

# GRAPPA Treatment Recommendations: An Update from the GRAPPA 2013 Annual Meeting

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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. 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. Guidelines were previously published in 2009 based on an evidence-based systematic review. Given important recent developments and robust ongoing research into the treatment of PsA, GRAPPA undertook to update the guidelines. Herein we outline the specific methods and procedures used both in the initial and the current evidence-based, systematic reviews of treatments for PsA. We also review the numerous discussions regarding how best to finalize and publish these new guidelines in 2014. (J Rheumatol 2014;41:1237–9; doi:10.3899/jrheum.140179)

*Key Indexing Terms:*

PSORIATIC ARTHRITIS  
DACTYLITIS

PSORIASIS  
TREATMENT

ENTHESITIS  
BIOLOGICS

A core function of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), as highlighted in its mission statement, is “to develop guidelines, based upon the best scientific evidence, for the optimal treatment of patients with psoriatic arthritis (PsA).” This task was originally undertaken soon after the formation of GRAPPA in 2003, when a guidelines committee and a number of subcommittees were formed to study individual domains of the disease. The first step in the development of the 2009 GRAPPA treatment guidelines was the decision, based upon understanding of the extant medical literature related to disease manifestations and therapeutic interventions of PsA, to focus on 6 individual domains of PsA: peripheral arthritis, skin disease, nail disease, enthesitis, dactylitis, and axial disease. Next, a systematic review was undertaken of the evidence for therapies in PsA with a search of all literature published through 2003. Separate subcommittees focused on the evidence for the individual domains. In 2006, a number of articles were published

outlining the results of this systematic review<sup>1</sup>. Following these reviews, the guidelines committee synthesized this information into comprehensive recommendations for therapy, published in 2009<sup>2</sup>.

During this process, it was considered essential that determination of the most appropriate therapies for individual domains of PsA should involve both the activity and severity of disease and the cumulative effect of all the domains on function and quality of life. This led to the creation of the “GRAPPA grid,” which outlined different levels of evidence-based therapy for each domain of the disease (peripheral arthritis, skin and nails, enthesitis, dactylitis, and axial disease) at “mild,” “moderate,” and “severe” disease activity. Spirited discussions ultimately resulted in consensus concerning what constituted mild, moderate, and severe disease activity in each domain. Importantly, at each level, the effect of disease on the individual patient was considered, such that disease that affected patient function (e.g., for articular and polyarticular domains) and quality of life (e.g., for skin manifestations) would raise the activity level higher than it might be, based on other measures. Also considered was the effect of prior and concomitant therapies, i.e., disease activity would be considered higher if a patient had already unsuccessfully received therapies relevant to that level. Finally, several individual cases were presented to illustrate choice of therapies, using the grid to demonstrate its usefulness in actual clinical practice.

In 2012, GRAPPA members decided that the guidelines and the literature review on which they were based needed to be updated, given the decade of research and substantial

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new data since the original project. Thus, the Treatment Recommendations Committee was reconvened.

## Methodology

The Treatment Recommendations Committee is again codirected by Arthur Kavanaugh (University of California at San Diego, California, USA) and Christopher Ritchlin (University of Rochester, Rochester, New York, USA). The original committee directors and subcommittee chairs were asked to serve as experienced leaders and to collaborate with any new cochairs. In addition to the existing subcommittees (peripheral arthritis, skin and nails, enthesitis, dactylitis, and axial disease), another subcommittee was created to review comorbidities related to PsA. Also, a member of each subcommittee was designated to meet with representatives from other domain subcommittees to ensure appropriate focus on safety/toxicity within each group.

In the initial systematic review in 2003, each subcommittee performed its own literature search and review. In an attempt to streamline this process and make it more uniform, it was decided that in this update, an initial comprehensive literature search for all of PsA would be performed, with the results shared with each subcommittee. Each subcommittee would then undertake a secondary search.

The initial search was run in Medline and Embase on February 19, 2013. The key search terms included both free text and MeSH (US National Library of Medicine subject headings) topics and consisted of “psoriatic arthritis,” “psoriatic,” “enthesitis,” “enthesopathy,” or “dactylitis” in combination with any of the following: “drug treatment/therapy,” “disease-modifying antirheumatic 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 or after to ensure that articles published since the last systematic review would be the focus. This search identified 7481 papers, which were reviewed initially by title and abstract; of these, 1561 duplicates and 5626 papers that were not relevant were excluded. A total of 294 papers were highlighted for inclusion in the systematic review and shared with the subcommittees. In addition, results for key randomized controlled trials (RCT) were extracted to provide key outcomes for the large trials that could be used to calculate effect sizes for comparison of therapies. The subcommittees then performed a secondary search, as well as hand searches of references from retrieved articles.

