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

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Running Head: GRAPPA Treatment Recs for PsA

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

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ABSTRACT (n = 232)

Objective: 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 patients based on consensus at face-to-face meetings and via online surveys. We published literature reviews regarding treatment for the key domains of PsA (arthritis, spondylitis, enthesitis, dactylitis, skin, 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, with an online questionnaire.

Results: Six overarching principles had at least 80% agreement among both health care professionals (HCPs; n=135) and patient research partners (PRPs; n=10). We developed treatment recommendations and a schema incorporating these principles for arthritis, spondylitis, enthesitis, dactylitis, skin, and nail disease, and comorbidities in the setting of PsA, using the GRADE process. Over 80% agreement was reached for approval of the individual recommendations and the overall schema.

Conclusion: Herein, 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 HCPs, and PRPs). Further updates are anticipated as the therapeutic landscape in PsA evolves.

For Peer Review

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 over 500 rheumatologists, dermatologists, and patient research partners (PRPs) previously published treatment recommendations in 2009(3) based on a systematic evidence review published in 2006.(4-11) To be clinically relevant, such recommendations must be dynamic, requiring re-evaluation and appropriate modification over time. In PsA, significant recent developments in pathophysiology and disease assessment, particularly the important contribution of comorbidities coupled with major therapeutic advances, necessitated an update of the GRAPPA recommendations.

GRAPPA investigators and PRPs formed groups focused on the clinical domains of PsA: peripheral arthritis, axial disease, enthesitis, dactylitis, skin, and nail disease, with a new group focused on comorbidities. In addition, a representative from each group also 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 of the domains.(13-19) We applied the GRADE approach 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 social considerations.⁽²⁰⁾ We created a series of PICO questions (see *supplementary online data*) to address crucial practical questions faced by clinicians when making specific treatment choices. 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 considerations.

OBJECTIVE

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

METHODS

To help frame these updated GRAPPA recommendations, we developed new overarching principles for the treatment of PsA. Initially drafted by a small working group, these overarching principles were refined through several rounds of

dissemination to members, followed by live 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 six sub-groups 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 University of Leeds Library as detailed previously(12) in 2013 with relevant papers given to the groups. We convened an additional group to assess relevant comorbidities and they 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 PICO (population, intervention, comparator, outcomes) questions,(20) and then gathered relevant evidence to support the recommendation for individual drugs, classes of drugs, and treatment approaches within the six disease domains of PsA as well as the comorbidities group. Recommendations could be for or against a treatment, and could be strong or conditional, based upon the best scientific evidence and relevant clinical context per the GRADE system. Evidence was combined from the central 2013 literature review and additional literature reviews performed within the groups. To ensure that the recommendations were not outdated rapidly, each group completed a further literature update and review of abstracts through the American College of Rheumatology (ACR) Annual Meeting in November 2014, and the American Academy of Dermatology

meeting in March 2015. The comorbidities group performed a 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 manuscripts 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 via an online survey by the GRAPPA membership (with the supporting PICO questions) to allow feedback, followed by a vote to assess level of agreement.

Using these evidence-based data, each group summarized their treatment recommendations in a flowchart to guide therapy. Input from each group 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 in both face to face discussions at GRAPPA meetings and online surveys.

RESULTS

Overarching Principles

Six overarching principles for the care of patients with PsA were finalized after extensive feedback. Agreement was $\geq 80\%$ among GRAPPA members (135 health care providers and 10 patient research partners) for all of these principles from both physicians and PRPs (**Table 1**). The majority of disagreements related to minor wording changes, which were incorporated where possible following this survey, although a repeat survey was not performed.

GRADE Recommendations for Therapies

Each group produced a number of PICO questions addressing the efficacy and safety of the different therapies, developing a GRADE based strong/conditional recommendation for each therapy within their domain (**Supplementary Material 1**). These are summarized in **Table 2** showing which therapies are strongly or conditionally recommended within the domains. A survey of GRAPPA members showed an 87.2% support (n=176) for this summary table, including 83.3% of PRPs (n=6).

GRADE Recommendations for Comorbidities

The comorbidities group also produced a number of PICO questions addressing recommendations for the investigation and management of relevant comorbidities (**Supplementary Material 2**). Evidence for these issues is limited and the majority of these recommendations rely on expert opinion.

Identifying comorbidities is critical in the optimal management and treatment of PsA patients. 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 extra-articular 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 patients with normal body weight using tumor necrosis factor inhibitors (TNFi) appear to have a higher likelihood of reducing their disease activity than do overweight PsA patients.(22-24) Given the association of ophthalmic disease with the spondyloarthritides and an increased risk for 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 Human Immunodeficiency Virus, 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 in PsA patients; of note, a warning to weigh the risks and benefits of treatment among patients with a history of depression and/or suicidal thoughts/behavior

has been added to the package insert materials in the USA for new drugs for PsA and psoriasis. Although screening and management of comorbidities may be no different than for the general population, it is nevertheless important to actively identify them in order to optimize the care of patients with PsA.

Treatment Schema

Each disease domain group designed a flowchart for treatment of their domain using the GRADE 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 cut-offs are not evidence-based or applicable to all patients. **Figure 1** outlines potential therapeutic routes described as standard or expedited to allow therapy to be tailored to the individual patient. Individual treatment decisions with each patient 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 in therapy as appropriate. The schema was circulated to the full GRAPPA membership and 87.9% approved (n=176), including all six PRPs. For clarity, it was decided to use the historical term “DMARD” for conventional systemic drugs such as methotrexate and sulfasalazine, as this is commonly used nomenclature. It should be noted that this term is not meant to imply that such therapies have “disease

modifying” impact on radiographic damage in PsA. “Biologics” was used to describe the group of biological therapies targeting TNF, IL12/23, IL17 and others.

This 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. Within this consideration, it is likely that selection of therapy will be driven by the most severe element of a person’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 anti-inflammatory drugs (NSAIDs) are conditionally recommended for use in peripheral arthritis to improve symptoms of the disease with caution due to their potential adverse effects. Corticosteroids are conditionally recommended for peripheral arthritis either given systemically or intra-articularly with the smallest doses required (usually less than 7.5 mg/day) and for short periods to minimize adverse effects including psoriasis flare, after CS withdrawal. In disease-modifying antirheumatic drug (DMARD)-naïve patients, both DMARDs (methotrexate, leflunomide, sulfasalazine; cyclosporine is not recommended due to small evidence of its efficacy and its toxicity profile) and TNFi are strongly recommended for treatment. In many instances, DMARDs may be used first, but consideration should be given to early escalation of therapy particularly in patients with poor prognostic factors (e.g., raised inflammatory markers, high active joint counts).

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 PDE4i apremilast in DMARD-naïve patients are only currently available in abstract form, hence this is conditionally recommended. For patients failing DMARDs, PDE4i or biologics (including TNFi, interleukin [IL]12/23 inhibitor) are strongly recommended; at present a conditional recommendation is given for IL17i as the phase III data are only available in abstract form. It must be noted that there are no data available assessing the impact of PDE4i on radiographic damage in contrast to the TNFi, IL12/23i and IL17i. One phase 2 RCT showed modest effects with abatacept on joint symptoms in PsA Mease(25). Phase 3 trials are being conducted but results are not as yet known Since the manufacturer has not submitted it for regulatory approval 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 2 study. There is no definitive evidence to date assessing the benefit of concomitant DMARDs with biologic therapies. In the TNFi RCTs, similar efficacy results were commonly seen with or without methotrexate. However, registry data suggest a longer persistence of effect of the monoclonal antibodies with concomitant DMARDs, particularly with infliximab. In the case of biologic failure either due to adverse events or inefficacy, a large volume of observational data are now available supporting the conditional recommendation of “switching” to an alternative biologic either within a drug class or to a drug with a different mode of action. Many more recent RCTs include patients who have previously

failed one or more biologic therapy(26-28). There is limited data available on combining therapies and treatment strategy in PsA as outlined in the peripheral arthritis evidence review (13). MTX in combination with biologic agents, either non-TNFi or anti-TNFi, may have a role, but most studies suggest that the combination does not improve clinical symptoms beyond those attained by biologic monotherapy (13). Some registry studies have shown improved survival, mainly for 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 who have not responded to NSAIDs, physiotherapy, and sacroiliac injections (when appropriate), initiation of TNFi is recommended; DMARDs are not effective for treatment of this domain. No evidence is available for efficacy of sulfasalazine in axial disease within AS or PsA.(29) Clinical trial data showing efficacy for secukinumab (phase III trial)(30) and ustekinumab (an open-label proof-of-concept trial with 20 patients)(31) have been published in AS, but these agents are currently not approved for AS or axial PsA. Formal published data on switching agents for axial disease are not available.

Enthesitis: NSAIDs are the first line agents in treatment of enthesitis based on expert opinion, however data from RCTs are lacking (32). Physiotherapy is also often prescribed although formal studies of efficacy are lacking. In one study with defined enthesitis endpoints and placebo controls, sulfasalazine was not effective (33), and no published data support efficacy of other DMARDs in placebo-controlled studies (15, 32). There is high quality evidence for the effectiveness of, TNFi and ustekinumab (15).

Data on the efficacy of PDE4i (34) and secukinumab (35) for enthesitis in PsA are published as abstracts only. Formal data on switching are not available.

Dactylitis: In contrast to enthesitis, DMARDs were recommended as a first step in 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 biologics (TNFi or ustekinumab), but data on switching are not available. Published abstracts show efficacy for both PDE4i(34) and secukinumab(35) for dactylitis, but again, data on switching agents are not available.

Skin disease: Topical agents are generally the first level of treatment for psoriasis, particularly milder disease, followed by phototherapy and DMARDs. Treatment may be initiated with topical therapies in combination with phototherapy or DMARDs in patients with wide-spread disease. For patients who do not respond to these therapies, biologics are recommended. Biologics may be first-line therapy, with or without topical therapies and DMARDs, in certain patients. Switching from one DMARD to another, from a DMARD to a biologic, or from one biologic 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 produced in studies of biologics, particularly the TNF inhibitors, and these agents would certainly be recommended for PsA patients with moderate to severe nail involvement. High quality data are also published on alternative biologics, including ustekinumab and IL-17 inhibitors, and these agents could be considered alternative biologic therapies to TNFi. Efficacy on nail disease in psoriasis RCTs has been confirmed for PDE4i in multiple

abstracts but no published paper was available at this time. Despite the paucity of data, topical agents, corticosteroid injections, or non-biologic DMARDs could be considered, especially for patients with milder involvement or contraindications to other therapies.

Research Agenda

Tremendous advances have transpired in the therapeutic approach to PsA. 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.

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 as well as further enhancing PsA research.

