Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021

Laura C. Coates[1]✉, Enrique R. Soriano[2], Nadia Corp[3], Heidi Bertheussen[4], Kristina Callis Duffin[5], Cristiano B. Campanholo[6], Jeffrey Chau[7], Lihi Eder[8], Daniel G. Fernández-Ávila[9], Oliver FitzGerald[10], Amit Garg[11], Dafna D. Gladman[12], Niti Goel[13], Philip S. Helliwell[14], M. Elaine Husni[15], Deepak R. Jadon[16], Arnon Katz[17], Dhruvkumar Laheru[18], John Latella[19], Ying-Ying Leung[20], Christine Lindsay[21], Ennio Lubrano[22], Luis Daniel Mazzuoccolo[23], Philip J. Mease[24], Denis O'Sullivan[25], Alexis Ogdie[26], Wendy Olsder[27], Penelope Esther Palominos[28], Lori Schick[29], Ingrid Steinkoenig[30], Maarten de Wit[31], D. A. van der Windt[3], Arthur Kavanaugh[32] and the GRAPPA Treatment Recommendations domain subcommittees, ***

Abstract | Since the second version of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations were published in 2015, therapeutic options for psoriatic arthritis (PsA) have advanced considerably. This work reviews the literature since the previous recommendations (data published 2013–2020, including conference presentations between 2017 and 2020) and reports high-quality, evidence-based, domain-focused recommendations for medication selection in PsA developed by GRAPPA clinicians and patient research partners. The overarching principles for the management of adults with PsA were updated by consensus. Principles considering biosimilars and tapering of therapy were added, and the research agenda was revised. Literature searches covered treatments for the key domains of PsA: peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail psoriasis; additional searches were performed for PsA-related conditions (uveitis and inflammatory bowel disease) and comorbidities. Individual subcommittees used a GRADE-informed approach, taking into account the quality of evidence for therapies, to generate recommendations for each of these domains, which were incorporated into an overall schema. Choice of therapy for an individual should ideally address all disease domains active in that patient, supporting shared decision-making. As safety issues often affect potential therapeutic choices, additional consideration was given to relevant comorbidities. These GRAPPA treatment recommendations provide up-to-date, evidence-based guidance on PsA management for clinicians and people with PsA.

Psoriatic arthritis (PsA) is a heterogeneous condition associated with a high burden of disease and significant comorbidities. In recent years, there has been substantial expansion of treatment options and therapeutic approaches for PsA. This range of options can present challenges to busy clinicians selecting optimal therapies for their patients. One of the founding missions of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) is to develop, and to update on an ongoing basis, recommendations for the optimal treatment of patients with PsA, based upon the best scientific evidence. The original GRAPPA recommendations were published in 2009 (REF.[1]), with a revised version in 2015 (REF.[2]). The process to develop this

✉e-mail: laura.coates@ndorms.ox.ac.uk

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latest version of the recommendations began once again in 2019 in order to address recent important advances in the treatment of PsA. In this Evidence-Based Guideline, we present updated treatment recommendations for medication selection in PsA developed by GRAPPA members and patient research partners (PRPs).

We recognize that throughout the world, there are regional differences in the health-care professionals who care for people with PsA. In many countries, care can be led by rheumatologists, dermatologists, internal medicine specialists or primary care providers, depending on the local situation. In addition, an increasing number of allied health personnel, such as nurse practitioners and physicians' assistants, perform this role. These recommendations are intended for all clinicians caring for patients with PsA.

These treatment recommendations, similar to the previous versions, utilize a domain-based approach, spanning the six domains of PsA: peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis and nail psoriasis. In addition, as was a key feature of the 2015 recommendations, they include important comorbidities with a potential influence on treatment. In contrast to the 2015 version, for these new recommendations comorbidities were split into 'related conditions' (comprising inflammatory bowel disease (IBD) and uveitis) and 'comorbidities', allowing for a slightly different approach to extra-musculoskeletal disease-related manifestations and other comorbidities. Sub-committees were formed to address each of these eight areas.

