thus, it is essential for the clinician to document the extent of disease involvement and craft a therapeutic plan that addresses the different domains of disease. In an effort to update previous treatment recommendations developed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), several evidence-based, systemic reviews of therapies for PsA were completed, analyzed, and circulated for consensus. (J Rheumatol 2014;41:2273–6; doi:10.3899/jrheum.140875)

Key Indexing Terms:
PERIPHERAL ARTHRITIS | AXIAL DISEASE | PSORIASIS
NAIL PSORIASIS | ENTHESITIS | DACTYLITIS

Several national and international treatment guidelines for psoriatic arthritis (PsA) have been published, but management algorithms vary, and guidelines are complex, difficult to implement in daily practice, and are generally based on limited evidence. Further, variability from patient to patient in disease severity and the number and blend of domains involved greatly limit the applicability of treatment algorithms for the practicing clinician. Moreover, algorithms are often formulated based on extrapolated evidence from other inflammatory arthritides and can be strongly influenced by eminence-based input and pharmacoeconomic considerations.

A central mission of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is to develop treatment recommendations, based upon the best scientific evidence, for optimal treatment of patients with PsA. Previous recommendations were published in 2009[1], following the publication of a supplement in 2006[2] that systematically appraised the evidence for therapies in each of the different domains of psoriatic disease. The literature search for these recommendations included evidence published up to 2003. For treatment recommendations to be of value, they must be dynamic, applicable in daily practice, and up to date. Since 2003, many clinical trials have assessed new methodologies and outcome measures in PsA, with increased therapeutic options. Thus, it is time to update treatment recommendations for patients with PsA.

In the last decade, an expanding medical literature has documented the prevalence and significance of the many comorbidities associated with PsA, and most importantly, how these various disorders affect morbidity, mortality, and therapeutic response. In particular, the high prevalence of obesity coupled with the metabolic syndrome must be factored into treatment decisions and strategies. Since the previous recommendations, several well-designed studies have provided valuable initial insights into the interaction between comorbidities and treatment response in PsA and other forms of inflammatory arthritis. Therefore, a major goal was to tailor the revised PsA recommendations to specifically address how clinicians might best translate knowledge regarding comorbidities into treatment decisions.

The GRAPPA Treatment Guidelines committee decided to follow the Appraisal of Guidelines, Research, and Evaluation (AGREE) instrument throughout the development and appraisal of these revised treatment recommendations[3]. AGREE contains 23 items in 6 domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. The AGREE instrument was to be consulted during

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formulation of the treatment recommendations and also to formally evaluate the recommendations following completion.

In the 2006 review, the quality of evidence was graded according to the categories of evidence presented by the Agency for Health Care Policy Research (AHCPR) ranging from 1A for a metaanalysis of randomized controlled trials (RCT) to 4 for expert committee opinions. However, the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) group has developed a new system to formally evaluate levels of evidence from medical literature[4]. In the GRADE system, the quality of evidence for each outcome is rated initially as high or low dependent on the study design [randomized controlled trials (RCT) are high, observational studies are low]. Ratings can be modified upward if the study has a large effect magnitude, evidence of a dose response, or if the effect is unlikely to be due to confounding. Conversely, ratings can be modified downward if the evidence is indirect or if the study has significant limitations, is imprecise, has inconsistent results, or is likely to be affected by publication bias. The final result is a grading of the evidence as high, moderate, low, or very low. Following grading of the evidence, the individual subcommittees were to provide some quantifiable estimation of the relevance of the research. It was suggested that Cohen's effect size could be calculated[5], as was done previously, to estimate effect size of continuous variables; however, for certain categorical outcome measures such as the American College of Rheumatology (ACR) 20, 50, and 70 responses, number-needed-to-treat (NNT) was deemed more appropriate.

Based on the format followed in 2006, subcommittees were convened to assess the evidence within the individual domains of psoriatic disease (peripheral arthritis, skin, nails, enthesitis, dactylitis, and axial disease) to critically appraise the evidence and to develop specific recommendations that would be circulated to the membership to determine consensus. In addition, a new subcommittee was convened to address key comorbidities in psoriatic disease that may negatively affect overall health and affect treatment decisions. One member from each of these groups also collaborated in an additional committee to evaluate the toxicity of individual therapies in their respective domain.