2. Biomarkers. Despite tremendous advances in therapies and treatment strategies, there is still an unmet need identifying the optimal therapeutic approach for individual PsA patients. 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 for patients with PsA.(36, 37) 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,(38) joint damage,(39) and functional ability.(39, 40) 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 more than 700 PsA patients, the majority were on topical therapy only (31%) or no treatment at all (28%), and 16% reported not seeing any healthcare provider in the past year for their PsA.(41)

4. Treatment strategies. Novel treatment strategies are being assessed in PsA. For example, treat-to-target, a concept well established in rheumatoid arthritis,(42) 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 more extensively studied in RA is whether therapies can be tapered or even discontinued by patients reaching their therapeutic goals. It remains to be determined whether this will be possible, and for which patients, in PsA.

DISCUSSION

Herein, the members of GRAPPA present updated evidence-based treatment recommendations for patients with PsA. Optimal management of PsA using a multidisciplinary and multispecialty approach is required but remains a major challenge. The heterogeneity of the disease requires assessment of multiple PsA domains to identify appropriate treatments for each individual. Assessment of comorbidities is also

key when planning therapy and can either lead to an escalation in therapy for related diseases, such as inflammatory bowel disease or uveitis, or requires a dose alteration or restriction of therapies in the presence of liver disease or increased risk of infection.

These recommendations are evidence-based wherever 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 GRADE, the format recommended by a number of international bodies including the World Health Organization. The recommendations had strong patient involvement (PRPs were represented 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 PRPs and we recorded the extent of agreement for recommendations in each domain, including comorbidities. To maximise impartiality, GRAPPA members from the pharmaceutical industry were excluded from discussions and voting on the recommendations. To maximise feedback, all non-pharmaceutical members were invited to respond although their individual conflicts of interest are not available.

While other relevant information may be available, it is worth noting that these recommendations were not developed specifically for patients with psoriasis alone, nor for children with PsA. They are designed to be relevant across international boundaries although it must be recognized that access to some therapies is not universal. We also recognize that limited available evidence exists particularly for some relevant clinical

questions. For example, high quality evidence to support the standard treatment approaches in PsA are not published in every domain, and we lack evidence-based studies on the potential additive or even synergistic benefit of combinations of agents (e.g., methotrexate and TNFi). 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 treatments 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 recent 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 using grey font 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 the recommendations may change with new evidence in future. Just as these recommendations are updates of those published in 2009, they will require further updating to ensure that the recommendations reflect current evidence and practice.

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For Peer Review

Table 1. Overarching principles and agreement by members

No	Principle	Physician agreement (n=135)	Patient agreement (n=10)
1	The ultimate goals of therapy for all patients with psoriatic arthritis (PsA) are: a) 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. b) To optimize functional status, improve quality of life and wellbeing, and prevent structural damage to the greatest extent possible. c) 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	83.7%	80%

No	Principle	Physician agreement (n=135)	Patient agreement (n=10)
	<p>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.</p>		
3	<p>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, MRI). The most widely accepted metrics that have been validated for PsA should be utilized whenever possible.</p>	88.9%	80%
4	<p>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.</p>	85.2%	100%
5	<p>Therapeutic decisions need to be individualized, and are made jointly by the patient and their doctor.</p>	89.6%	80%

No	Principle	Physician agreement (n=135)	Patient agreement (n=10)
	<p>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.</p>		
6	<p>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.</p>	89.6%	80%

Table 2: Summary of GRADE recommendations for therapies by domain.

Indication	Recommended Strong	Recommended Weak	Not recommended Strong	No recommendations as lack of evidence
Peripheral Arthritis DMARD Naïve	DMARDs (MTX, SSZ, LEF), TNFi	NSAIDs, oral CS, IA CS, <i>PDE4i</i>		IL12/23i, IL17i
Peripheral Arthritis DMARD Inadequately Responsive	TNFi, ustekinumab, PDE4i	NSAIDs, oral CS, IA CS, <i>IL17i</i>		
Peripheral Arthritis Biologic Inadequately Responsive	TNFi	NSAIDs, oral CS, IA CS, IL12/23i, <i>IL17i</i> , PDE4i		
Axial PsA, Biologic Naïve (based on AS literature)	NSAIDs, Physiotherapy, simple analgesia, TNFi	<i>IL17i</i> , CS SIJ injections, bisphosphonates (<i>IL12/23i</i>)	DMARDs, IL6i, CD20i	
Axial PsA,	NSAIDs,	TNFi, <i>IL12/23i</i> ,		

Indication	Recommended Strong	Recommended Weak	Not recommended Strong	No recommendations as lack of evidence
Biologic Inadequately Responsive (based on AS literature)	Physiotherapy, simple analgesia	<i>IL17i</i>		
Enthesitis	TNFi, IL12/23i,	NSAIDs, physiotherapy, CS injections (with extreme caution since injecting corticosteroids in weight-bearing enthesal sites can lead to rupture of entheses), <i>PDE4i</i> , <i>IL17i</i>		DMARDs
Dactylitis	TNFi (INF, ADM, GOL,	CS injections, DMARDs (MTX, LEF, SSZ), TNFi		

Indication	Recommended Strong	Recommended Weak	Not recommended Strong	No recommendations as lack of evidence
	CZP)	(ETN), IL12/23i, <i>IL17i (SEC)</i> , <i>PDE4i</i>		
Psoriasis (plaque)	Topical therapies, phototherapy, DMARDs (MTX, LEF, CyA), TNFi, IL12/23i, IL17i, PDE4i			
Nail psoriasis	TNFi, IL12/23i	Topical therapies, procedural therapies, DMARDs (CyA, LEF, Acitretin, MTX), IL17i,		

Indication	Recommended Strong	Recommended Weak	Not recommended Strong	No recommendations as lack of evidence
		<i>PDE4i</i>		

Italicized text identifies conditional recommendations for drugs without current regulatory approvals or where recommendations are based on abstract data only.

Italicized text in brackets identifies a conditional recommendation based only on abstract data from a small open-label proof-of-concept trial.

ADM = adalimumab, AS = ankylosing spondylitis, CD20i = CD20 inhibitor, CS = corticosteroids, CyA = cyclosporin, CZP = certolizumab, DMARDs = disease modifying anti-rheumatic drugs, GOL = golimumab, IA = intra-articular, IL6i = interleukin 6 inhibitor, IL17i = interleukin 17 inhibitor, IL12/23i = interleukin 12/23 inhibitor, INF = infliximab, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal anti-inflammatory drugs, PDE4i = phosphodiesterase 4 inhibitor (apremilast), SEC = secukinumab, SIJ = sacroiliac injections, SSZ = sulfasalazine, TNFi = tumor necrosis factor inhibitor

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

Comorbidity	Non-steroidal Anti-inflammatory Drugs	Glucocorticoids	Hydroxychloroquine	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast
Cardiovascular Disease	C	?	NI	NI	NI	NI	NI	NI	NI	NI	NI	NI	?	NI
Congestive Heart Failure	C	C	NI	NI	NI	NI	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

Comorbidity	Non-steroidal Anti-inflammatory Drugs	Glucocorticoids	Hydroxychloroquine	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast
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
Human Immunodeficiency Virus								SM	SM	SM	SM	SM	?	

Comorbidity	Non-steroidal Anti-inflammatory Drugs	Glucocorticoids	Hydroxychloroquine	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast
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A = Approved for primary therapy of the comorbid condition

C = Reason for caution

NI = no information available

OL = Off-label use for the therapy of the comorbid condition

P = Preferred therapy

SM = Requires special monitoring

? = Data insufficient but concerns have been raised

* When treating patients with chronic infections that can affect the liver, consider consultation with providers having expertise in the area.

Corticosteroids used as preferred therapy for uveitis are given as topical and/or intraocular injections in preference to oral steroids

Table 4: Case studies using treatment recommendations

Case 1 43-year-old man, psoriasis for 10 years, psoriatic arthritis for 1 year. Current evaluation: SJ2 TJ3 (PIPs and DIPs); no axial symptoms; 3 tender enthesial sites; no dactylitis; psoriasis self-rated 1/10 with BSA 2% (elbows, knees, buttocks) and no nail involvement. Prior therapy has been only NSAIDs, and topical steroids, which he remains on 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 iritis (see comorbidity table) along with the combination of individual domains, supports escalation of therapy. Hence, TNF inhibitor therapy is a reasonable choice, and should be discussed with the patient. In some areas, clinicians may be obliged to use MTX before access to a TNF inhibitor is allowed. Other newer therapies could be considered (e.g., IL-12/23 inhibitor, PDE4i [apremilast], IL-17 inhibitors) although clinicians have longer experience with older medications.

Case 59-year-old woman, psoriasis for 15 years, psoriatic arthritis for 9 months.

- 2** Current evaluation: SJ6, TJ8 (knees, wrist, fingers); no axial symptoms; 1 tender enthesial site; no dactylitis; psoriasis self-rated 4/10 with BSA 8% (trunk, scalp, arms, legs) and nail involvement. Prior treatment: cyclosporine led to hypertension, NSAIDs worsened renal function. Cannot access UV therapy. Currently on topical steroids. Additional history notable for poorly controlled diabetes, obesity, and recurrent sinusitis with one hospitalization for pneumonia in the past year.

Treatment recommendation options: methotrexate, PDE4i, leflunomide, biologics

Discussion: Referring to the treatment schema, moderate to severe activity in the peripheral joints and skin seem to be the main drivers of therapy. However, comorbidities (see table) are very important in this case. Excluding failed therapies, these options remain. MTX is a difficult choice due to obesity and diabetes as potential drivers of hepatotoxicity with MTX. The recurrent infections are a concern across 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 34 year old woman with psoriasis for 4 years, psoriatic arthritis for 2 years.

- 3** Current evaluation: SJ8 TJ12 (wrist, knee, fingers, toes); no axial symptoms; 7 tender enthesial sites (knees, feet, pelvic rim); dactylitis of 2 toes (causing inability to walk as required for her work); skin self-rated 1/10 with 1% BSA (trunk) without nail involvement. Prior treatments: methotrexate tried, but caused liver function abnormalities possibly related to alcohol use. Current treatment with NSAIDs, topical low dose steroids, and assist devices (heel cup for foot enthesitis). Treatment with TNF was recommended but the patient was hesitant to do injections or infusions. After considerations of options, and discussion of sulfasalazine, leflunomide, and PDE4i, patient chose sulfasalazine. On re-evaluation 4 months later, there was no improvement. Patient agreed to therapy with TNF inhibitor. After 3 months of therapy, she reported improvement across domains of “around 40%” (but was not achieving the minimal disease activity criteria) and also noted mild but bothersome injection site reactions.

Treatment recommendations (in no order of preference): A different TNF inhibitor, IL-12/23 inhibitor, IL-17 inhibitor, leflunomide, and PDE4i.

Discussion: Referring to the treatment schema, there are several alternatives as noted. Given the significant impact on the patient’s quality of life, treatment needs to be highly effective for this patient. In this case, it can be debated

whether the patient is a “TNFi failure,” and also whether switching to alternative TNFi or to another biologic with a different mode of action would be preferred.