In these recommendations, a Grading of Recommendations, Assessment, Development and Evaluations (GRADE)-informed methodology was utilized to provide a transparent approach to grading the quality of evidence underpinning the recommendations[3].

Methods

Overarching principles were first included in the 2015 update of the GRAPPA treatment recommendations[2], and these principles were revised and discussed among the GRAPPA membership. Two additional topical issues, the use of biosimilars and tapering of therapy, were addressed by the development of new position statements. Up-to-date recommendations were developed for the use of therapies for the six PsA domains, related conditions and comorbidities. The research agenda, itemizing areas considered important for future study to inform optimal therapeutic approaches, was modified.

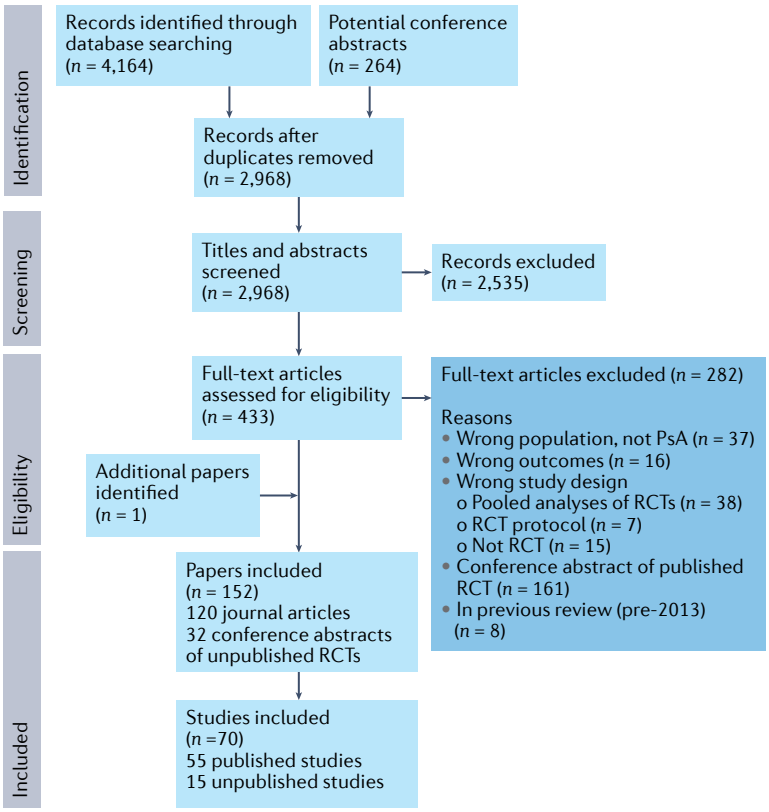
The eight sub-committees (one for each of the six domains of PsA, related conditions and comorbidities) were formed from the GRAPPA membership. All GRAPPA members were invited to participate and asked to select a preferred and alternative sub-committee in which to participate. Interested members were divided into the sub-committees according to their preferences, aiming for 15–20 members per group. The GRAPPA recommendations steering committee (L.C.C., E.R.S., A.K.) selected leaders for each sub-committee. The musculoskeletal domain groups were led by rheumatologists, and the skin psoriasis and nail psoriasis groups were led by dermatologists. Each sub-committee included a PRP with experience of that area of disease. The lists of members of the GRAPPA subcommittees are available in Supplementary Box 1.

The sub-committees developed and refined PICO (population, intervention, comparator, outcomes) questions first within their own subcommittee and then with the methodologists (N.C. and D.A.v.d.W.) and the steering committee (see Supplementary Table 1 and Supplementary Box 2). Based on these PICO questions, a strategy for the main evidence review was developed (see Supplementary Tables 2–6) and searches were undertaken of MEDLINE, EMBASE and Cochrane Library, as previously reported (FIG. 1 and Coates et al.[4]). These systematic literature searches were limited to literature published from 2013 to identify new data published since the previous 2015 recommendations. The searches were initially run in 2019 but were updated in 2020 owing to delays in the recommendation development process related to the COVID-19 pandemic (see Supplementary Table 7). The searches gave precedence to data from randomized controlled trials (RCTs). Additional searches identified evidence published in abstract form at key rheumatology and dermatology

