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SPECIAL ARTICLE

Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis

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Objective. **To update the 2009 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations for the spectrum of manifestations affecting patients with psoriatic arthritis (PsA).**

Methods. **GRAPPA rheumatologists, dermatologists, and PsA patients drafted overarching principles for the management of PsA, based on consensus achieved at face-to-face meetings and via online surveys. We conducted literature reviews regarding treatment for the key domains of PsA (arthritis, spondylitis, enthesitis, dactylitis, skin disease, and nail disease) and convened a new group to identify pertinent comorbidities and their effect on treatment. Finally, we drafted treatment recommendations for each of the clinical manifestations and assessed the level of agreement for the overarching principles and treatment recommendations among GRAPPA members, using an online questionnaire.**

Results. **Six overarching principles had ≥80% agreement among both health care professionals (n = 135) and**

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patient research partners (n = 10). We developed treatment recommendations and a schema incorporating these principles for arthritis, spondylitis, enthesitis, dactylitis, skin disease, nail disease, and comorbidities in the setting of PsA, using the Grading of Recommendations, Assessment, Development and Evaluation process. Agreement of >80% was reached for approval of the individual recommendations and the overall schema.

***Conclusion*. We present overarching principles and updated treatment recommendations for the key manifestations of PsA, including related comorbidities, based on a literature review and consensus of GRAPPA members (rheumatologists, dermatologists, other health care providers, and patient research partners). Further updates are anticipated as the therapeutic landscape in PsA evolves.**

Psoriatic arthritis (PsA), a disease characterized by inflammatory arthritis, enthesitis, dactylitis, and spondylitis in patients with psoriasis, (1,2) is remarkably diverse in presentation and course. To assist the clinician in the management of PsA, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), a global association of more than 500 rheumatologists, dermatologists, and patient research partners, previously (in 2009) published treatment recommendations (3) based on a systematic evidence review published in 2006 (4–11). To be clinically relevant, such recommendations must be dynamic, requiring reevaluation and appropriate modification over time. In PsA, significant recent developments in pathophysiology and disease assessment, particularly regarding the important contribution of comorbidities coupled with major therapeutic advances, necessitated an update of the GRAPPA recommendations.

GRAPPA investigators and patient research partners formed groups focused on the clinical domains of PsA: peripheral arthritis, axial disease, enthesitis, dactylitis, skin disease, and nail disease, with a new group focused on comorbidities. In addition, a representative from each group focused on treatment safety. Each group then conducted a systematic literature review of the PsA treatment literature (12) and excerpted and published the evidence base for treatment effect for each

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of the domains (13–19). We applied the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach (20) to formulate these recommendations (20), which included determination of the strength of recommendation of each therapy (strong, conditional) based on the quality and breadth of evidence that the treatment can achieve desirable effects (e.g., reduction of morbidity and mortality, improvement in quality of life, reduction in burden of treatment and resource utilization), contextualized to individual patient and societal considerations (20). The final treatment schema was critically reviewed and edited via in-person discussion and online survey. It is important to note that the purpose of these recommendations is to provide optimal care for PsA patients regardless of economic or political factors.

We developed these GRAPPA recommendations to provide up-to-date systematic and evidence-based guidance for the treatment and management of PsA in adults. These recommendations are not specifically relevant for patients with juvenile idiopathic arthritis or psoriasis only. As noted, updated recommendations were needed due to significant advances in the field since publication of the 2009 GRAPPA treatment recommendations. For example, several new compounds were approved since the 2006 literature review, and further evidence on existing therapies has accumulated. The target audience for these GRAPPA recommendations is anyone involved in the treatment of patients with PsA.

METHODS

To help frame the updated GRAPPA recommendations, we developed new overarching principles for the treatment of PsA. Initially drafted by a small working group, these principles were refined through several rounds of dissemination to members, followed by in-person review and discussion at GRAPPA meetings. Subsequently, we posted the principles online for further comment and to obtain agreement among GRAPPA membership. GRAPPA members updated the reviews that were previously published (13–19), reviewing subsequent literature within 6 subgroups addressing peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, and nail disease in the setting of PsA. A central literature search was performed in collaboration with the University of Leeds Library in 2013 as detailed previously (12), with relevant articles provided to the groups. This was done prior to the development of the questions, not in keeping with true GRADE methodology. We convened an additional group to assess relevant comorbidities, and this group performed an independent literature review. The psoriasis and nail group were led by dermatologists, and rheumatologists led the musculoskeletal manifestation groups.