BSA = body surface area; DIP = distal interphalangeal joint; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate, NSAID = nonsteroidal anti-inflammatory drug; PDE4i = phosphodiesterase 4 inhibitor (apremilast); PIP = proximal interphalangeal joint; SJ = swollen joint; TJ = tender joint; TNFi = tumor necrosis factor inhibitor

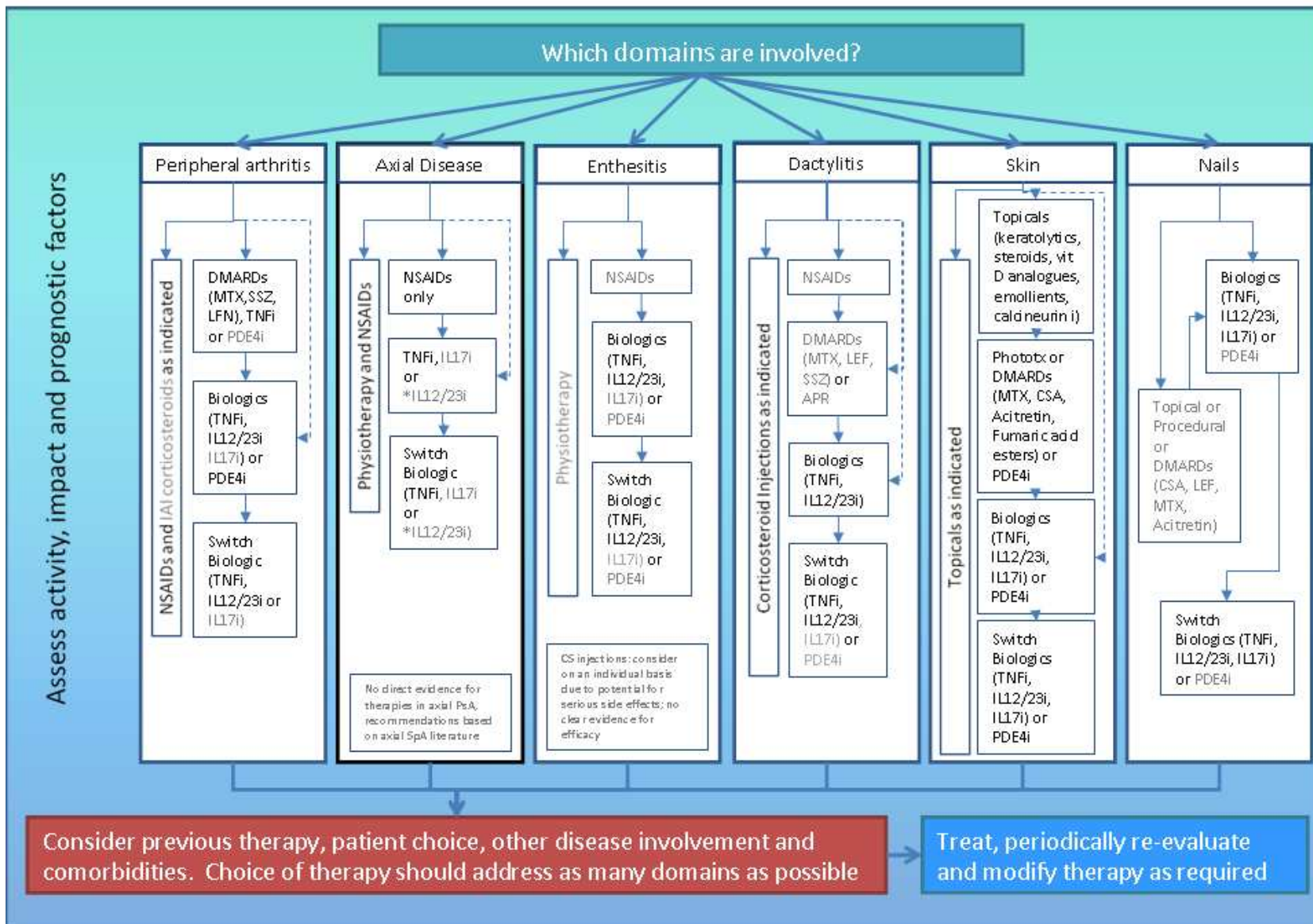
For Peer Review

Figure Legend

Figure 1: GRAPPA Treatment Schema for Active PsA

Grey text identifies conditional recommendations for drugs without current regulatory approvals or where recommendations are based on abstract data only.

DMARDs = disease modifying anti-rheumatic drugs, IL17i = interleukin 17 inhibitors, IL12/23i = interleukin 12/23 inhibitors, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal anti-inflammatory drugs, PDE4i = phosphodiesterase 4 inhibitor (apremilast), SSZ = sulfasalazine, TNFi = tumor necrosis factor inhibitor



KEY —————> Standard Therapeutic Route - - - - -> Expedited Therapeutic Route

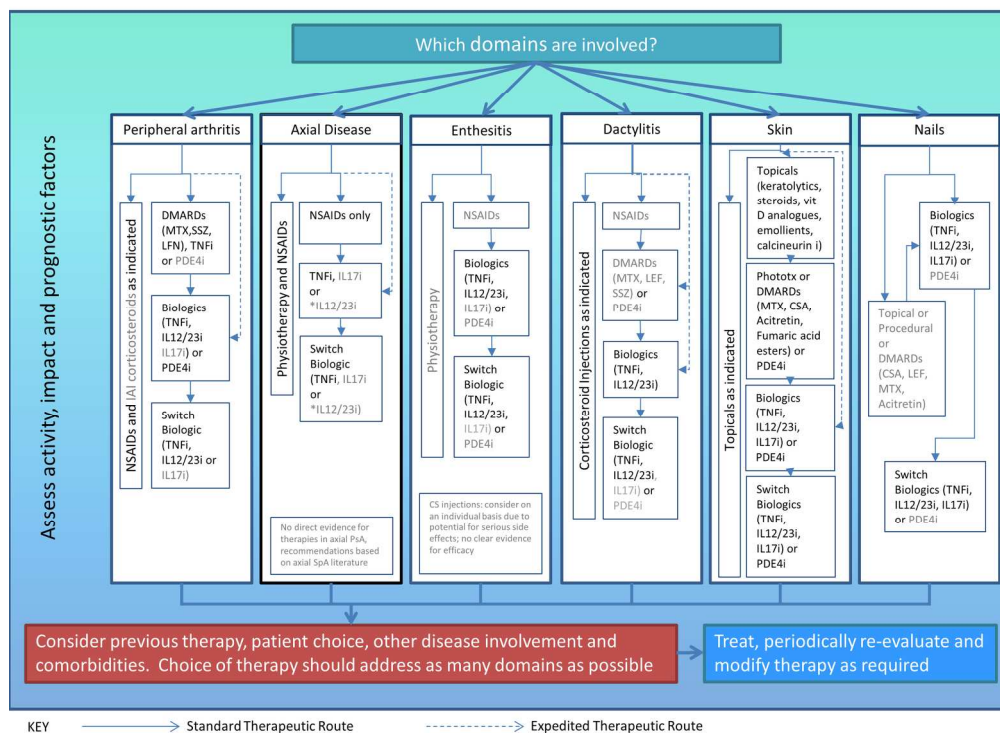


Figure 1: GRAPPA Treatment Schema for Active PsA
 Grey text identifies conditional recommendations for drugs without current regulatory approvals or where recommendations are based on abstract data only.

DMARDs = disease modifying anti-rheumatic drugs, IL17i = interleukin 17 inhibitors, IL12/23i = interleukin 12/23 inhibitors, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal anti-inflammatory drugs, PDE4i = phosphodiesterase 4 inhibitor (apremilast), SSZ = sulfasalazine, TNFi = tumor necrosis factor inhibitor

190x142mm (300 x 300 DPI)

GRAPPA Treatment Recommendations: PICO and GRADE Recommendations by Group

Peripheral Arthritis

1. In patients with active peripheral PsA what is the impact of non-steroidal anti-inflammatory drugs (NSAIDs) on symptoms, disease progression and adverse events? NSAIDs can be considered to relieve symptoms of peripheral PsA, at a standard or lower dose and with careful monitoring for side effects if used in a sustained manner. Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Short term desirable effect. No effect on disease progression proven. Adverse events are common.
Quality of evidence	Low quality
Values and preferences	Not clear
Costs (resource allocation)	Low cost

2. In patients with active peripheral PsA what is the impact of oral steroids on symptoms, disease progression and adverse events? Chronic systemic corticosteroids are **not** recommended in the treatment of psoriatic arthritis and are only advisable in discrete circumstances for short-term disease control and not for chronic use. Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Short term desirable effect. No effect on disease progression proven. Potential for significant adverse events with long term use.
Quality of evidence	Very low quality
Values and preferences	Not clear
Costs (resource allocation)	Low cost

3. In patients with active peripheral PsA, with or without ongoing DMARD treatment, what is the impact of intra-articular steroids on symptoms, disease progression and adverse events? Intra-articular corticosteroids are recommended for symptom alleviation in the treatment of psoriatic mono-, oligo- and polyarthritis. Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Short term desirable effect. No effect on disease progression proven. Adverse events are rare.
Quality of evidence	Very low quality
Values and preferences	Not clear
Costs (resource allocation)	Low cost

4. In patients with active peripheral PsA what is the impact of conventional disease modifying anti-rheumatic drugs (cDMARDs) on symptoms, disease progression and adverse events?
 Conventional DMARDs (methotrexate, leflunomide, sulfasalazine) are recommended as a first line therapy for symptoms of peripheral PsA
 Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Clear desirable effect. Favorable balance between desirable and undesirable effects. No clear harmful effect of a short term delay (3-6 months) in introducing more effective treatments.
Quality of evidence	Moderate quality
Values and preferences	Probably well positioned in values and preferences
Costs (resource allocation)	Low cost

5. In patients with active peripheral PsA who are DMARD-naive what is the impact of TNF inhibitors on symptoms, disease progression and adverse events?
 TNF inhibitors should be used to treat symptoms and disease progression of peripheral PsA in people who are DMARD naive
 Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Strongly favors desirable effects on symptoms and disease progression.
Quality of evidence	High Quality RCT data for adalimumab, etanercept, golimumab, infliximab
Values and preferences	well established values and preferences
Costs (resource allocation)	High cost.