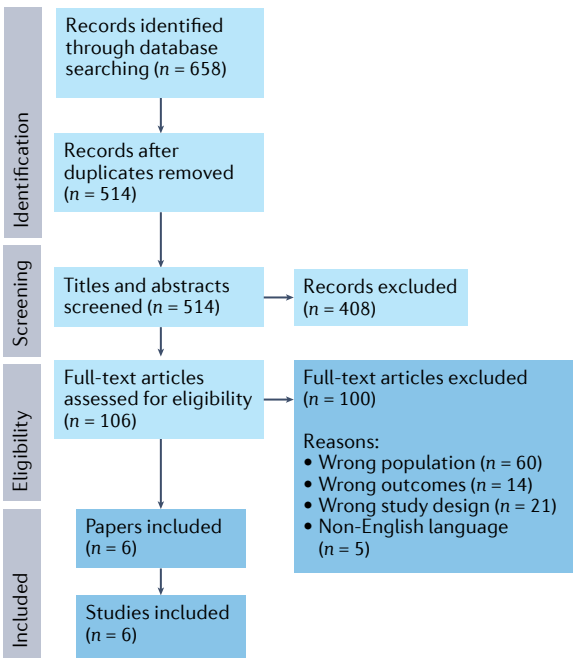
Author addresses

[1]Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences, University of Oxford, Oxford, UK.
[2]University Institute and Rheumatology Unit, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.
[3]Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Staffordshire, UK.
[4]Oslo, Norway.
[5]University of Utah, Salt Lake City, UT, USA.
[6]Santa Casa de Sao Paulo, Sao Paulo, Brazil.
[7]Hong Kong, China.
[8]Women's College Research Institute, University of Toronto, Toronto, ON, Canada.
[9]Pontificia Universidad Javeriana — Hospital Universitario San Ignacio, Bogotá, Colombia.
[10]School of Medicine, Conway Institute for Biomolecular Research, University College Dublin, Dublin, Ireland.
[11]Donald and Barbara Zucker School of Medicine at Hofstra Northwell, Hempstead, NY, USA.
[12]University of Toronto, Toronto, ON, Canada.
[13]Duke University School of Medicine, Durham, NC, USA.
[14]University of Leeds, Leeds, UK.
[15]Cleveland Clinic, Cleveland, OH, USA.
[16]University of Cambridge, Cambridge, UK.
[17]Haifa, Israel.
[18]Department of Dermatology, Royal Berkshire Foundation, Reading, UK.
[19]Windsor, CT, USA.
[20]Singapore General Hospital, Duke-NUS Medical School, Singapore, Singapore.
[21]Propser, TX, USA.
[22]Academic Rheumatology Unit, University of Molise, Campobasso, Italy.
[23]Department of Dermatology, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.
[24]Swedish Medical Center/Providence St. Joseph Health and University of Washington, Seattle, WA, USA.
[25]Dublin, Ireland.
[26]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.
[27]Eindhoven, The Netherlands.
[28]Rheumatology Division, Hospital de Clinicas de Porto Alegre, Porto Alegre, Brazil.
[29]Seattle, WA, USA.
[30]Cleveland, OH, USA.
[31]Department of Medical Humanities, VU University Medical Centre, Amsterdam, Netherlands.
[32]Division of Rheumatology Allergy and Immunology, University of California, San Diego, La Jolla, CA, USA.
*A list of authors and their affiliations appears at the end of the paper.
**A list of members and their affiliations appears in the Supplementary Information.