The review of the evidence to create treatment recommendations was performed using the GRADE system (20). As the basis for the recommendations, each group developed appropriate questions regarding therapeutic options in each different domain. The development of these was based on PICO (population, intervention, comparator, outcomes) questions as outlined in the GRADE methodology, but was simplified (see Supplementary Material, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39573/abstract). We then gathered relevant evidence to support the recommendation for individual drugs, classes of drugs, and treatment approaches within the 6 disease domains of PsA as well as the comorbidities. Recommendations could be for or against a treatment and could be strong or conditional, based on the best scientific evidence and relevant clinical context per the GRADE system. Evidence was combined from the central 2013 literature review and the additional literature reviews performed within the groups. To ensure that the recommendations would not rapidly become outdated, each group completed a further literature update and review of abstracts presented at the annual meetings of the American College of Rheumatology (November 2014) and the American Academy of Dermatology (March 2015). The comorbidities group performed individual literature searches for each comorbidity that was identified as a key issue in PsA at earlier GRAPPA meetings (19,21).

The entire group decided that recommendations based on high-quality studies published only as abstracts should be considered conditional only, and clearly demarcated by lighter text in the treatment schema. The group acknowledged that these abstracts would likely be published as peer-reviewed articles in the near future and that the data would impact treatment decisions. The recommendations for specific agents within each domain were summarized in a treatment table and reviewed (with the supporting questions and summary of evidence) by the GRAPPA membership via online survey to allow feedback, followed by a vote to assess level of agreement.

Using these evidence-based data, each group summarized its treatment recommendations in a flow chart to guide therapy. Input from all of the individual groups was combined into a single schema, which was sent to the full GRAPPA membership (including the group/committee members) via an online survey for feedback and agreement.

Throughout the development of these recommendations, GRAPPA members who are pharmaceutical industry representatives have been excluded from participation both in face-to-face discussions at GRAPPA meetings and in online surveys.

RESULTS

Overarching principles. Six final overarching principles for the care of patients with PsA were developed after extensive feedback. There was ≥80% agreement among GRAPPA members who responded to the survey (135 health care providers and 10 patient research partners) for all of these principles, within both the group of health care providers and the group of patient research partners (Table 1). The majority of disagreements related to minor wording changes, which were incorporated where possible following the survey, although a repeat survey was not performed. Full con-

Table 1. Overarching principles and agreement by members of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis

Principle	Health care professional agreement, % (n = 135)	Patient agreement, % (n = 10)
1. The ultimate goals of therapy for all patients with psoriatic arthritis (PsA) are as follows: 1) To achieve the lowest possible level of disease activity in all domains of disease; as definitions of remission and low or minimal disease activity become accepted, these will be included in the goal. 2) To optimize functional status, improve quality of life and well-being, and prevent structural damage to the greatest extent possible. 3) To avoid or minimize complications, both from untreated active disease and from therapy.	92.6	80
2. Assessment of patients with PsA requires consideration of all major disease domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, and nail disease. The impact of disease on pain, function, quality of life, and structural damage should be examined. In addition, activity in other potential related conditions should be considered, including cardiovascular disease, uveitis, and inflammatory bowel disease. Multidisciplinary and multispecialty assessment and management will be most beneficial for individual patients.	83.7	80
3. Clinical assessment ideally includes patient-reported measures with a comprehensive history and physical examination, often supplemented by laboratory tests and imaging techniques (e.g., x-ray, ultrasound, magnetic resonance imaging). The most widely accepted metrics that have been validated for PsA should be utilized whenever possible.	88.9	80
4. A comprehensive assessment of relevant comorbidities (including but not restricted to obesity, metabolic syndrome, gout, diabetes, cardiovascular disease, liver disease, depression, and anxiety) should be undertaken and documented.	85.2	100
5. Therapeutic decisions need to be individualized, and are made jointly by the patient and his or her doctor. Treatment should reflect patient preferences, with the patients provided with the best information and relevant options provided to them. Treatment choices may be affected by various factors, including disease activity, structural damage, comorbid conditions, and previous therapies.	89.6	80
6. Ideally, patients should be reviewed promptly, offered regular evaluation by appropriate specialists, and have treatment adjusted as needed in order to achieve the goals of therapy. Early diagnosis and treatment is likely to be of benefit.	89.6	80

flict of interest disclosure was not collected from each respondent as part of the survey.

GRADE recommendations for therapies. Each group produced a number of questions addressing the efficacy and safety of the different therapies, developing a GRADE-based strong/conditional recommendation for each therapy within the group's domain (see Supplementary Material part 1, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39573/abstract). These are summarized in Table 2, showing which therapies were strongly or conditionally recommended within the domains. In a survey of GRAPPA members, 87.2% of the 176 respondents supported this summary table, including 83.3% of the patient research partners (n = 6).

GRADE recommendations for comorbidities. The comorbidities group also produced a number of questions addressing recommendations for the investigation and management of relevant comorbidities (Supplementary Material part 2, http://onlinelibrary.wiley.com/doi/10.1002/art.39573/abstract). Evidence for these issues is limited, and the majority of these recommendations rely on expert opinion.