6. In patients with active peripheral PsA who are DMARD-naive what is the impact of IL12/23 inhibitor on symptoms, disease progression and adverse events?
 IL12/23 inhibitors is not recommended to treat symptoms of peripheral PsA in people who are DMARD naive
 Strength of recommendation – conditionally not recommended

Factor	Comment
Balance between desirable and undesirable effects	No data in DMARD naïve patients
Quality of evidence	No data available
Values and preferences	Not clear
Costs (resource allocation)	High cost

7. In patients with active peripheral PsA who are DMARD-naïve what is the impact of IL17 inhibitors on symptoms, disease progression and adverse events?
 IL17 inhibitors should (not) be used to treat symptoms of peripheral PsA in people who are DMARD naïve
 Strength of recommendation – conditionally not recommended

Factor	Comment
Balance between desirable and undesirable effects	No data in DMARD naïve patients
Quality of evidence	No data available
Values and preferences	Not clear
Costs (resource allocation)	High cost

8. In patients with active peripheral PsA who are DMARD-naïve what is the impact of apremilast on symptoms, disease progression and adverse events?
 Apremilast can be considered to treat symptoms of peripheral PsA in people who are DMARD naïve
 Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Likely effect on symptoms of peripheral PsA, no data on disease progression, adverse events are uncommon
Quality of evidence	Low quality (abstract of 1 RCT only)
Values and preferences	Not clear
Costs (resource allocation)	High cost

9. In patients with active peripheral PsA who have failed conventional DMARDs what is the impact of TNF inhibitors on symptoms, disease progression and adverse events?
 TNF inhibitors should be used to treat symptoms and disease progression of peripheral PsA in people who have failed conventional DMARDs
 Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Strongly favors desirable effects.
Quality of evidence	High Quality
Values and preferences	well established values and preferences
Costs (resource allocation)	High cost.

10. In patients with active peripheral PsA who have failed conventional DMARDs what is the impact of IL12/23 inhibitors on symptoms, disease progression and adverse events?
IL12/23 inhibitors should be used to treat symptoms and disease progression of peripheral PsA in people who have failed conventional DMARDs
Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Strongly favors desirable effects.
Quality of evidence	High Quality
Values and preferences	well established values and preferences
Costs (resource allocation)	High cost.

11. In patients with active peripheral PsA who have failed conventional DMARDs what is the impact of IL17 inhibitors on symptoms, disease progression and adverse events?
IL17 inhibitors should be used to treat symptoms and disease progression of peripheral PsA in people who have failed conventional DMARDs
Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Strongly favors desirable effects.
Quality of evidence	High Quality studies but phase III studies only in abstract form currently
Values and preferences	well established values and preferences
Costs (resource allocation)	High cost.

12. In patients with active peripheral PsA who have failed conventional DMARDs what is the impact of apremilast on symptoms, disease progression and adverse events?
Apremilast should be used to treat symptoms of peripheral PsA in people who have failed conventional DMARDs
Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Strongly favors desirable effects on symptoms, no data on disease progression.
Quality of evidence	High Quality
Values and preferences	well established values and preferences
Costs (resource allocation)	High cost.

13. In patients with active peripheral PsA what is the impact of switching to an alternate TNF inhibitor or to an alternate targeted biological agent on symptoms, disease progression and adverse events in the case of inadequate response or adverse effects with a first targeted biological agent?

Switching TNF inhibitors or to an alternate targeted biological agent for inadequate response or adverse effects can be considered to treat symptoms of peripheral PsA in people with PsA that are not responding to a previous targeted biological agent.
Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Effective on symptoms of peripheral PsA, likely effect on disease progression (TNFi), adverse events are common (TNFi, IL17i, IL12/23i), adverse events uncommon with apremilast
Quality of evidence	Low quality, little data
Values and preferences	Clear
Costs (resource allocation)	High cost

Axial

1. In patients with active PsA-related axial disease what is the impact of non-steroidal anti-inflammatory drugs (NSAIDs) on symptoms, disease progression and adverse events?
NSAIDs should be used to treat symptoms of axial disease in people with PsA.
Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Short term desirable effect, positive effect on disease progression, adverse events are common
Quality of evidence	High quality
Values and preferences	Not clear
Costs (resource allocation)	Low cost

2. In patients with active PsA-related axial disease what is the impact of physiotherapy and simple analgesia on symptoms, disease progression and adverse events?

Physiotherapy and simple analgesia should be used to treat symptoms of axial disease in people with PsA

Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Short term desirable effect, no effect on disease progression, adverse events are uncommon
Quality of evidence	High quality
Values and preferences	Not clear
Costs (resource allocation)	Low cost

3. In patients with active PsA-related axial disease what is the impact of conventional disease modifying anti-rheumatic drugs (cDMARDs) on symptoms, disease progression and adverse events?

Conventional DMARDs should not be used to treat symptoms of axial disease in people with PsA

Strength of recommendation – strongly not recommended

Factor	Comment
Balance between desirable and undesirable effects	No effect on symptoms or signs of axial disease or on disease progression, adverse events are common
Quality of evidence	High quality
Values and preferences	Not clear
Costs (resource allocation)	Low cost

4. In patients with active PsA-related axial disease that is not responding to NSAIDs, what is the impact of TNF inhibitors on symptoms, disease progression and adverse events? TNF inhibitors should be used to treat symptoms of axial disease in people with PsA that are not responding to NSAIDs

Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Effective on symptoms and signs of axial disease, possible effect on disease progression, adverse events are common
Quality of evidence	High quality
Values and preferences	Clear
Costs (resource allocation)	High cost

5. In patients with active PsA-related axial disease that is not responding to NSAIDs, what is the impact of IL12/23 inhibitor on symptoms, disease progression and adverse events?

IL12/23 inhibitors can be considered to treat symptoms of axial disease in people with PsA that are not responding to NSAIDs

Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	No effect on disease progression, adverse events are uncommon
Quality of evidence	Low quality (abstract data only)
Values and preferences	Not clear
Costs (resource allocation)	High cost

6. In patients with active PsA-related axial disease that is not responding to NSAIDs, what is the impact of IL17 inhibitors on symptoms, disease progression and adverse events? IL17 inhibitors should be used to treat symptoms of axial disease in people with PsA that are not responding to NSAIDs

Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	No effect on disease progression, adverse events are uncommon
Quality of evidence	Low quality (abstract data only for phase III)
Values and preferences	Not clear
Costs (resource allocation)	High cost

7. In patients with active PsA-related axial disease that is not responding to NSAIDs, what is the impact of IL6 inhibitor on symptoms, disease progression and adverse events? IL6 inhibitors should not be used to treat symptoms of axial disease in people with PsA that are not responding to NSAIDs

Strength of recommendation – strongly not recommended

Factor	Comment
Balance between desirable and undesirable effects	No effect on symptoms or signs of axial disease or on disease progression, adverse events are common
Quality of evidence	High quality
Values and preferences	Not clear
Costs (resource allocation)	High cost

8. In patients with active PsA-related axial disease that is not responding to NSAIDs, what is the impact of anti-CD20 antibodies (rituximab) on symptoms, disease progression and adverse events?

Anti-CD20 antibody should not be used to treat symptoms of axial disease in people with PsA that are not responding to NSAIDs

Strength of recommendation – strongly not recommended

Factor	Comment
Balance between desirable and undesirable effects	No effect on symptoms or signs of axial disease or on disease progression, adverse events are common
Quality of evidence	High quality
Values and preferences	Not clear
Costs (resource allocation)	High cost

9. In patients with active PsA-related axial disease that is not responding to NSAIDs, what is the impact of sacroiliac joint injections on symptoms, disease progression and adverse events?

Local injection of corticosteroid to the sacroiliac joints can be considered to treat symptoms of axial disease in people with PsA that are not responding to NSAIDs.

Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Short term desirable effect, no effect on disease progression, adverse events are uncommon
Quality of evidence	Low quality
Values and preferences	Not clear
Costs (resource allocation)	Low cost

10. In patients with active PsA-related axial disease that is not responding to NSAIDs, what is the impact of bisphosphonates on symptoms, disease progression and adverse events?

Bisphosphonate infusions can be considered to treat symptoms of axial disease in people with PsA that are not responding to NSAIDs.

Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Short term desirable effect, no effect on disease progression, adverse events are uncommon
Quality of evidence	Low quality
Values and preferences	Not clear
Costs (resource allocation)	Low cost

11. In patients with active PsA-related axial disease what is the impact of switching to an alternate TNF inhibitor or to an alternate targeted biological agent on symptoms, disease

progression and adverse events in the case of inadequate response or adverse effects with a first targeted biological agent?

Switching TNF inhibitors or to an alternate targeted biological agent for inadequate response or adverse effects can be considered to treat symptoms of axial disease in people with PsA that are not responding to a previous targeted biological agent.

Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Effective on symptoms and signs of axial disease, possible effect on disease progression, adverse events are common
Quality of evidence	Low quality
Values and preferences	Clear
Costs (resource allocation)	High cost

Enthesitis

1. In patients with active PsA-related enthesitis what is the impact of non-steroidal anti-inflammatory drugs (NSAIDs) on symptoms and adverse events?

NSAIDs can be considered as an initial therapy for enthesitis with careful monitoring for side effects

Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Potential desirable effect, adverse events possible but serious adverse effects are uncommon
Quality of evidence	No RCTs, expert consensus
Values and preferences	Not assessed, likely high acceptability to patients
Costs (resource allocation)	Low cost

2. In patients with active PsA-related enthesitis what is the impact of physical therapy on symptoms and adverse events?

Physical therapy can be considered to improve symptoms and functional deficit associated with enthesitis

Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Potential benefit, no adverse events likely
Quality of evidence	No RCTs, expert consensus
Values and preferences	Generally well tolerated and received
Costs (resource allocation)	Relatively low cost

3. In patients with active PsA-related enthesitis what is the impact of local corticosteroid injections on symptoms and adverse events?

Local corticosteroid injections can be considered with caution for enthesitis

Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Potential desirable effect, serious adverse events are possible
Quality of evidence	Extrapolated results from meta-analysis of controlled trials in tendinopathy, high
Values and preferences	Not assessed
Costs (resource allocation)	Low cost

4. In patients with active PsA-related enthesitis what is the impact of conventional disease modifying anti-rheumatic drugs (cDMARDs) on symptoms and adverse events?

cDMARDs are not recommended for the treatment of enthesitis

Strength of recommendation – strongly not recommended

Factor	Comment
Balance between desirable and undesirable effects	No demonstrated benefit, adverse events are common
Quality of evidence	One RCT
Values and preferences	Not assessed
Costs (resource allocation)	Low to moderate cost

5. In patients with active PsA-related enthesitis what is the impact of TNF inhibitors on symptoms and adverse events?

TNF alpha inhibitors as a class are recommended as initial or second line therapy in the treatment of refractory or moderate to severe enthesitis

Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Demonstrated benefit, potential serious adverse events
Quality of evidence	High quality RCTs (golimumab, certolizumab, infliximab) Non-placebo controlled (etanercept) Not enough evidence for adalimumab
Values and preferences	Not assessed
Costs (resource allocation)	High cost

6. In patients with active PsA-related enthesitis what is the impact of IL12/23 inhibitors on symptoms and adverse events?