a Intervention RCTs for PsA



b Prognosis and phenotype of individuals with PsA and related conditions (IBD and uveitis)



c Screening of comorbidities and related conditions in patients with PsA

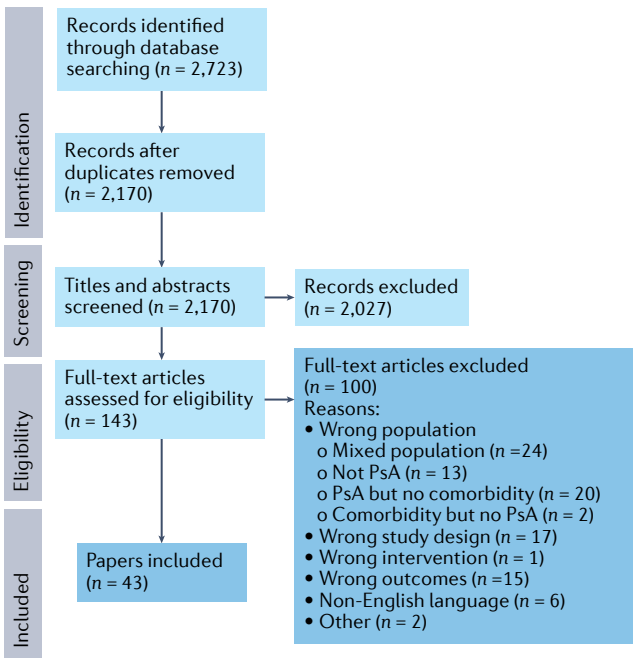


Fig. 1 | **Flowcharts representing the results of the evidence searches.** Systematic literature reviews were undertaken to identify evidence related to medications for psoriatic arthritis (PsA) published since 2013, to inform the 2021 update of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations for PsA. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagrams showing the results of (**a**) the main search for intervention randomized controlled trials (RCTs) for PsA (19 February 2013 to 28 August 2020) and additional searches related to (**b**) prognosis and phenotype of individuals with PsA and related conditions (inflammatory bowel disease (IBD) and uveitis) (19 February 2013 to 12 November 2020) and (**c**) screening of comorbidities and related conditions in patients with PsA (19 February 2013 to 10 November 2020). The detailed search strategies can be found in Supplementary Tables 2–6.

conferences (ACR, EULAR and American Academy of Dermatology annual meetings) from 2017 to 2020. Data that had only been published in abstract form at the time the recommendations were created were included so as to provide consideration of the newest data in this fast-evolving discipline, but, as in 2015, it was decided that data derived from abstracts alone should be clearly identified in the recommendations.

Data extraction and risk of bias assessment was combined across the six PsA domain groups to prevent duplication of effort (see Supplementary Table 8); single reviewers (senior GRAPPA researchers with experience in systematic literature reviews) extracted relevant data and assessed bias using the Cochrane risk-of-bias tool for RCTs[5] and incorporated them into a pre-designed Excel spreadsheet. These were all independently checked by a second reviewer (N.C. or D.A.v.d.W.). Data were shared with all sub-committees for interpretation. As the evidence review for this update only included studies published between 2013 and 2020 (and not all evidence), we did not conduct meta-analysis or indirect comparisons (as part of network meta-analysis).

Several key considerations were implemented across groups to facilitate consistency of approach. Individual drugs with an ostensibly shared ultimate mechanism of action would be considered as a group unless there was solid evidence for within-class differences (for example, the five current inhibitors of TNF (infliximab, etanercept, adalimumab, golimumab and certolizumab pegol), despite some differences in construct, all presumably act by inhibiting TNF and are hence grouped as 'TNF inhibitors'; of note, evidence-based differences are called out, such as the inefficacy of etanercept in the treatment of IBD. Among inhibitors of IL-23, at present most data in PsA are for guselkumab; IL-23 inhibitors in development, such as risankizumab and tildrakizumab, will likely also be considered, alongside guselkumab, as a group of IL-23 inhibitors, unless evidence shows differences in their efficacy. In the future, additional data on existing agents as well as those in development might warrant separation of agents currently considered to be within a group. For example, the available IL-17 inhibitors (the IL-17A inhibitors secukinumab and ixekizumab and the IL-17 receptor A inhibitor brodalumab) are considered 'IL-17 inhibitors'; the IL-17A/F inhibitor bimekizumab, which is in development, would likely be added to this group in the future unless data suggest otherwise. Similarly, the Janus kinase (JAK) inhibitors tofacitinib, upadacitinib and filgotinib are grouped together, although there are differences in their ex vivo specificity for the different JAK isoforms. If data show differences in efficacy or tolerability among these agents, they could be separated; the same holds true for JAK-targeting agents in development, such as deucravacitinib.