Identifying comorbidities is critical to the optimal management and treatment of PsA. Common comorbidities include cardiovascular disease (CVD), diabetes, obesity, metabolic syndrome, osteoporosis, non-alcoholic fatty liver disease (NAFLD), and depression; in addition, some comorbidities might be considered extraarticular manifestations of disease, such as inflammatory bowel disease (IBD) and ophthalmic disease (e.g., uveitis). Given the increased prevalence and incidence of CVD and diabetes among PsA patients, appropriate screening is recommended. All PsA patients should be encouraged to achieve and maintain a healthy body weight. This is of specific relevance to PsA, as the likelihood of reduction

Table 2. Summary of GRADE recommendations for PsA therapies, by disease domain*

Indication	Recommended (strong)	Recommended (conditional)	Not recommended (strong)	No recommendations due to lack of evidence
Peripheral arthritis, DMARD-naive	DMARDs (MTX, SSZ, LEF), TNFi	NSAIDs, oral CS, IA CS, *PDE-4i*		IL-12/23i, IL-17i
Peripheral arthritis, inadequate response to DMARDs	TNFi, IL-12/23i, PDE-4i	NSAIDs, oral CS, IA CS, *IL-17i*		
Peripheral arthritis, inadequate response to biologic treatment	TNFi	NSAIDs, oral CS, IA CS, IL-12/23i, *IL-17i*, PDE-4i		
Axial PsA, biologic-naive†	NSAIDs, physiotherapy, simple analgesia, TNFi	*IL-17i*, SI joint CS injections, bisphosphonates, [*IL-12/23i*]	DMARDs, IL-6i, CD20i	
Axial PsA, inadequate response to biologic treatment†	Physiotherapy, simple analgesia	NSAIDs, TNFi, *IL-12/23i, IL-17i*		
Enthesitis	TNFi, IL-12/23i	NSAIDs, physiotherapy, CS injections (with extreme caution since injecting CS in weight-bearing entheseal sites can lead to rupture of entheses), *PDE-4i*, *IL-17i*		DMARDs
Dactylitis	TNFi (infliximab, adalimumab, golimumab, CZP)	CS injections, DMARDs (MTX, SSZ, LEF), TNFi (etan.), IL-12/23i, *IL-17i*, *PDE-4i*		
Psoriasis (plaque)	Topical therapies, phototherapy, DMARDs (MTX, LEF, CSA), TNFi, IL-12/23i, IL-17i, PDE-4i			
Nail psoriasis	TNFi, IL-12/23i	Topical therapies, procedural therapies, DMARDs (CSA, LEF, acitretin, MTX), IL-17i, *PDE-4i*		

* Italicized text signifies conditional recommendations for drugs without current regulatory approvals or for which recommendations are based on data published in abstract form only; italicized text in brackets signifies conditional recommendations based only on data from a small open-label proof-of-concept trial, published in abstract form only. GRADE = Grading of Recommendations, Assessment, Development and Evaluation; PsA = psoriatic arthritis; DMARD = disease-modifying antirheumatic drug; MTX = methotrexate; SSZ = sulfasalazine; LEF = leflunomide; TNFi = tumor necrosis factor inhibitor; NSAIDs = nonsteroidal antiinflammatory drugs; CS = corticosteroids; IA = intraarticular; PDE-4i = phosphodiesterase 4 inhibitor (apremilast); IL-12/23i = interleukin-12/23 inhibitor; SI = sacroiliac; CZP = certolizumab pegol; etan. = etanercept; CSA = cyclosporin A.
† Based on ankylosing spondylitis literature.

Table 3. Considerations for treatment of patients with psoriatic arthritis and concomitant comorbidities*

	NSAIDs	CS	HCQ	SSZ	MTX	LEF	CSA	Etan.	Adali-mumab	Inflix-imab	CZP	Goli-mumab	Uste-kinumab	Apremi-last
Cardiovascular disease	C	?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Congestive heart failure	C	C	NI	NI	NI	NI	NI	C	C	C	C	C	NI	NI
Obesity	NI	NI	NI	NI	C	NI	NI	NI	NI	NI	NI	NI	NI	NI
Metabolic syndrome	NI	C	NI	NI	C	NI	NI	NI	NI	NI	NI	NI	NI	NI
Diabetes	NI	C	NI	NI	C	NI	NI	NI	NI	NI	NI	NI	NI	NI
Ulcerative colitis	?	NI	NI	A	NI	NI	OL	NI	A	A	NI	A	NI	NI
Crohn's disease	?	NI	NI	A	OL	NI	NI	NI	A	A	A	NI	NI	NI
Uveitis	NI	P†	NI	NI	NI	NI	NI	?	P	P	NI	NI	NI	NI
Osteoporosis	NI	C	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI
Malignancy	NI	NI	NI	NI	NI	NI	NI	C	C	C	C	C	?	NI
Fatty liver disease	C	NI	NI	C	C	C	NI	NI	NI	NI	NI	NI	NI	NI
Chronic kidney disease	C	NI	NI	NI	C	?	SM	NI	NI	NI	NI	NI	NI	NI
Depression	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	?
Chronic hepatitis B‡	C	NI	NI	NI	C	C	NI	SM	SM	SM	SM	SM	?	NI
Chronic hepatitis C‡	C	NI	NI	NI	C	C	NI	?/P	?	?	?	?	?	NI
HIV	NI	NI	NI	NI	NI	NI	NI	SM	SM	SM	SM	SM	?	NI