Ustekinumab is recommended as initial or second line therapy in the treatment of refractory of moderate to severe enthesitis

Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Demonstrated benefit, potential serious adverse events
Quality of evidence	High quality RCTs
Values and preferences	Not assessed
Costs (resource allocation)	High cost

7. In patients with active PsA-related enthesitis what is the impact of apremilast on symptoms and adverse events?

Apremilast is recommended as initial or second line therapy in the treatment of refractory of moderate to severe enthesitis

Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Demonstrated benefit, low risk of adverse events
Quality of evidence	High quality RCT
Values and preferences	Not assessed
Costs (resource allocation)	High cost

8. In patients with active PsA-related enthesitis what is the impact of IL17 inhibitors on symptoms and adverse events?

IL17 inhibitors can be considered as an initial or second line therapy in the treatment of refractory of moderate to severe enthesitis

Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Demonstrated benefit (secukinumab), no benefit (brodalumab), potential risk of serious adverse events
Quality of evidence	Low, abstract data only from RCT
Values and preferences	Not assessed
Costs (resource allocation)	High cost

Dactylitis

1. In patients with active PsA-related dactylitis what is the impact of local corticosteroid injections on symptoms and adverse events?

Local corticosteroid injections can be considered for symptom improvement in dactylitis
Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Short term desirable effect. No known effect on disease progression. Adverse events of steroid injections are minor: very small chance (less than 1/1000) of infection.
Quality of evidence	No RCT, little evidence
Values and preferences	Simple treatment regularly administered in practice. Site of injection variable. Options include intra-articular, and into the tendon sheath.
Costs (resource allocation)	Low cost

2. In patients with active PsA-related dactylitis what is the impact of conventional disease modifying anti-rheumatic drugs (cDMARDs) on symptoms and adverse events?
cDMARDs (methotrexate, leflunomide, sulfasalazine) can be considered for the treatment of dactylitis

Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	As these treatments are likely to be given for active disease elsewhere, favorable balance between desirable and undesirable effects
Quality of evidence	Weak evidence from RCT. Stronger evidence from observational studies
Values and preferences	If dactylitis only feature the systemic effects of treatment must be considered but individualised decisions necessary eg may be more urgent in finger of someone who uses hands to do job
Costs (resource allocation)	Low cost

3. In patients with active PsA-related dactylitis what is the impact of TNF inhibitors on symptoms and adverse events?

TNF alpha inhibitors (adalimumab, certolizumab, golimumab and infliximab) are recommended as initial or second line therapy in the treatment of refractory or moderate to severe dactylitis

Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Strongly favors desirable effects. Treatment unlikely to be given solely for dactylitis so beneficial effects on enthesitis, spondylitis and peripheral arthritis must also be taken into consideration
Quality of evidence	Strong evidence in RCTs for adalimumab, certolizumab, golimumab, infliximab but dactylitis only ever a secondary outcome Not enough evidence for etanercept
Values and preferences	Well established values and preferences in light of above as skin improvement and other articular both important trade offs
Costs (resource allocation)	High cost

4. In patients with active PsA-related dactylitis what is the impact of IL12/23 inhibitors on symptoms and adverse events?
Ustekinumab can be considered as an initial targeted biological therapy or second line therapy in the treatment of refractory or moderate to severe dactylitis
Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Favors desirable effects but MACE events still under examination in prospective cohort studies.
Quality of evidence	High quality RCT
Values and preferences	Probably well positioned in values and preferences but will depend on extent of skin involvement and other musculoskeletal involvement
Costs (resource allocation)	High cost

5. In patients with active PsA-related dactylitis what is the impact of apremilast on symptoms and adverse events?
Apremilast can be considered as a second line therapy in the treatment of refractory or moderate to severe dactylitis
Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Likely benefit, low risk of adverse events
Quality of evidence	Low, abstract of pooled data from 3 RCTs
Values and preferences	Not assessed
Costs (resource allocation)	High cost

6. In patients with active PsA-related dactylitis what is the impact of IL17 inhibitors on symptoms and adverse events?

IL17 inhibitors can be considered as second line therapy in the treatment of refractory of moderate to severe dactylitis

Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Demonstrated benefit (secukinumab), potential risk of serious adverse events
Quality of evidence	Low, abstract data only from RCT
Values and preferences	Not assessed
Costs (resource allocation)	High cost

Psoriasis

1. In patients with active psoriasis what is the impact of topical therapies on symptoms and adverse events?

Topical therapies are recommended as the basic approach to treat any psoriasis. It is recommended as the sole therapy for mild disease, and combined with systemic therapies can be used in more active disease. The combination of calcipotriol and betamethasone is considered the gold standard for plaque psoriasis. Exceptions on specific anatomical sites (eg face, genitals) apply.

Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Minimal undesirable effects (mild irritation of the skin), short term desirable effects (good clinical efficacy)
Quality of evidence	High quality
Values and preferences	Time consuming, low patient adherence
Costs (resource allocation)	Low costs

2. In patients with active psoriasis what is the impact of conventional disease modifying anti-rheumatic drugs (cDMARDs) on symptoms and adverse events?

Conventional DMARDs (methotrexate, leflunomide, cyclosporin) are recommended as a first line therapy for psoriasis

Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Clear desirable effect. Favorable balance between desirable and undesirable effects in psoriasis in the presence or absence of PsA
Quality of evidence	Moderate quality
Values and preferences	Probably well positioned in values and preferences
Costs (resource allocation)	Low cost

3. In patients with active psoriasis what is the impact of TNF inhibitors on symptoms and adverse events?
 TNF inhibitors should be used to treat psoriasis in people who are DMARD naïve or DMARD failures
 Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Clear desirable effect. Favorable balance between desirable and undesirable effects in psoriasis in the presence or absence of PsA
Quality of evidence	High Quality RCT data for adalimumab, certolizumab, etanercept, golimumab, infliximab
Values and preferences	well established values and preferences
Costs (resource allocation)	High cost.

4. In patients with active psoriasis what is the impact of IL12/23 inhibitor on symptoms and adverse events?
 IL12/23 inhibitors should be used to treat psoriasis in people who are DMARD naïve or DMARD failures
 Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Clear desirable effect. Favorable balance between desirable and undesirable effects in psoriasis in the presence or absence of PsA
Quality of evidence	High Quality RCT data
Values and preferences	well established values and preferences
Costs (resource allocation)	High cost

5. In patients with active psoriasis what is the impact of IL17 inhibitors on symptoms, disease progression and adverse events?
 IL17 inhibitors (brodalumab, ixekizumab, secukinumab) should be used to treat psoriasis in people who are DMARD naïve or DMARD failures.
 Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Clear desirable effect. Favorable balance between desirable and undesirable effects in psoriasis in the presence or absence of PsA
Quality of evidence	High Quality RCT data
Values and preferences	well established values and preferences
Costs (resource allocation)	High cost

6. In patients with active psoriasis what is the impact of apremilast on symptoms and adverse events?

Apremilast should be used to treat psoriasis in people who are DMARD naïve or DMARD failures

Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Clear desirable effect. Minimal serious side effects. Favorable balance between desirable and undesirable effects in psoriasis in the presence or absence of PsA
Quality of evidence	High Quality RCT data
Values and preferences	Acceptable to patients, oral drug, no regular monitoring required.
Costs (resource allocation)	High cost

7. In patients with active psoriasis about to start systemic therapy for PsA, should concomitant topicals be used?

Concomitant topical therapy can usually be limited to emollients and pharmacotherapy of single lesions or sites in limited psoriasis as many systemic treatments for PsA will have a beneficial effect on the skin.

Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Minimal undesirable effects (mild irritation of the skin), short term desirable effects (good clinical efficacy)
Quality of evidence	Moderate quality
Values and preferences	Time consuming, low patient adherence
Costs (resource allocation)	Low costs

8. In patients with markedly active psoriasis about to start systemic therapy for PsA, should certain therapies be used in preference?

In patients with markedly active psoriasis, the following therapies for PsA should be used in preference: methotrexate, cyclosporin, TNFi, IL12/23i, IL17i, apremilast

Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	The above-mentioned drugs all exhibit a good safety profile combined with sufficient to excellent efficacy when used to treat PsA and/or PsO
Quality of evidence	High quality RCTs
Values and preferences	Acceptable to patients, oral drugs may be preferred
Costs (resource allocation)	Low costs (cDMARDs) High costs (TNFi, IL12/23i, IL17i, apremilast)

Nail psoriasis

- In patients with nail psoriasis what is the impact of topical therapies (calcipotriol, tacrolimus, and tazarotene) on symptoms and adverse events?
Topical therapies (calcipotriol, tacrolimus, and tazarotene) can be considered for symptom improvement in nail psoriasis
Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Likely mild improvement in disease, serious adverse effects are unlikely
Quality of evidence	Lower quality clinical trials
Values and preferences	Acceptable to patients
Costs (resource allocation)	Low cost

- In patients with nail psoriasis what is the impact of procedural therapies (including pulsed dye laser and intralesional corticosteroids) on symptoms and adverse events?
Procedural therapies (including pulsed dye laser and intralesional corticosteroids) can be considered for symptom improvement in nail psoriasis
Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Likely mild improvement in disease, serious adverse effects are unlikely
Quality of evidence	Lower quality clinical trials
Values and preferences	Poorly tolerated by patients
Costs (resource allocation)	Low cost

- In patients with active nail psoriasis what is the impact of conventional disease modifying anti-rheumatic drugs (cDMARDs) on symptoms and adverse events?
cDMARDs (cyclosporine, leflunomide, acitretin and methotrexate) can be considered for the treatment of nail psoriasis
Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Likely mild-to-moderate improvement in disease, serious adverse effects are more likely than topical or procedural options.
Quality of evidence	Lower quality clinical in most, except higher quality RCTs evaluating methotrexate
Values and preferences	Acceptable to patients
Costs (resource allocation)	Low cost

4. In patients with active active nail psoriasis what is the impact of TNF inhibitors on symptoms and adverse events?
 TNF alpha inhibitors are recommended as initial or second line therapy in the treatment of refractory moderate to severe active nail psoriasis
 Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Likely significant improvement in disease, potential risk for serious adverse effects
Quality of evidence	High quality
Values and preferences	Well accepted by patients
Costs (resource allocation)	High cost

5. In patients with active active nail psoriasis what is the impact of IL12/23 inhibitors on symptoms and adverse events?
 Ustekinumab is recommended as a second line therapy in the treatment of refractory of moderate to severe active nail psoriasis
 Strength of recommendation – strongly recommended

Factor	Comment
Balance between desirable and undesirable effects	Likely significant improvement in disease, potential risk for serious adverse effects
Quality of evidence	High quality
Values and preferences	Well accepted by patients, infrequent dosing
Costs (resource allocation)	High cost

6. In patients with active active nail psoriasis what is the impact of IL17 inhibitors on symptoms and adverse events?
 IL17 inhibitors can be considered as a second line therapy in the treatment of refractory of moderate to severe active nail psoriasis
 Strength of recommendation – conditionally recommended

Factor	Comment
Balance between desirable and undesirable effects	Likely moderate improvement in disease, potential risk for serious adverse effects
Quality of evidence	Single lower quality clinical trial
Values and preferences	Not assessed
Costs (resource allocation)	High cost

For Peer Review

GRAPPA Treatment Recommendations: PICO Questions for Comorbidities/Extraarticular Manifestations

The following recommendations should be addressed by the patient's treating clinicians including the rheumatologist, dermatologist, primary care physician, and/or other members of the care team. The implementation of these recommendations may vary according to local and/or national guidelines.