The primary goal methodologically was to use data from PsA studies. Although for the vast majority of PsA studies published to date the primary outcome was based on responses related to peripheral arthritis, substantial information was often available regarding outcomes across other PsA domains. However, for some areas, such as uveitis and IBD, much of the evidence came from studies outside of PsA; in those cases, these data were identified in the additional searches performed for the related conditions and comorbidities groups (see Supplementary Tables 3–5). For other domains, such as axial disease, skin psoriasis and nail psoriasis, there was a mixture of data sources for agents with different mechanisms of action. For some agents, for example, TNF inhibitors in the treatment of skin psoriasis, there are abundant data specifically in PsA studies, whereas for agents with other mechanisms of action most data were not from PsA studies and hence were extrapolated. The axial disease group decided to widen their search to capture data in other forms of axial spondyloarthritis (axSpA), given the limited literature specifically on axial PsA.

It is worth noting that the goal of these recommendations is not to provide primary recommendations for the treatment of related conditions (such as IBD) but rather to serve as a resource for consideration in the approach to patients with PsA who also have these conditions. The related conditions group included specialists in ophthalmology and gastroenterology to ensure sufficient expertise and oversight (see the GRAPPA subcommittee members list in Supplementary Box 1). However, medications specific to those conditions, such as mycophenolate mofetil for uveitis or vedolizumab for IBD, were not included in these recommendations, as they are not routinely used for the treatment of psoriatic disease. Wider searches looking beyond RCT data were also run to address screening, treatment and evidence for prognosis and phenotype of disease in those with related conditions and comorbidities. Further detail on these searches is available in Supplementary Tables 4–6.

As GRAPPA guidelines are international, and as regulatory approvals can vary substantially in different jurisdictions, specific licensing or regulatory language from any individual area was not considered to be 'evidence'; data from the published research studies formed the basis of the recommendations.

These data were used in the GRADE-informed process to take account of study design, methodological limitations, inconsistency, imprecision and indirectness of evidence, and to establish an evidence table split by the six PsA domains[6]. Graded evidence tables (see Supplementary Table 9) were used by the groups to formulate recommendations, starting with the existing recommendations for drugs included in 2015 and then adding new therapies or updating recommendations for older therapies based on the new evidence tables. The new evidence could strengthen or weaken a previously published recommendation or, in extreme cases, reverse the recommendation for or against a treatment. These adjustments were done by consensus initially within subcommittees and then across subcommittees with discussion between all group leaders.

A survey that was sent to all GRAPPA members in May 2021, including clinicians and PRPs, requested voting on agreement with and elicited specific feedback on the components of the recommendations. For each principle, position statement or recommendation, respondents were asked to indicate if they agreed with it as written, agreed with minor comments, or disagreed with it. Free text was used for feedback comments, which

were incorporated into the wording of the final overarching principles and position statements. Throughout the entire development of these recommendations, GRAPPA members working in the pharmaceutical industry were recused from any participation. There were a total of 170 respondents from a membership of 892, of whom 9 were PRPs and 161 were clinicians (126 rheumatologists, 24 dermatologists, 11 other).

Recommendations

Overarching principles and position statements. The six overarching principles from 2015 were reviewed and minor changes were made to their wording (TABLE 1). The word 'doctor' was replaced with 'clinician' to recognize the many allied health-care professionals who care for people with PsA, and more detail was added to the overarching principle addressing comorbidities. An initial principle was added to introduce the aim of the GRAPPA recommendations.

The additional position statements were developed and discussed at GRAPPA annual meetings in 2019 and 2020 (TABLE 2). These statements were reviewed by the GRAPPA members in May 2021.