* HCQ = hydroxychloroquine; C = reason for caution; ? = data insufficient but concerns have been raised; NI = no information available; A = approved for primary therapy of the comorbid condition; OL = off-label use for therapy of the comorbid condition; P = preferred therapy; SM = requires special monitoring (see Table 2 for other definitions).
† Corticosteroids used as preferred therapy for uveitis are most commonly given as topical and/or intraocular injections in preference to oral steroids.
‡ When treating patients with chronic infections that can affect the liver, consider consultation with providers who have expertise in the area.

in disease activity with tumor necrosis factor inhibitor (TNFi) treatment appears to be higher among patients with normal body weight than among PsA patients who are overweight (22–24). Given the association of ophthalmic disease with the spondyloarthritides and an increased risk of IBD among PsA patients, consideration of screening for eye disease and gastrointestinal disease is recommended as a part of the review of systems. Screening should also be considered for anxiety or depression and for skin cancer in patients with both a history of ultraviolet (UV) phototherapy and TNFi use. Comorbidities such as NAFLD, osteoporosis, and malignancy also may influence management but have been less commonly associated with PsA.

Recommendations for treatment of comorbidities in PsA are summarized in Table 3. Screening for HIV, hepatitis B virus, hepatitis C virus, and tuberculosis should be strongly considered, in accordance with local guidelines and standards of medical practice, before initiation of therapies that may potentially alter normal immune responses. Depression and anxiety have a high prevalence among PsA patients; of note, a warning to weigh the risks and benefits of treatment in patients with a history of depression and/or suicidal thoughts/behavior has been added to the package insert materials in the US for new drugs for PsA and psoriasis. Although screening and management of comorbidities among patients with PsA may be no different from that for the general population, it is nevertheless important to actively identify comorbidities in order to optimize the care of these patients.

Treatment schema. Each disease domain group designed a flow chart for treatment of the given disease domain using the recommendations for therapies previously developed. These were combined into a single schema for the management of PsA. Following feedback from the membership, the distinction between mild, moderate, and severe disease, which was included in the previous GRAPPA grid, was removed because the cutoffs are not evidence based or applicable to all patients. Figure 1 outlines potential therapeutic routes, described as standard or expedited to allow tailoring of treatment to the individual patient. Treatment decisions for individual patients may be dependent on disease activity, prognostic factors, comorbidities, and local access to therapies. Central to the schema is the concept that optimal care is an iterative process. As alluded to in the overarching principles, we strongly recommend repeated evaluation over time and alteration of therapy as appropriate. The schema was circulated to the full GRAPPA membership and 87.9% of the respondents (n = 176) approved, including all 6 patient research partners. For clarity, it was decided to use the historical term "disease-modifying antirheumatic drug" (DMARD) for conventional systemic drugs such as methotrexate (MTX) and sulfasalazine (SSZ), as this is commonly used nomenclature. It should be noted that this term is not meant to imply that such therapies have a "disease-modifying" impact on radiographic damage in