PICO 1: In patients with PsA, should cardiovascular risk factors be addressed?

Summary: There is a substantive body of work suggesting an increased risk of cardiovascular disease among patients with psoriatic arthritis (PsA). However, there are no studies that address mitigation of cardiovascular risk and long-term outcomes as a result of cardiovascular risk.

Recommendation: Given evidence suggesting that PsA is associated with increased cardiovascular risk, a cardiovascular risk assessment should be strongly considered for all patients with PsA.

Grade strength of recommendation: Strong

Factor	Comment
Balance between desirable and undesirable effects	Low risk of undesirable effects, particularly given that this recommendation is also a recommendation for the general population
Quality of evidence	No studies
Values and preferences	Not clear
Costs (resource allocation)	Generally low cost but not clear

PICO 2: In patients with PsA, should screening for diabetes be performed?

Summary: A number of studies have now suggested an increased prevalence and incidence of diabetes among patients with PsA. However, there are no studies addressing long term outcomes in patients with PsA as a result of screening for diabetes. However, this is now a recommendation for the general population over age 45.

Recommendation: Given the association of diabetes with PsA, fasting glucose or hemoglobin A1C should be considered in all patients with PsA.

Grade strength of recommendation: Weak

Factor	Comment
Balance between desirable and undesirable effects	Low risk of undesirable effects
Quality of evidence	No studies
Values and preferences	Not clear
Costs (resource allocation)	Generally low cost but not clear

PICO 3: In patients with PsA, should obesity and achievement/maintenance of a healthy body weight be addressed?

Summary: Several studies have suggested that body mass index (BMI) may influence not only the development of psoriasis and PsA but also may impact disease activity and response to therapy. Lower body weight and weight loss have been associated with beneficial therapeutic effects for both TNF alpha inhibitors in patients with PsA or psoriasis alone and for cyclosporine in patients with psoriasis. Among patients with PsA, a recent prospective study found that obesity was associated with a Hazard Ratio of 4.9 (CI 3.02-7.87) for not achieving minimal disease activity (MDA). Of those that achieved MDA at 12 months, obesity was a significant risk factor for relapse at 24 months. Additionally, two recent studies suggesting improvement in response to therapy (achieving MDA) in patients with lower body weight.

Recommendation: Patients should be encouraged to achieve and maintain a healthy body weight.

Grade strength of recommendation: Strong

Factor	Comment
Balance between desirable and undesirable effects	Low risk of undesirable effects
Quality of evidence	Good evidence from two RCT for improved efficacy of TNF alpha inhibitors with lower body weight.
Values and preferences	Not clear
Costs (resource allocation)	Generally low cost but not clear

PICO 4: Among patients with PsA, how should the risk for eye disease or gastrointestinal side effects be addressed?

Summary: Among patients with PsA, there is an association with uveitis and other ophthalmic disorders including keratitis, blepharitis, conjunctivitis, episcleritis, and scleritis. Additionally, there is an increased risk for Crohn's disease among patients with PsA. There are no studies addressing interventions to address these risks.

Recommendation: Because PsA can be associated with ophthalmic disease and inflammatory bowel disease, rheumatologists should ask about relevant symptoms and should consider referral.

Grade strength of recommendation: Strong

Factor	Comment
Balance between desirable and undesirable effects	Low risk of undesirable effects
Quality of evidence	No studies
Values and preferences	Not clear
Costs (resource allocation)	low cost

PICO 5: Among patients with PsA utilizing TNF alpha inhibitors, should monitoring for skin cancer be performed?

Summary: Among patients with PsA, non-melanoma skin cancer is the most common form of cancer. Given that many patients with PsA have had extended courses of ultraviolet light therapy, these patients may be at increased risk for skin cancer. There are no studies addressing long term benefits of skin cancer screening in patients with PsA on immunosuppressive therapies.

Recommendation: Consider periodically performing skin examinations for the detection of skin cancer in patients with PsA utilizing TNF alpha inhibitors.

Grade strength of recommendation: Strong

Factor	Comment
Balance between desirable and undesirable effects	Low risk of undesirable effects
Quality of evidence	No studies
Values and preferences	Not clear
Costs (resource allocation)	Generally low cost but may add an additional dermatologist visit

PICO 6: In patients with PsA beginning an immunosuppressive therapy, should screening for hepatitis C (HCV) and hepatitis B (HBV) be performed?

Summary: Infection with HBV or HCV has implications for therapy selection in PsA. For example, methotrexate may cause increased liver toxicity in patients with HCV or HBV, and TNF alpha inhibitors have been associated with reactivation of HBV. Additionally, both HCV and HBV have been associated with inflammatory arthritis (although there is not strong evidence for an association with PsA in particular). Thus, knowledge of HBV or HCV status prior to initiating therapy is beneficial. There are no studies addressing long term benefits of screening for HBV or HCV in patients with PsA.

Recommendation: Strongly consider screening for HCV and HBV prior to beginning therapy with immunosuppressive agents.

Grade strength of recommendation: Strong

Factor	Comment
Balance between desirable and undesirable effects	Low risk of undesirable effects
Quality of evidence	No studies
Values and preferences	Not clear
Costs (resource allocation)	Cost of blood tests may vary by country

PICO 7: Among patients with PsA, should screening for human immunodeficiency virus (HIV) be performed prior to initiating an immunosuppressive therapy?

Summary: Given that HIV is an immunosuppressed state, adding an immunosuppressive therapy requires special monitoring. Thus, knowledge of the presence of HIV infection is important. There are no studies addressing long term benefits of HIV screening in patients with PsA.

Recommendation: Screening for HIV should be considered in patients with risk factors prior to starting immunosuppressive agents.

Grade strength of recommendation: Strong

Factor	Comment
Balance between desirable and undesirable effects	Low risk of undesirable effects
Quality of evidence	No studies
Values and preferences	Not clear
Costs (resource allocation)	Cost of HIV testing may vary by country

PICO 8: Among patients with PsA, should tuberculosis (TB) screening be performed before initiating a biologic therapy?

Summary: Therapies such as the TNF alpha inhibitors increase the risk for symptomatic TB among patients with latent TB. Thus, screening for latent TB and starting therapy when detected prior to initiating a biologic therapy is advisable. There are no studies addressing long term benefits of TB screening in patients with PsA.

Recommendation: Patients should be screened for latent TB infection prior to starting a biologic agent.

Grade strength of recommendation: Strong

Factor	Comment
Balance between desirable and undesirable effects	Low risk of undesirable effects
Quality of evidence	No studies
Values and preferences	Not clear
Costs (resource allocation)	Low cost but cost of screening may vary by country

PICO 9: Among patients with PsA, should screening for depression be performed?

Summary: Depression is common among patients with PsA and one new therapy (apremilast) has been associated with depression.

Recommendation: Consider screening for depression in all patients with PsA.

Grade strength of recommendation: Strong

Factor	Comment
Balance between desirable and undesirable effects	Low risk of undesirable effects
Quality of evidence	No studies
Values and preferences	Not clear
Costs (resource allocation)	

(Formatted for submission to Arthritis and Rheumatology)

Running Head: GRAPPA Treatment Recs for PsA

Group for Research and Assessment of Psoriasis and Psoriatic Arthritis:

Treatment Recommendations for Psoriatic Arthritis 2015

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ABSTRACT (n = 232)

Objective: 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 patients based on consensus at face-to-face meetings and via online surveys. We published literature reviews regarding treatment for the key domains of PsA (arthritis, spondylitis, enthesitis, dactylitis, skin, 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, with an online questionnaire.

Results: Six overarching principles had at least 80% agreement among both health care professionals (HCPs; n=135) and patient research partners (PRPs; n=10). We developed treatment recommendations and a schema incorporating these principles for arthritis, spondylitis, enthesitis, dactylitis, skin, and nail disease, and comorbidities in the setting of PsA, using the GRADE process. Over 80% agreement was reached for approval of the individual recommendations and the overall schema.

Conclusion: Herein, 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 HCPs, and PRPs). Further updates are anticipated as the therapeutic landscape in PsA evolves.

For Peer Review

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 over 500 rheumatologists, dermatologists, and patient research partners (PRPs) previously published treatment recommendations in 2009(3) based on a systematic evidence review published in 2006.(4-11) To be clinically relevant, such recommendations must be dynamic, requiring re-evaluation and appropriate modification over time. In PsA, significant recent developments in pathophysiology and disease assessment, particularly the important contribution of comorbidities coupled with major therapeutic advances, necessitated an update of the GRAPPA recommendations.

GRAPPA investigators and PRPs formed groups focused on the clinical domains of PsA: peripheral arthritis, axial disease, enthesitis, dactylitis, skin, and nail disease, with a new group focused on comorbidities. In addition, a representative from each group also 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 of the domains.(13-19) We applied the GRADE approach 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 social considerations.(20) We created a series of PICO questions (*vide infra* [see supplementary online data](#)) to address crucial practical questions faced by clinicians when making specific treatment choices. 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 considerations.

OBJECTIVE

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

METHODS

To help frame these updated GRAPPA recommendations, we developed new overarching principles for the treatment of PsA. Initially drafted by a small working group, these overarching principles were refined through several rounds of

dissemination to members, followed by live 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 six sub-groups 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 University of Leeds Library as detailed previously(12) in 2013 with relevant papers given to the groups. We convened an additional group to assess relevant comorbidities and they performed an new-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 PICO (population, intervention, comparator, outcomes) questions,(20) and then gathered relevant evidence to support the recommendation for individual drugs, classes of drugs, and treatment approaches within the six disease domains of PsA as well as the comorbidities group. Recommendations ~~per the GRADE system~~ could be for or against a treatment, and could be strong or conditional, based upon the best scientific evidence and relevant clinical context per the GRADE system. Evidence was combined from the central 2013 literature review and additional literature reviews performed within the groups. To ensure that the recommendations were not outdated rapidly, each group completed a further literature update and review of abstracts through the American College of Rheumatology (ACR) Annual Meeting in November 2014, and the American Academy

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of Dermatology meeting in March 2015. [The comorbidities group performed a 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 manuscripts 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 [via an online survey](#) by the GRAPPA membership (with the supporting PICO questions) to allow feedback, followed by a vote to assess level of agreement.

Using these evidence-based data, each group summarized their treatment recommendations in a flowchart to guide therapy. Input from each group was combined into a single schema, which was [assessed by sent to the full GRAPPA membership \(including the group/committee members\)](#) via [Survey Monkey 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 in both face to face discussions at GRAPPA meetings and online surveys.](#)

RESULTS

Overarching Principles

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Six overarching principles for the care of patients with PsA were finalized after extensive feedback. Agreement was $\geq 80\%$ among GRAPPA members ([135 health care providers and 10 patient research partners](#)) for all of these principles from both physicians and PRPs (**Table 1**). The majority of disagreements related to minor wording changes, which were incorporated [where possible](#) following this survey, [although a repeat survey was not performed](#).