Voting showed high levels of agreement (all >85% agreement, shown in TABLE 1) with the wording of the overarching principles from both clinicians and PRPs. Agreement from PRPs was slightly lower for the position statement on tapering (71.4%), and many of the comments related to concerns about tapering medication in patients who have low disease activity rather than remission. This concern raised by PRPs highlights the importance of shared decision-making with individual patients in various situations arising in clinical practice.

GRADE recommendations for therapies. Each of the six domain groups and the related conditions group synthesized the evidence they extracted from the literature reviews and developed recommendations by consensus. A summary of these recommendations is given in TABLE 3. Using the GRADE approach resulted in strong or conditional recommendations either for or against different therapies, or a decision that no recommendation could be made if there was insufficient or contrasting evidence. Recommendations regarding each domain were presented for discussion in the wider group, and minor changes were made for consistency of interpretation across the groups. Wherever possible, drugs were grouped by class unless there was strong evidence of differences in efficacy within the class. The summary table (TABLE 3) shows the recommendation for each drug class within the different domains of PsA and related conditions but does not provide a hierarchy within the strong or conditional recommendations, as these nuances are addressed in the text.

Table 1 | **Overarching principles**

Overarching principles	PRP agreement (%) ($n = 9$)	Clinician agreement (%) ($n = 161$)
These recommendations, which include the most current data concerning the optimal therapeutic approaches to PsA, present contextual considerations to empower shared decision-making	100	96.3
The ultimate goals of therapy for all patients with PsA are: 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 To optimize functional status, improve quality of life and wellbeing, and prevent structural damage to the greatest extent possible To avoid or minimize complications, both from untreated active disease and from therapy	87.5	96.3
Assessment of patients with PsA requires consideration of all disease domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis, psoriatic nail disease, uveitis and IBD. The impact of disease on pain, function, quality of life and structural damage should be examined	87.5	94.4
Clinical assessment ideally includes patient-reported measures with a comprehensive history and physical examination, often supplemented by laboratory tests and imaging techniques (for example, X-ray, ultrasound or MRI). The most widely accepted metrics that have been validated for PsA should be utilized whenever possible	87.5	95.0
Comorbidities and related conditions should be considered and their impact on the approach to the condition and its treatment addressed appropriately. Such conditions include obesity, metabolic syndrome, cardiovascular disease, depression and anxiety, liver disease (for example, non-alcoholic fatty liver disease), chronic infections, malignancy, bone health (for example, osteoporosis), central sensitization (for example, fibromyalgia) and reproductive health. Multidisciplinary and multispeciality assessment and management may be most beneficial for individual patients	87.5	93.8
Therapeutic decisions need to be individualized and are made jointly by the patient and their clinician. Treatment should reflect patient preferences, with patients being provided with the best information concerning relevant options. Treatment choices may be affected by various factors, including disease activity, previous therapies, prognostic factors such as structural damage, comorbid conditions and patient factors such as cost, convenience and choice	100	93.2
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	100	95.0

IBD, irritable bowel syndrome; PRP, patient research partner; PsA, psoriatic arthritis.

Table 2 | **Position statements**

Issue	Statement	PRP agreement (%) ($n = 9$)	Physician agreement (%) ($n = 161$)
Biosimilars	Biosimilars must be approved through a robust regulatory review. 'Biomimics' or 'intended copies' are not biosimilars. This may require ongoing education for both patients' and clinicians' education to ensure a thorough understanding	85.7	92.5
	Periodic re-evaluation of biosimilar products after their initial approval would be important to ensure ongoing quality		
	Extrapolation to PsA, even when no studies of a given biosimilar were conducted in PsA, is acceptable. Ideally, additional studies specifically in PsA can be conducted if they were not part of the initial approval process		
	Patients and clinicians must be involved in decisions about switching		
	Pharmacovigilance is crucial; naming conventions need to allow tracking of specific agents and batches		
	Multiple switches need to be studied in a rigorous fashion on an ongoing basis		
	Savings realized from the use of biosimilars should be utilized to improve access for larger numbers of patients		
	Immunogenicity is a potential concern that should be monitored on an ongoing basis		
Tapering	For patients who achieve the goals of therapy (for example, ideally remission, or low disease activity if remission is not achievable), tapering and ultimately discontinuing therapy may be considered	71.4	91.9
	Potential benefits of tapering may include lower risks of adverse effects as well as pharmacoeconomic benefits		
	The decision to taper therapy should be made with the patients' thorough understanding and direct involvement		
	Discussions between patient and clinician should inform the optimal approach to tapering for each individual (for example, decreasing dosages, increasing treatment intervals, appropriate time intervals for making changes)		
	Patients and clinicians need to understand that the potential drawbacks of tapering include:		
	Reactivation of disease activity, with the possibility that re-achievement of the target may not be immediate and may not always be achieved		
	At present it is not possible to predict a priori which patients might be able to successfully taper, which patients may be able to come off all medications and which patients will not be able to taper at all		
	Although focused on active domains such as peripheral arthritis, it is not known how tapering of effective therapy might influence other outcomes, such as the increased risk of cardiovascular disease presumably related to systemic inflammation		