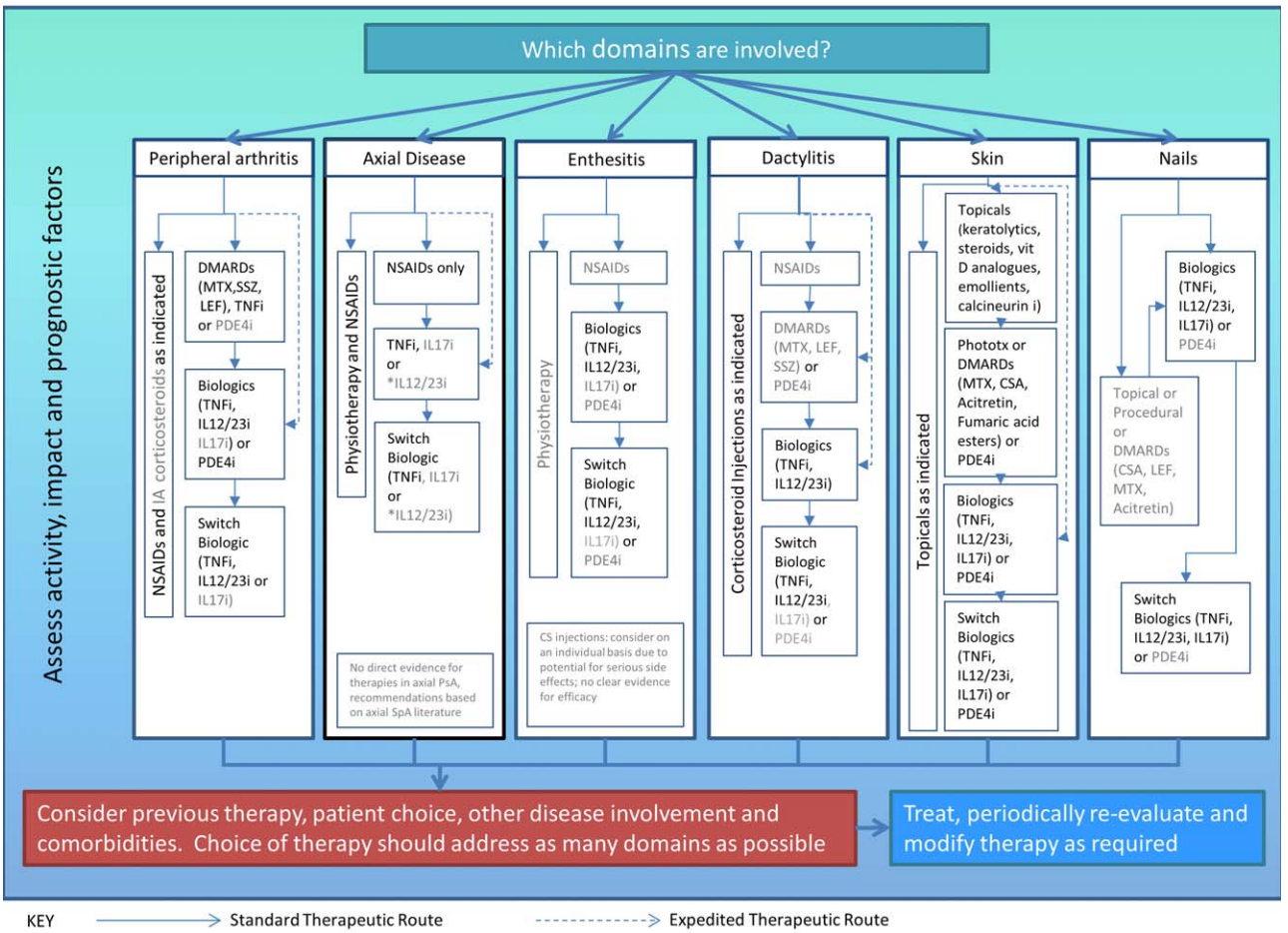

Figure 1. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis treatment schema for active psoriatic arthritis (PsA). Light text identifies conditional recommendations for drugs that do not currently have regulatory approvals or for which recommendations are based on abstract data only. NSAIDs = nonsteroidal antiinflammatory drugs; IA = intraarticular; DMARDs = disease-modifying antirheumatic drugs; MTX = methotrexate; SSZ = sulfasalazine; LEF = leflunomide; TNFi = tumor necrosis factor inhibitor; PDE-4i = phosphodiesterase 4 inhibitor (apremilast); IL-12/23i = interleukin-12/23 inhibitor; SpA = spondyloarthritis; CS = corticosteroid; vit = vitamin; phototx = phototherapy; CSA = cyclosporin A.

PsA. "Biologic agents" was used to describe the group of biologic therapies targeting TNF, interleukin-12/23 (IL-12/23), IL-17, and others.

The schema is designed to assist in decision making for individual patients, with assessment of which disease domains are involved and their relevant comorbidities. Many patients have multiple manifestations of their disease and the choice of treatment should be considered carefully to ensure that it addresses as many of those as possible. It is likely that selection of therapy will be driven by the most severe element of a patient's disease. The possibilities for how the schema and supporting materials might actually be used are illustrated through case examples in Table 4. Further notes regarding this schema are provided below.

Peripheral arthritis. Nonsteroidal antiinflammatory drugs (NSAIDs) are conditionally recommended for use in peripheral arthritis to improve symptoms of the disease, but with caution due to their potential adverse effects. Corticosteroids are conditionally recommended for peripheral arthritis, to be administered either systemically or intraarticularly, at the smallest dosages required for efficacy (usually <7.5 mg/day) and for short periods, to minimize adverse effects, including psoriasis flare, after withdrawal of the treatment. In DMARD-naive patients, both DMARDs (MTX, leflunomide, and SSZ; cyclosporine is not recommended due to scant evidence of its efficacy and its toxicity profile) and TNFi are strongly recommended for treatment. In many instances, DMARDs may be used first, but