The initial search was run in Medline and Embase on February 19, 2013. Key search terms included both free text and MeSH (US National Library of Medicine medical subject heading) topics and included "psoriatic arthritis," "psoriatic," "enthesitis," "enthesopathy," or "dactylitis" in combination with any of the following: "drug treatment/therapy," "disease modifying anti-rheumatic drugs/DMARDs," "biologic," "biological therapy," and the proprietary and trade names of all therapies used in PsA. The search was limited to articles in English and publications since 2003 to ensure that articles published since the last systematic review were selected. A total of 7481 papers were identified in the search (Figure 1); of these, 294 articles were highlighted for inclusion in the systematic review and shared with the members of the subcommittees. In addition, results for key RCT were extracted to preexisting data extraction forms, thus providing key outcomes for the large trials to calculate effect sizes for comparison of therapies. Individual groups then performed a secondary search, as well as hand searches of references from retrieved articles. In addition, each group was charged with performing an independent literature review within their individual topic. Articles retrieved from the 2 independent literature searches as well as the hand searches would be combined to form the evidence base.

When the treatment recommendation revision project began in 2012, the process was discussed at GRAPPA meetings that were typically held several times a year, often in conjunction with key rheumatology and dermatology congresses. At these meetings, relevant stakeholders, including patients with PsA, rheumatologists, dermatologists, and epidemiologists engaged in discussions to refine the process of formation of the treatment recommendations. Of note, representatives from the pharmaceutical industry, some of whom are active members of GRAPPA, participated in the general discussions of the process, but they did not participate in the systematic literature review or in the synthesis and development of the recommendations.

The evidence for different therapies was considered

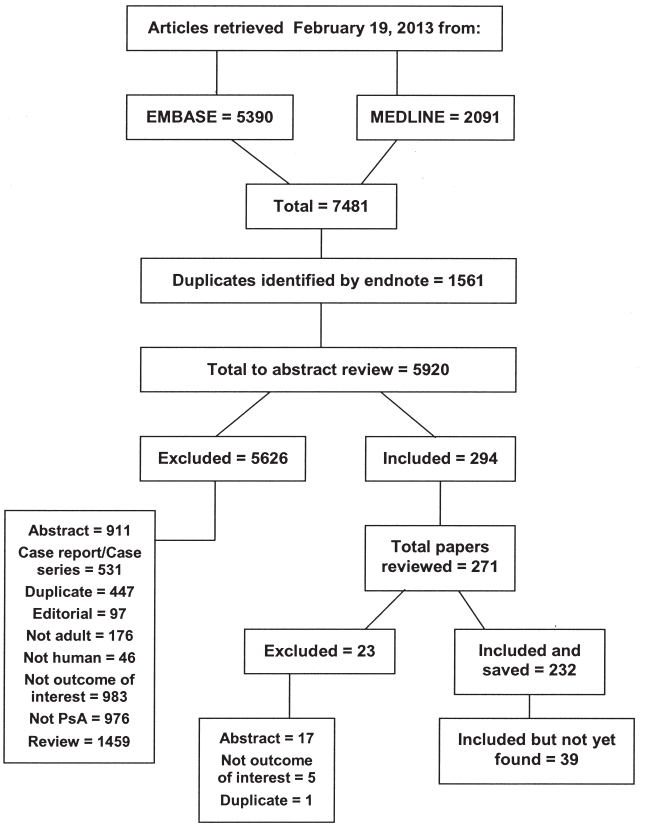

Figure 1. GRAPPA treatment recommendations search results.

within each disease domain, and these results are reported in detail in the accompanying articles summarized below. Clearly, therapeutic decisions for individual patients must take into consideration not only the sum of activity in each of the individual domains, but also the presence of any comorbidities, as well as response to previous therapies.

Peripheral arthritis (for details, see Acosta Felquer, *et al*[6]). Peripheral joint disease may be progressive in PsA patients despite the availability of a wide range of traditional and novel therapies. Although nonsteroidal antiinflammatory drugs (NSAID) have been commonly prescribed for peripheral arthritis, little new evidence supporting efficacy could be documented. However, new data were reported on traditional use of disease-modifying antirheumatic drugs (DMARD), specifically methotrexate (MTX), where results from 2 RCT suggested its potential efficacy. Limited data from observational and open-label studies provide additional lower-level evidence for the efficacy of MTX, leflunomide, and cyclosporine in PsA.

Higher levels of evidence support the use of anti-tumor necrosis factor (TNF) agents in PsA. Statistically significant improvements in measures of joint disease were demonstrated with etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol compared with placebo, although effect sizes were not always available. Other biological DMARD, specifically ustekinumab, abatacept, brodalumab, and secukinumab, also demonstrated statistically significant improvements compared to placebo. Apremilast, a small molecule that specifically inhibits phosphodiesterase 4, was superior to placebo in a series of 4 Phase III studies.

Results with combination therapies were also reported, particularly MTX in combination with anti-TNF therapies and other biologics in trials without placebo controls.