GRADE Recommendations for Therapies

Each group produced a number of PICO questions addressing the efficacy and safety of the different therapies, developing a [GRADE based strong/conditional](#) recommendation for each therapy within their domain (**Supplementary Material 1**). These are summarized in **Table 2** showing which therapies are strongly or conditionally recommended within the domains. A survey of GRAPPA members showed an 87.2% support (n=176) for this summary table, including 83.3% of PRPs (n=6).

GRADE Recommendations for Comorbidities

The comorbidities group also produced a number of PICO questions addressing recommendations for the investigation and management of relevant comorbidities (**Supplementary Material 2**). [Evidence for these issues is limited and the majority of these recommendations rely on expert opinion.](#)

Identifying comorbidities is critical in the optimal management and treatment of PsA patients. 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 extra-articular 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 patients with normal body weight using tumor necrosis factor inhibitors (TNFi) appear to have a higher likelihood of reducing their disease activity than do overweight PsA patients.(22-24) Given the association of ophthalmic disease with the spondyloarthritis and an increased risk for 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 Human Immunodeficiency Virus, 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 in PsA patients; of note, a warning to weigh the risks and benefits of treatment among patients with a history of depression and/or suicidal thoughts/behavior

has been added to the package insert materials in the USA for new drugs for PsA and psoriasis. Although screening and management of comorbidities may be no different than for the general population, it is nevertheless important to actively identify them in order to optimize the care of patients with PsA.

Treatment Schema

Each disease domain group designed a flowchart for treatment of their domain using the GRADE 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 cut-offs are not evidence-based or applicable to all patients. **Figure 1** outlines potential therapeutic routes described as standard or expedited to allow therapy to be tailored to the individual patient. Individual treatment decisions with each patient 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 in therapy as appropriate. The schema was circulated to the full GRAPPA membership and 87.9% approved (n=176), including all six PRPs. For clarity, it was decided to use the historical term “DMARD” for conventional systemic drugs such as methotrexate and sulfasalazine, as this is commonly used nomenclature. It should be noted that this term is not meant to imply that such therapies have “disease

modifying” impact on radiographic damage in PsA. “Biologics” was used to describe the group of biological therapies targeting TNF, IL12/23, IL17 and others.

This 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. Within this consideration, it is likely that selection of therapy will be driven by the most severe element of a person’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 anti-inflammatory drugs (NSAIDs) are conditionally recommended for use in peripheral arthritis to improve symptoms of the disease with caution due to their potential adverse effects. Corticosteroids are conditionally recommended for peripheral arthritis either given systemically or intra-articularly with the smallest doses required (usually less than 7.5 mg/day) and for short required periods -to minimize adverse effects-including psoriasis flare, after CS withdrawal. In disease-modifying antirheumatic drug (DMARD)-naïve patients, both DMARDs (methotrexate, leflunomide, sulfasalazine; cyclosporine is not recommended due to small evidence of its efficacy and its toxicity profile) and TNFi are strongly recommended for treatment. In many instances, DMARDs may be used first, but consideration should be given to early escalation of therapy particularly in patients with poor prognostic factors (e.g., raised inflammatory markers, high active joint counts).

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 PDE4i apremilast in DMARD-naïve patients are only currently available in abstract form, hence this is conditionally recommended. For patients failing DMARDs, PDE4i or biologics (including TNFi, interleukin [IL]12/23 inhibitor) are strongly recommended; at present a conditional recommendation is given for IL17i as the phase III data are only available in abstract form. It must be noted that there are no data available assessing the impact of PDE4i on radiographic damage in contrast to the TNFi, IL12/23i and IL17i.

One phase 2 RCT showed modest effects with abatacept on joint symptoms in PsA Mease(25). Phase 3 trials are being conducted but results are not as yet known, but asSince the manufacturer has not submitted it for regulatory approval 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 2 study. There is no definitive evidence to date assessing the benefit of concomitant DMARDs with biologic therapies. In the TNFi RCTs, similar efficacy results were commonly seen with or without methotrexate. However, registry data suggest a longer persistence of effect of the monoclonal antibodies with concomitant DMARDs, particularly with infliximab. In the case of biologic failure either due to adverse events or inefficacy, a large volume of observational data are now available supporting the conditional recommendation of “switching” to an alternative biologic either within a drug class or to a drug with a different mode of action. Many more recent RCTs include patients who have previously

failed one or more biologic therapy(26-28). There is limited data available on combining therapies and treatment strategy in PsA as outlined in the peripheral arthritis evidence review (13). MTX in combination with biologic agents, either non-TNFi or anti-TNFi, may have a role, but most studies suggest that the combination does not improve clinical symptoms beyond those attained by biologic monotherapy (13). Some registry studies have shown improved survival, mainly for 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 who have not responded to NSAIDs, physiotherapy, and sacroiliac injections (when appropriate), initiation of TNFi is recommended; DMARDs are not effective for treatment of this domain. No evidence is available for efficacy of sulfasalazine in axial disease within AS or PsA.(29) Clinical trial data showing efficacy for secukinumab (phase III trial)(30) and ustekinumab (an open-label proof-of-concept trial with 20 patients)(31) have been published in AS, but these agents are currently not approved for AS or axial PsA. Formal published data on switching agents for axial disease are not available.

Enthesitis: NSAIDs are the first line agents in treatment of enthesitis based on expert opinion, however data from RCTs are lacking (32). Physiotherapy is also often prescribed although formal studies of efficacy are lacking. In one study with defined enthesitis endpoints and placebo controls, sulfasalazine was not effective_(33), and no published data support efficacy of other DMARDs in placebo-controlled studies_(15, 32). There is high quality evidence for the effectiveness of so the next step is the biologics,

TNFi ~~and/or~~ ustekinumab_(15). Data on the efficacy of PDE4i_(34) and secukinumab (35) for enthesitis in PsA are published as abstracts only. Formal data on switching are not available.

Dactylitis: In contrast to enthesitis, DMARDs were recommended as a first step in 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 biologics (TNFi or ustekinumab), but data on switching are not available. Published abstracts show efficacy for both PDE4i(34) and secukinumab(35) for dactylitis, but again, data on switching agents are not available.

Skin disease: Topical agents are generally the first level of treatment for psoriasis, particularly milder disease, followed by phototherapy and DMARDs. Treatment may be initiated with topical therapies in combination with phototherapy or DMARDs in patients with wide-spread disease. For patients who do not respond to these therapies, biologics are recommended. Biologics may be first-line therapy, with or without topical therapies and DMARDs, in certain patients. Switching from one DMARD to another, from a DMARD to a biologic, or from one biologic 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 produced in studies of biologics, particularly the TNF inhibitors, and these agents would certainly be recommended for PsA patients with moderate to severe nail involvement. High quality data are also published on alternative biologics, including ustekinumab and IL-17 inhibitors, and these agents could be considered alternative biologic therapies to TNFi.

Efficacy on nail disease in psoriasis RCTs has been confirmed for PDE4i in multiple abstracts but no published paper was available at this time. Despite the paucity of data, topical agents, corticosteroid injections, or non-biologic DMARDs could be considered, especially for patients with milder involvement or contraindications to other therapies.

Research Agenda

Tremendous advances have transpired in the therapeutic approach to PsA. 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.

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 as well as further enhancing PsA research.

2. **Biomarkers.** Despite tremendous advances in therapies and treatment strategies, there is still an unmet need identifying the optimal therapeutic approach for individual PsA patients. 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 for patients with PsA.(36, 37) 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,(38) joint damage,(39) and functional ability.(39, 40) 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 more than 700 PsA patients, the majority were on topical therapy only (31%) or no treatment at all (28%), and 16% reported not seeing any healthcare provider in the past year for their PsA.(41)

4. Treatment strategies. Novel treatment strategies are being assessed in PsA. For example, treat-to-target, a concept well established in rheumatoid arthritis,(42) 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 more extensively studied in RA is whether therapies can be tapered or even discontinued by patients reaching their therapeutic goals. It remains to be determined whether this will be possible, and for which patients, in PsA.

DISCUSSION

Herein, the members of GRAPPA present updated evidence-based treatment recommendations for patients with PsA. Optimal management of PsA using a

multidisciplinary and multispecialty approach is required but remains a major challenge. The heterogeneity of the disease requires assessment of multiple PsA domains to identify appropriate treatments for each individual. Assessment of comorbidities is also key when planning therapy and can either lead to an escalation in therapy for related diseases, such as inflammatory bowel disease or uveitis, or requires a dose alteration or restriction of therapies in the presence of liver disease or increased risk of infection.

These recommendations are evidence-based wherever 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 GRADE, the format recommended by a number of international bodies including the World Health Organization. The recommendations had strong patient involvement (PRPs were represented 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 PRPs and we recorded the extent of agreement for recommendations in each domain, including comorbidities. To maximise impartiality, GRAPPA members from the pharmaceutical industry were excluded from discussions and voting on the recommendations. To maximise feedback, all non-pharmaceutical members were invited to respond although their individual conflicts of interest are not available.

While other relevant information may be available, it is worth noting that these recommendations were not developed specifically for patients with psoriasis alone, nor

for children with PsA. They are designed to be relevant across international boundaries although it must be recognized that access to some therapies is not universal. We also recognize that limited available evidence exists particularly for some relevant clinical questions. For example, high quality evidence to support the standard treatment approaches in PsA are not published in every domain, and we lack evidence-based studies on the potential additive or even synergistic benefit of combinations of agents (e.g., methotrexate and TNFi). 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 treatments 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 recent 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 using grey font 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 the recommendations may change with new evidence in future. Just as these recommendations are updates of those published in 2009, they will require further updating to ensure that the recommendations reflect current evidence and practice.

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For Peer Review

Table 1. Overarching principles and agreement by members

No	Principle	Physician	Patient
		agreement (n=135)	agreement (n=10)
1	The ultimate goals of therapy for all patients with psoriatic arthritis (PsA) are: a) 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. b) To optimize functional status, improve quality of life and wellbeing, and prevent structural damage to the greatest extent possible. c) 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	83.7%	80%

No	Principle	Physician agreement	Patient agreement
		(n=135)	(n=10)
	<p>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.</p>		
3	<p>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, MRI). The most widely accepted metrics that have been validated for PSA should be utilized whenever possible.</p>	88.9%	80%
4	<p>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.</p>	85.2%	100%
5	<p>Therapeutic decisions need to be individualized, and are made jointly by the patient and their doctor.</p>	89.6%	80%

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No	Principle	Physician agreement (n=135)	Patient agreement (n=10)
	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.		
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%

Table 2: Summary of GRADE recommendations for therapies by domain.