Table 4. Psoriatic arthritis case studies using treatment recommendations*

Case description and treatment recommendations	Discussion
Case 1: 43-year-old man, psoriasis for 10 years, PsA for 1 year. Current evaluation: 2 swollen joints, 3 tender joints (PIP and DIP); no axial symptoms; 3 tender entheseal sites; no dactylitis; psoriasis self-assessment score 1 (1−10 scale with 1 being worst) with affected body surface area 2% (elbows, knees, buttocks) and no nail involvement. Prior treatment: NSAIDs and topical steroids only, which he is still receiving at present. Additional history notable for 3 episodes of iritis over the past 18 months, treated with steroid eye drops. Treatment recommendation options: TNF inhibitor, DMARD	Discussion: With reference to the treatment schema, for the individual domains of peripheral arthritis and enthesitis and skin, DMARD treatment (e.g., LEF, MTX) could be a viable choice given the relatively modest activity in each domain. However, the presence of recurrent uveitis (see Table 3) along with the combination of individual domains support escalation of therapy. Hence, TNFi therapy is a reasonable choice, and should be discussed with the patient. In some areas, clinicians may be required to prescribe MTX before access to a TNFi is allowed. Other newer therapies (e.g., IL-12/23i, PDE-4i, IL-17i) could be considered, although clinicians have longer experience with older medications.
Case 2: 59-year-old woman, psoriasis for 15 years, PsA for 9 months. Current evaluation: 6 swollen joints, 8 tender joints (knees, wrist, fingers); no axial symptoms; 1 tender entheseal site; no dactylitis; psoriasis self-assessment score 4 with affected body surface area 8% (trunk, scalp, arms, legs) and nail involvement. Prior treatment: CSA led to hypertension; NSAIDs worsened renal function. Cannot access UV therapy. Currently receiving topical steroids. Additional history notable for poorly controlled diabetes, obesity, and recurrent sinusitis with 1 hospitalization for pneumonia in the past year. Treatment recommendation options: MTX, PDE-4i, LEF, biologic agents	Discussion: With reference to the treatment schema, moderate-to-severe activity in the peripheral joints and skin seems to be the main driver of therapy. However, comorbidities (see Table 3) are very important in this case. Excluding therapies previously tried and found to produce unacceptable side effects, these options remain. MTX is a difficult choice due to obesity and diabetes as potential drivers of hepatotoxicity with this treatment. The recurrent infections are a concern with regard to most immunomodulatory therapies. Clearly, extended discussion of potential risk/benefit with the patient is required, along with close monitoring. Assessment of existing radiographic damage may also inform treatment choice.
Case 3: 34 year old woman, psoriasis for 4 years, PsA for 2 years. Current evaluation: 8 swollen joints, 12 tender joints (wrist, knee, fingers, toes); no axial symptoms; 7 tender entheseal sites (knees, feet, pelvic rim); dactylitis of 2 toes (causing inability to walk as required for her work); psoriasis self-assessment score 1 with affected body surface area 1% (trunk) without nail involvement. Prior treatment: MTX tried, but caused liver function abnormalities possibly related to alcohol use. Currently receiving NSAIDs and topical low-dose steroids and uses an assistive device (heel cup for foot enthesitis). Treatment with TNFi was recommended but the patient was hesitant to undergo injections or infusions. After consideration of options and discussion of SSZ, LEF, and PDE-4i, patient chose SSZ. On reevaluation 4 months later, there was no improvement. Patient agreed to begin TNFi therapy. After 3 months of therapy, she reported improvement across domains of "around 40%" (but was not meeting criteria for minimal disease activity) and also noted mild but bothersome injection-site reactions. Treatment recommendation options (in no order of preference): a different TNFi, IL-12/23i, IL-17i, LEF, PDE-4i	Discussion: With reference to the treatment schema, there are several alternatives as noted. Given the significant impact of the disease on the patient's quality of life, treatment needs to be highly effective for this patient. In this case, it can be debated whether TNFi treatment is unsuccessful in the patient and also whether switching to an alternative TNFi or to another biologic agent with a different mode of action would be preferred.

* PIP = proximal interphalangeal; DIP = distal interphalangeal; UV = ultraviolet (see Table 2 for other definitions).

consideration should be given to early escalation of therapy, particularly in patients with poor prognostic factors (e.g., increased levels of inflammatory markers, high counts of joints with active disease). Despite the lack of evidence from randomized controlled trials (RCTs), DMARDs are recommended based on data from observational studies, their low costs and universal access, and the lack of evidence that a short time delay in the introduction of more effective therapies would impact long-term function and quality of life.

Data concerning the phosphodiesterase 4 inhibitor (PDE-4i) apremilast in DMARD-naive patients are currently available only in abstract form; hence, this is conditionally recommended. For patients in whom DMARD treatment has been unsuccessful, PDE-4i or biologic agents (including TNFi and IL-12/23i) are strongly recommended; at present a conditional recommendation is given for IL-17i as phase III data are available only in abstract form. It must be noted that there are no available data on the impact of PDE-4i on radio-

graphic damage, in contrast to TNFi, IL-12/23i, and IL-17i. One phase II RCT showed modest effects of abatacept on joint symptoms in PsA (25). Phase III trials are being conducted, but results are not yet known. Since the manufacturer has not applied for regulatory approval of this treatment for PsA anywhere in the world, it was not included in the current recommendations. We recognize that off-label use may occur based on the positive phase II study results. There is no definitive evidence to date on the benefit of concomitant DMARDs with biologic therapies. In the TNFi RCTs, similar efficacy results were commonly seen with or without MTX. However, registry data suggest that effect of the monoclonal antibodies, particularly infliximab, persists longer with concomitant DMARD treatment.