## Proceedings at the 2013 GRAPPA Annual Meeting

A plenary session for all GRAPPA members was held at the 2013 Annual Meeting to introduce the background for the treatment recommendations project and the need for updating the guidelines. An outline was presented of the framework proposed for developing the treatment guidelines: the Appraisal of Guidelines, Research and Evaluation

(AGREE) instrument<sup>3</sup>, which included 23 items in 6 domains that should be considered and evaluated in guideline development. These 6 domains cover scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. The committee proposed that the AGREE instrument be consulted throughout the process of guideline development and used as a framework for assessment following completion.

The 2006 methodology was reviewed to assess the quality of evidence. At that time, the research was graded according to the categories of evidence presented by the Agency for Health Care Policy Research (AHCPR) and ranged from 1A for a metaanalysis of RCT to 4 for expert committee opinions. Guidelines were then graded from A to D dependent on the category level of the supporting evidence. Members determined to use this process again as an initial method to assess the stringency of the literature.

However, to aid in the subsequent incorporation of evidence into guidelines, an additional method was proposed for grading the evidence for these updated reviews. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) group<sup>4</sup> developed a system for grading of evidence from medical literature in 2000, which has since been adopted by a number of organizations, including the Cochrane Collaboration, the World Health Organization, the American College of Physicians, and the UK National Institute for Health and Clinical Excellence. In the GRADE system, the quality of evidence for each outcome is rated initially as high or low depending on the study design (RCT are high, observational studies are low). Ratings are then modified upward if the study has a large effect of magnitude, evidence of a dose response, or if the effect is unlikely to be due to confounding. Ratings can also 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. This system results in a final 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 such research. It was suggested that Cohen’s effect size could be used again to estimate effect size of continuous variables; however, for certain binary composite outcome measures such as the American College of Rheumatology (ACR) 20, 50, and 70 responses, “number needed to treat” would be more appropriate.

Laura Coates (University of Leeds, UK) next presented the results of the systematic literature review done to date and highlighted the timetable for further literature reviews. Except for the subcommittees for skin and nails, the subcommittees were to meet again at the ACR Annual Meeting in San Diego in October 2013 and present their work to date. Subcommittees for skin and nail disease were

to reconvene at the American Academy of Dermatology (AAD) Annual Meeting in Denver in March 2014.

Following the plenary at the GRAPPA meeting, the subcommittees formed breakout groups to review the literature search to date, decide whether further literature review was required for their subcommittee, and plan how they were going to develop specific recommendations for individual drugs or classes of drugs in specific situations based on the evidence provided. A patient representative was present in each of the groups to give their perspective to the planned review. Each subcommittee also nominated a representative for the safety/toxicity group.

Subcommittee members reported the results of their discussions to the full group in a feedback session. The majority of groups believed they needed to extend the literature review slightly to ensure that they did not miss evidence specific to their field. This was particularly true for the axial PsA group because very little evidence was available specific to axial PsA; thus, the group decided, as in 2003, to widen the search to other forms of axial spondyloarthritis. Of note, the newly added comorbidities subcommittee met for the first time to discuss its task.

For the new guidelines, the previously established GRAPPA grid will be reviewed and updated. In addition to consideration of patient preferences/effect and prior/concomitant therapy, recommended therapies will be viewed through a “filter” based on comorbidities. In some instances, therapy might be accelerated based upon additional areas of disease involvement. For example, tumor necrosis factor inhibitors might be considered for patients with low levels of disease activity who have concomitant uveitis. Alternatively, the choice of therapy might be “downgraded” in the presence of a certain safety issue or concern.

### Work undertaken since the 2013 Annual Meeting

At a GRAPPA meeting adjacent to the ACR Annual Meeting in San Diego, all subcommittees except the skin and nail subcommittees met again in breakout groups with patient representation to discuss the progress to date with literature review, grading, and data extraction, and to formalize timelines for future publication. These groups are now preparing manuscripts that outline the diagnostic and treatment advances that have taken place since 2009 for their respective domains. Following the AAD Meeting in March 2014, the dermatologists will meet to formulate recommendations for skin and nail disease in the setting of PsA and formal recommendations will be drafted and approved.

The updating of the systematic review of treatment of PsA is well under way, with a number of subcommittees convened to lead on grading, data extraction, and future publication of this evidence. The goal is to complete this process and publish an updated evidence-based GRAPPA treatment recommendation in 2014.

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