Indication	Recommended Strong	Recommended Weak	Not recommended Strong	No recommendations as lack of evidence
Peripheral Arthritis DMARD Naïve	DMARDs (MTX, SSZ, LEF), TNFi	NSAIDs, oral steroidCS , IA steroidCS , <i>PDE4i</i>		IL12/23i, IL17i
Peripheral Arthritis DMARD Inadequately Responsive	TNFi, ustekinumab, PDE4i	NSAIDs, oral steroidCS , IA steroidCS , <i>IL17i</i>		
Peripheral Arthritis Biologic Inadequately Responsive	TNFi	NSAIDs, oral steroidCS , IA steroidCS , IL12/23i, <i>IL17i</i> , PDE4i		
Axial PsA, Biologic Naïve (based on AS)	NSAIDs, Physiotherapy, simple	<i>IL17i</i> , corticosteroidCS SIJ	DMARDs, IL6i, CD20i	

Indication	Recommended Strong	Recommended Weak	Not recommended Strong	No recommendations as lack of evidence
literature)	analgesia, TNFi	injections, bisphosphonates (<i>IL12/23i</i>)		
Axial PsA, Biologic Inadequately Responsive (based on AS literature)	NSAIDs, Physiotherapy, simple analgesia	TNFi, <i>IL12/23i</i> , <i>IL17i</i>		

Indication	Recommended Strong	Recommended Weak	Not recommended Strong	No recommendations as lack of evidence
Enthesitis	TNFi, IL12/23i,	NSAIDs, physiotherapy, corticosteroid CS injections (with extreme caution due to risk of tendon rupture since injecting corticosteroids in weight-bearing entheses sites can lead to rupture of entheses), PDE4i, IL17i	DMARDs	DMARDs
Dactylitis	TNFi (INF, ADM, GOL, CZP)	Corticosteroid CS injections, DMARDs (MTX,		TNFi (etanercept)

Indication	Recommended Strong	Recommended Weak	Not recommended Strong	No recommendations as lack of evidence
Psoriasis (plaque)	Topical therapies, phototherapy, DMARDs (MTX, LEF, CyA), TNFi, IL12/23i, IL17i, PDE4i	LEF, SSZ), <u>TNFi</u> <u>(ETN)</u> , IL12/23i, <i>IL17i (SEC)</i> <i>PDE4i</i>		
Nail psoriasis	TNFi, IL12/23i	Topical therapies, procedural therapies, DMARDs (CyA, LEF, Acitretin,		

Indication	Recommended Strong	Recommended Weak	Not recommended Strong	No recommendations as lack of evidence
		MTX), IL17i, <i>PDE4i</i>		

Italicized text identifies conditional recommendations for drugs without current regulatory approvals or where recommendations are based on abstract data only.

Italicized text in brackets identifies a conditional recommendation based only on abstract data from a small open-label proof-of-concept trial.

ADM = adalimumab, AS = ankylosing spondylitis, CD20i = CD20 inhibitor, CS = corticosteroids,
 CyA = cyclosporin, CZP = certolizumab, DMARDs = disease modifying anti-rheumatic drugs,
 GOL = golimumab, IA = intra-articular, IL6i = interleukin 6 inhibitor, IL17i = interleukin 17 inhibitor,
 IL12/23i = interleukin 12/23 inhibitor, INF = infliximab, LEF = leflunomide, MTX = methotrexate,
 NSAIDs = nonsteroidal anti-inflammatory drugs, PDE4i = phosphodiesterase 4 inhibitor
 (apremilast), SEC = secukinumab, SIJ = sacroiliac injections, SSZ = sulfasalazine, TNFi = tumor
 necrosis factor inhibitor

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

Comorbidity	Non-steroidal Anti-inflammatory Drugs	Glucocorticoids	Hydroxychloroquine	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast
Cardiovascular Disease	C	?	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	?	<u>NI</u>
Congestive Heart Failure	C	C	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	?	?	?	?	?	?	<u>NI</u>
Obesity	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	C	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>
Metabolic Syndrome	<u>NI</u>	C	<u>NI</u>	<u>NI</u>	C	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>
Diabetes	<u>NI</u>	C	<u>NI</u>	<u>NI</u>	C	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>
Ulcerative Colitis	?	<u>NI</u>	<u>NI</u>	A	<u>NI</u>	<u>NI</u>	OL	<u>NI</u>	A	A	<u>NI</u>	A	<u>NI</u>	<u>NI</u>
Crohn's Disease	?	<u>NI</u>	<u>NI</u>	A	OL	<u>NI</u>	<u>NI</u>	<u>NI</u>	A	A	A	<u>NI</u>	<u>NI</u>	<u>NI</u>
Uveitis	<u>NI</u>	P [#]	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	?	P	P	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>

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Comorbidity	Non-steroidal Anti-inflammatory Drugs	Glucocorticoids	Hydroxychloroquine	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast
Osteoporosis	<u>NI</u>	C	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>
Malignancy	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	C	C	C	C	C	?	<u>NI</u>
Fatty Liver Disease	C	<u>NI</u>	<u>NI</u>	C	C	C	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>
Chronic Kidney Disease	C	<u>NI</u>	<u>NI</u>	<u>NI</u>	C	?	SM	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>
Depression	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	<u>NI</u>	?
Chronic Hepatitis B *	C	<u>NI</u>	<u>NI</u>	<u>NI</u>	C	C	<u>NI</u>	SM	SM	SM	SM	SM	?	<u>NI</u>
Chronic Hepatitis C *	C	<u>NI</u>	<u>NI</u>	<u>NI</u>	C	C	<u>NI</u>	?/P	?	?	?	?	?	<u>NI</u>
Human Immunodeficiency Virus								SM	SM	SM	SM	SM	?	

Comorbidity	Non-steroidal Anti-inflammatory Drugs	Glucocorticoids	Hydroxychloroquine	Sulfasalazine	Methotrexate	Leflunomide	Cyclosporine	Etanercept	Adalimumab	Infliximab	Certolizumab	Golimumab	Ustekinumab	Apremilast
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A = Approved for primary therapy of the comorbid condition

C = Reason for caution

NI = no information available

OL = Off-label use for the therapy of the comorbid condition

P = Preferred therapy

SM = Requires special monitoring

? = Data insufficient but concerns have been raised

* When treating patients with chronic infections that can affect the liver, consider consultation with providers having expertise in the area.

Corticosteroids used as preferred therapy for uveitis are given as topical and/or intraocular injections in preference to oral steroids

Table 4: Case studies using treatment recommendations

Case 1 43-year-old man, psoriasis for 10 years, psoriatic arthritis for 1 year. Current evaluation: SJ2 TJ3 (PIPs and DIPs); no axial symptoms; 3 tender enthesial sites; no dactylitis; psoriasis self-rated 1/10 with BSA 2% (elbows, knees, buttocks) and no nail involvement. Prior therapy has been only NSAIDs, and topical steroids, which he remains on 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, DMARDMTX

Discussion: With reference to the treatment schema, for the individual domains of peripheral arthritis and enthesitis and skin, esDMARD treatment, e.g. LEF, MTX, could be a viable choice given the relatively modest activity in each domain. However, the presence of recurrent iritis (see comorbidity table) along with the combination of individual domains, supports escalation of therapy. Hence, TNF inhibitor therapy is a reasonable choice, and should be discussed with the patient. In some areas, clinicians may be obliged to use MTX before access to a TNF inhibitor is allowed. Other newer therapies could be considered (e.g., IL-12/23 inhibitor, PDE4i [apremilast], IL-17 inhibitors) although clinicians have longer experience with older medications.

Case 59-year-old woman, psoriasis for 15 years, psoriatic arthritis for 9 months.

- 2** Current evaluation: SJ6, TJ8 (knees, wrist, fingers); no axial symptoms; 1 tender enthesial site; no dactylitis; psoriasis self-rated 4/10 with BSA 8% (trunk, scalp, arms, legs) and nail involvement. Prior treatment: cyclosporine led to hypertension, NSAIDs worsened renal function. Cannot access UV therapy. Currently on topical steroids. Additional history notable for poorly controlled diabetes, obesity, and recurrent sinusitis with one hospitalization for pneumonia in the past year.

Treatment recommendation options: methotrexate, PDE4i, leflunomide, biologics

Discussion: Referring to the treatment schema, moderate to severe activity in the peripheral joints and skin seem to be the main drivers of therapy. However, comorbidities (see table) are very important in this case. Excluding failed therapies, these options remain. MTX is a difficult choice due to obesity and diabetes as potential drivers of hepatotoxicity with MTX. The recurrent infections are a concern across 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 34 year old woman with psoriasis for 4 years, psoriatic arthritis for 2 years.

- 3** Current evaluation: SJ8 TJ12 (wrist, knee, fingers, toes); no axial symptoms; 7 tender enthesial sites (knees, feet, pelvic rim); dactylitis of 2 toes (causing inability to walk as required for her work); skin self-rated 1/10 with 1% BSA (trunk) without nail involvement. Prior treatments: methotrexate tried, but caused liver function abnormalities possibly related to alcohol use. Current treatment with NSAIDs, topical low dose steroids, and assist devices (heel cup for foot enthesitis). Treatment with TNF was recommended but the patient was hesitant to do injections or infusions. After considerations of options, and discussion of sulfasalazine, leflunomide, and PDE4i, patient chose sulfasalazine. On re-evaluation 4 months later, there was no improvement. Patient agreed to therapy with TNF inhibitor. After 3 months of therapy, she reported improvement across domains of “around 40%” (but was not achieving the minimal disease activity criteria) and also noted mild but bothersome injection site reactions.

Treatment recommendations (in no order of preference): A different TNF inhibitor, IL-12/23 inhibitor, IL-17 inhibitor, leflunomide, and PDE4i.

Discussion: Referring to the treatment schema, there are several alternatives as noted. Given the significant impact on the patient’s quality of life, treatment needs to be highly effective for this patient. In this case, it can be debated

whether the patient is a “TNFi failure,” and also whether switching to alternative TNFi or to another biologic with a different mode of action would be preferred.

BSA = body surface area; DIP = distal interphalangeal joint; DMARD = disease modifying anti-rheumatic drug; MTX = methotrexate, NSAID = nonsteroidal anti-inflammatory drug; PDE4i = phosphodiesterase 4 inhibitor (apremilast); PIP = proximal interphalangeal joint; SJ = swollen joint; TJ = tender joint; TNFi = tumor necrosis factor inhibitor

For Peer Review

Figure Legend**Figure 1: GRAPPA Treatment Schema for Active PsA**

Grey text identifies conditional recommendations for drugs without current regulatory approvals or where recommendations are based on abstract data only.

DMARDs = disease modifying anti-rheumatic drugs, IL17i = interleukin 17 inhibitors, IL12/23i = interleukin 12/23 inhibitors, LEF = leflunomide, MTX = methotrexate, NSAIDs = nonsteroidal anti-inflammatory drugs, PDE4i = phosphodiesterase 4 inhibitor (apremilast), SSZ = sulfasalazine, TNFi = tumor necrosis factor inhibitor