In the case of biologic agent treatment failure due to either adverse events or inefficacy, a large volume of observational data are now available supporting the conditional recommendation of switching either to an alternative biologic agent within a drug class or to a drug with a different mode of action. Many more recent RCTs include patients who have previously been treated unsuccessfully with one or more biologic agent (26–28). There are limited data available on combining therapies and treatment strategies in PsA, as outlined in the peripheral arthritis evidence review (13). MTX in combination with biologic agents (either non-TNFi) or TNFi, may have a role, but most studies suggest that the combination does not improve clinical symptoms beyond the improvement attained with biologic monotherapy (13). Some registry studies have shown improved survival, mainly with infliximab (13).

Axial disease. The treatment recommendations for axial disease are derived from diagnostic criteria, screening, monitoring, and response to therapy in ankylosing spondylitis (AS) since these data are not available for axial PsA. For patients with axial symptoms that have not responded to NSAIDs, physiotherapy, and sacroiliac joint injections (when appropriate), initiation of TNFi is recommended; DMARDs are not effective for treatment of diseases in this domain. There is no available evidence on the efficacy of SSZ in axial disease within AS or PsA (29). NSAIDs are conditionally recommended, usually as an adjunct to further therapy, for patients with an inadequate response to TNFi. Formal published data on switching agents for axial disease are not available but observational data support switching as in the other domains, leading to a conditional recommendation in the case of inadequate response to TNFi treatment. Clinical trial data showing efficacy of secukinumab (phase III trial) (30) and ustekinumab (open-label proof-of-concept trial with 20 patients) (31) in AS have been published, but these agents are currently not approved for AS or axial PsA.

Enthesitis. NSAIDs are the first-line agents for treatment of enthesitis, based on expert opinion; however, data from RCTs are lacking (32). Physiotherapy is also often prescribed, although formal studies of efficacy have not been published. In one study with defined enthesitis end points and placebo controls, SSZ was not effective (33), and no published data support the efficacy of other DMARDs in placebo-controlled studies (15,32). There is high-quality evidence of the effectiveness of TNFi and ustekinumab (15). Data on the efficacy of PDE-4i (34) and secukinumab (35) for enthesitis in PsA are published in abstract form only. Formal data on treatment switching are not available.

Dactylitis. In contrast to enthesitis, DMARDs were recommended as first-line treatment of dactylitis, based on limited studies for this indication. Corticosteroid injections should also be considered, although no formal studies of this intervention have been published. There are efficacy data for biologic agents (TNFi or ustekinumab), but data on treatment switching are not available. Published abstracts show efficacy of both PDE-4i (34) and secukinumab (35) in dactylitis, but again, data on switching agents are not available.

Skin disease. Topical agents are generally the first-line treatment of psoriasis, particularly milder disease, followed by phototherapy and DMARDs. Treatment may be initiated with topical agents in combination with phototherapy or DMARDs in patients with widespread disease. For patients who do not respond to these therapies, biologic agents are recommended. Biologic agents may be first-line therapy, with or without topical treatments and DMARDs, in certain patients. Switching from one DMARD to another, from a DMARD to a biologic treatment, or from one biologic treatment to another can be done.

Nail disease. Recommendations for the treatment of nail disease in PsA rely on data from studies in skin psoriasis; there are relatively few studies, some of which had methodologic issues affecting their interpretation (11,18). The best data were obtained in studies of biologic agents, particularly TNFi, and these agents would certainly be recommended for PsA patients with moderate-to-severe nail involvement. High-quality data on alternative biologic treatments, including ustekinumab and IL-17 inhibitors, have also been published (36,37), and these agents could be considered alternative biologic therapies to TNFi. Efficacy of PDE-4i in the treatment of nail disease in psoriasis has been reported in multiple abstracts describing RCTs (38,39), but no published article was available at the time of the literature review.

(A full-length article describing PDE-4i efficacy for the condition has subsequently been published [40]). Despite the paucity of data, topical agents, corticosteroid injections, or nonbiologic DMARDs could be considered, especially for patients with milder involvement or contraindications to other therapies.

Research agenda. Tremendous advances in the therapeutic approach to PsA have transpired. Indeed, such progress, along with a desire to codify the data into recommendations that could assist clinicians caring for PsA patients, were a major impetus to the formation of GRAPPA. Substantial developments since the initial GRAPPA recommendations necessitated their update. With greater success, the goals of treatment have become increasingly elevated, as reflected in the overarching principles presented herein. In order to better achieve those lofty goals, we eagerly anticipate research into and data from a number of key areas, as described below.

1. Outcome measures. It is hoped that development, refinement, and ultimately, implementation of PsA-specific outcome measurements will facilitate evaluation and treatment of individual patients in the clinic in addition to further enhancing PsA research.