PRP, patient research partner; PsA, psoriatic arthritis.

Treatment schema

Although GRAPPA utilizes a domain-based approach in the recommendations, the majority of patients present with multi-domain disease and treatment decisions need to reflect this reality. Therefore, the recommendations for each domain were combined in a single treatment schema to guide therapeutic decisions (FIG. 2). The schema highlights that the initial approach should be to assess disease activity in each of the domains as well as to consider comorbidities, previous therapies and patient preference. Given the international scope of these recommendations and limited evidence on treatment strategy, the order of treatment requires flexibility and is dependent on the health-care setting. Therefore, the schema incorporates standard 'step-up' approaches, starting with topical therapies for psoriasis and conventional synthetic DMARDs (csDMARDs) for arthritis, as well as expedited treatment routes whereby biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) can be used as first-line therapy if available. Importantly, this schema represents an iterative process with periodic re-evaluation of efficacy and tolerability and adjustment of treatment as appropriate.

Wherever possible, treatment for an individual with PsA should be selected to address all active domains of the disease and any related conditions. It is likely that treatment may be driven by the most severe or impactful domain of disease, particularly where strong evidence of differential efficacy exists. Further notes on the individual domains are provided below.

Peripheral arthritis. NSAIDs and intra-articular and oral glucocorticoids are conditionally recommended for relieving symptoms of peripheral arthritis as per the 2015 recommendation[2], as no new relevant data were identified. For treatment-naive patients, there remains a low level of evidence to support the use of csDMARDs for the treatment of peripheral arthritis. However, in view of supportive observational data[7–10] and universal accessibility, the use of csDMARDs (methotrexate, sulfasalazine or leflunomide) is strongly recommended. In many circumstances, csDMARDs can be used as first-line therapy, with regular assessment of clinical response (every 12–24 weeks) and early escalation of therapy (between 12 and 24 weeks) advised as necessary. It is important to acknowledge that new, high-quality data support the superiority of TNF inhibitors over

csDMARDs as first-line therapy, particularly in patients with early disease[8–10]. The decision to use TNF inhibition as first-line therapy should be made as part of a shared decision-making process between the clinician and the patient, with consideration of the risks, benefits and the individual's preference.

For all RCTs reviewed for phosphodiesterase 4 inhibitors (PDE4i), TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors and JAK inhibitors, there were no differences in efficacy for these treatment options in subgroups of patients with or without concurrent csDMARDs. In a large RCT that was adequately powered to compare methotrexate, etanercept and their combination, there was no difference in efficacy between the etanercept monotherapy arm and the etanercept–methotrexate combination arm[8]. These findings support the conclusion that a combination of csDMARDs with bDMARDs might not be necessary to achieve short-term response. With JAK inhibitors, the evidence is scarce but also points in the same direction. However, the potential benefit of concomitant therapy with csDMARDs with all bDMARDs is incompletely defined, with conflicting evidence derived largely from uncontrolled studies; further study is indicated to define potential benefits.