Axial disease (for details, see Nash, *et al*[7]). Axial disease in patients with PsA is frequently compared to ankylosing spondylitis (AS), and many therapies used in AS have been analyzed in PsA. Unfortunately, scant data are available on traditional therapies for axial disease in PsA (e.g., NSAID, MTX, etc.), but limited new data are available for targeted biologics and novel agents. Although improvement in axial disease is not often specified as an endpoint, significant benefits have been noted in RCT of anti-TNF therapies in AS, psoriasis, and PsA, particularly regarding disease activity, range of motion, physical function, and quality of life, both as monotherapy and in combination with other DMARD. Other biologics (e.g., ustekinumab, brodalumab) have reported some success in axial PsA in small open-label studies. Guidelines from the Assessment of Spondylo-Arthritis International Society (ASAS) are sometimes borrowed for use in PsA patients with axial disease.

Enthesitis (for details, see Orbai, *et al*[8]). Enthesitis or inflammation at sites where ligaments, tendons, and joint capsules attach to bone is prevalent in PsA and may be centrally involved in its disease pathogenesis. The authors discuss 5 different enthesitis outcome measures used across 12 clinical trials to assess enthesitis in PsA. Based on high quality data from RCT of anti-TNF agents, level 1b evidence is available for infliximab, golimumab, and certolizumab efficacy in enthesitis. Level 1b evidence is also available for the biologic ustekinumab and the novel agent apremilast.

Dactylitis (for details, see Rose, *et al*[9]). Dactylitis, or "sausage digit," is a hallmark clinical feature of PsA. Traditionally, NSAID, local corticosteroid injections, and DMARD have been used to treat dactylitis. In this review, the authors found large variabilities in study designs, outcome measures, and availability of primary data. However, significant improvements in dactylitis were observed with the use of ustekinumab, certolizumab, and infliximab. One etanercept study demonstrated improvement in dactylitis scores, but a placebo-controlled trial is required that targets dactylitis as an endpoint. The role of anakinra remains uncertain.

Psoriasis (for details, see Boehncke, *et al*[10]). To comprehensively treat patients with both PsA and psoriasis, we must control both disease domains. However, efficacy data from PsA or psoriasis studies, using the same drug, often show discrepancies. Some experts allege as the reason for this phenomenon that many patients with PsA have relatively mild psoriasis, and the milder the psoriasis, the more difficult it is to assess efficacy. Of the studies reviewed, half related to MTX and half to biologics. Among the biologic therapies, the anti-TNF drugs adalimumab, certolizumab, 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 and apremilast.

Efficacy data are also available from psoriasis trials, which demonstrate remarkable efficacy for brodalumab, ixekizumab, and secukinumab, and it is anticipated that many of these agents may be approved for this indication in the near future.

Nail disease (for details, see Armstrong, *et al*[11]). Nail involvement in psoriatic diseases causes significant physical and functional disabilities. Therapies include topical (e.g., calcipotriol, tacrolimus, tazarotene, and 5-fluorouracil), procedural (pulsed dye laser), and systemic. Among systemic therapies, cyclosporine has modest efficacy; oral MTX seems unlikely to result in significant improvement; and acitretin and leflunomide had modest efficacy in psoriatic nail dystrophy. Anti-TNF therapies, specifically adalimumab, certolizumab, etanercept, golimumab, and infliximab, were highly efficacious in treating psoriatic nail disease. Newer biologic therapies that have been studied include ustekinumab and interleukin 17 inhibitors.

Comorbidities (for details, see Ogdie, *et al*[12]). The authors

discuss numerous comorbidities associated with PsA. Cardiovascular disease, which includes increased prevalence of ischemic heart disease, cerebrovascular disease, diastolic dysfunction, left ventricular dysfunction, abnormal carotid intimal thickness, and cardiovascular death, represents a major source of morbidity for patients with PsA. Increased prevalence of obesity and metabolic syndrome have also been observed and may negatively affect disease activity and response to therapy. Diabetes, specifically Type II diabetes mellitus, may be explained by increased obesity and unhealthy lifestyle, and possibly related to insulin resistance driven by PsA inflammation.

Other comorbidities include inflammatory bowel disease, autoimmune ophthalmic disease (e.g., uveitis, keratitis, blepharitis, conjunctivitis, episcleritis, scleritis), and osteoporosis. Data are inconsistent regarding malignancy associated with PsA. Fatty liver disease, particularly non-alcoholic fatty liver disease, has an increased prevalence in patients with psoriasis, but studies in PsA are limited. Kidney disease has been associated with both psoriasis and PsA.

In conclusion, these articles form an update in the evidence-based review of therapies in psoriatic disease, including data published up to 2013. Treatment recommendations from GRAPPA will follow, based on this systematic assessment of the literature, but it is recognized that in such a heterogeneous disease, the final decision on therapy in an individual patient must be based on a thoughtful discussion with their healthcare team.

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