2. Biomarkers. Despite tremendous advances in therapies and treatment strategies, there is still an unmet need to identify the optimal therapeutic approach for individual patients with PsA. Also, the heterogeneity of PsA remains largely unexplained. Although we know that 30% of psoriasis patients will develop PsA, often after several years, we cannot reliably identify such patients.

3. Better identification and treatment of patients. Several reports emphasize potentially poor outcome in patients with PsA (41,42). Moreover, recent evidence demonstrated that a delay in diagnosis and delayed access to appropriate treatment are key predictors of poor outcome, in terms of response to therapy (43), joint damage (44), and functional ability (44,45). Unfortunately, data from market surveys and other sources show that many PsA patients may not be receiving appropriate therapy. For example, in a telephone survey of >700 PsA patients, the majority were receiving topical therapy only (31%) or no treatment at all (28%), and 16% reported not having seen any health care provider for their PsA in the past year (46).

4. Treatment strategies. Novel treatment strategies in PsA are being assessed. For example, treat-to-target, a concept that is well established in rheumatoid arthritis (47), is now being explored in PsA. Understanding the overall long-term utility of this approach in PsA will be crucial to defining the best treatment approach. Another concept that has been studied more extensively in rheumatoid arthritis is whether therapy can be tapered or even discontinued in patients for whom treatment goals have been reached. It remains to be determined whether this will be possible, and for which patients, in PsA.

DISCUSSION

Herein, members of GRAPPA present updated evidence-based recommendations for the treatment of patients with PsA. Optimal management of PsA using a multidisciplinary and multispecialty approach is necessary but remains a major challenge. The heterogeneity of the disease requires assessment of multiple PsA domains to identify appropriate treatments for individual patients. Assessment of comorbidities is also key when planning therapy and can lead to an escalation in treatment for related diseases, such as IBD or uveitis, or to dosage alteration or restriction of therapies in the presence of liver disease or increased risk of infection.

The recommendations are evidence based whenever possible and result from literature searches updated to October 2014 (and also include data from the American Academy of Dermatology annual meeting in March 2015). We performed our evidence review using some of the methodology outlined in GRADE, the format endorsed by a number of international bodies including the World Health Organization. Development of the recommendations had strong patient involvement (patient research partners were included in each group), and their feedback was incorporated in the overall schema and tables presented here. First, international experts and patients reached consensus in the individual groups over multiple iterations, both for the individual domains and for the overall project. Subsequently, we obtained consensus on the formal recommendations from the entire GRAPPA membership and patient research partners and we recorded the extent of agreement for recommendations in each domain, including comorbidities. To maximize impartiality, GRAPPA members from the pharmaceutical industry were excluded from discussions and voting on the recommendations. To maximize feedback, all non–pharmaceutical industry members were invited to respond, although information on any conflicts of interest among these individuals was not available, and we recognize that this represents a limitation to our methodology.

It is worth noting that these recommendations were not developed specifically for patients with psoriasis alone, or for children with PsA. They are, however, designed to be relevant across international boundaries, although it must be recognized that access to some therapies is not universal. We also recognize that existing evi-

dence is limited, particularly for some pertinent clinical questions. For example, high-quality evidence to support the standard treatment approaches in PsA is not published for every domain, and evidence-based studies on the potential additive or even synergistic benefit of combinations of agents (e.g., MTX and TNFi) are lacking. Most importantly, evidence is not available at this time to support optimal treatment pathways, such as the treatment of early PsA, the overall utility of treat-to-target in PsA, and whether it is better to switch to therapies with a different mechanism of action in patients who have insufficient clinical responses to one agent in a class.

The members of GRAPPA agreed to include the latest literature including high-quality abstracts from recent meetings; thus, agents not yet licensed or approved for PsA were included. These agents are clearly demarcated in the schema, and details of these therapies are provided in the text. In these cases, drugs are only given conditional recommendations, but have been included to provide up-to-date information.

These recommendations represent the literature at present, but may change with the availability of new evidence in the future. Just as these recommendations are updates of those published in 2009, they will require further updating to ensure that current evidence and practice are reflected.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Coates had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Coates, Kavanaugh, Mease, Soriano, Acosta-Felquer, Armstrong, Bautista-Molano, Cauli, FitzGerald, Gladman, Gottlieb, Helliwell, Husni, Love, Lubrano, McHugh, Nash, Ogdie, Parkinson, Rosen, Schwartzman, Toloza, Ritchlin.

Acquisition of data. Coates, Kavanaugh, Mease, Soriano, Acosta-Felquer, Armstrong, Bautista-Molano, Boehncke, Cauli, Espinoza, Gladman, Gottlieb, Husni, Love, Lubrano, McHugh, Nash, Ogdie, Orbai, Parkinson, Rosen, Schwartzman, Siegel, Toloza, Tuong, Ritchlin.

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