For patients with an inadequate response to csDMARDs, high-quality evidence supports the use of TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors and JAK inhibitors; and moderate-quality evidence supports IL-12/23 inhibitors or PDE4 inhibitors being superior to placebo. Similar magnitudes of effect sizes for efficacy were observed across RCTs for TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors and JAK inhibitors compared with placebo, whereas effect sizes for PDE4 inhibitors and IL-12/23 inhibitors seemed to be lower (see Supplementary Table 9). These classes of drugs are all strongly recommended on the basis of this evidence. Concerning the choice between different bDMARDs or tsDMARDs, two head-to-head RCTs compared IL-17 inhibition with TNF inhibition[11,12], and one compared

Table 3 | **Summary of recommendations for treatment of PsA**

Indication	Strong recommendation for	Conditional recommendation for	Conditional recommendation against	Strong recommendation against	No recommendation: insufficient or conflicting evidence
Peripheral arthritis, DMARD naive	csDMARDs (except CsA), TNFi, IL-12/23i, IL-17i, IL-23i, JAKi, PDE4i	NSAIDs, oral GC, IA GC	–	–	–
Peripheral arthritis, DMARD inadequate response	TNFi, IL-12/23i, IL-17i, IL-23i, JAKi, PDE4i	csDMARDs, NSAIDs, oral GC, IA GC, CTLA4-Ig	–	–	–
Peripheral arthritis, bDMARD experienced	TNFi, IL-17i, IL-23i, JAKi	NSAIDs, oral GC, IA GC, IL-12/23i, PDE4i, CTLA4-Ig	–	–	–
Axial disease, bDMARD naive	NSAIDs, physiotherapy, simple analgesia, TNFi, IL-17i, JAKi	GC SIJ injections, bisphosphonates	PDE4i	csDMARDs	IL-12/23i, IL-23i
Enthesitis	TNFi, IL-12/23i, IL-17i, IL-23i, JAKi, PDE4i	NSAIDs, physiotherapy, MTX, CTLA4-Ig, GC injections (with extreme caution)	–	–	Other csDMARDs
Dactylitis	TNFi, IL-12/23i, IL-17i, IL-23i, JAKi, PDE4i	NSAIDs, GC injections, MTX, CTLA4-Ig	Other csDMARDs	–	–
Psoriasis (plaque)	Topical therapies, phototherapy, cdDMARDs (MTX, fumarate, fumaric acid esters, CsA), TNFi, IL-12/23i, IL-17i, IL-23i, PDE4i, JAKi	Acitretin	–	–	–
Nail psoriasis	TNFi, IL-12/23i, IL-17i, IL-23i, PDE4i	Topical GC, tacrolimus and calcipotriol combination or individual therapies, pulsed dye laser, csDMARDs (MTX, LEF, CsA), acitretin, JAKi	–	–	Topical CsA, tazarotene, fumarate, fumaric acid esters, UVA and UVB phototherapy, alitretinoin
IBD: Crohn's disease	TNFi (not ETN), IL-12/23i	IL-23i, JAKi, MTX	–	IL-17i	ETN
IBD: UC	TNFi (not ETN), IL-12/23i	IL-23i, JAKi, MTX	–	IL-17i	ETN, PDE4i
Uveitis	–	TNFi (not ETN), CsA, MTX	ETN	–	Other csDMARDs, IL-17i, IL-12/23i

bDMARD, biologic DMARD; csDMARD, conventional synthetic DMARD (MTX, SSZ, LEF, CsA; unless otherwise specified); CsA, ciclosporin; ETN, etanercept; GC, glucocorticoids; IA, intra-articular; IBD, inflammatory bowel disease; IL-12–IL-23i, IL-12–IL-23 inhibitor; IL-17i, IL-17 inhibitor; IL-23i, IL-23 inhibitor; JAKi, Janus kinase inhibitor; LEF, leflunomide; MTX, methotrexate; PDE4i, phosphodiesterase 4 inhibitor (apremilast); PsA, psoriatic arthritis; SIJ, sacroiliac joint; SSZ, sulfasalazine; TNFi, TNF inhibitor; UC, ulcerative colitis.

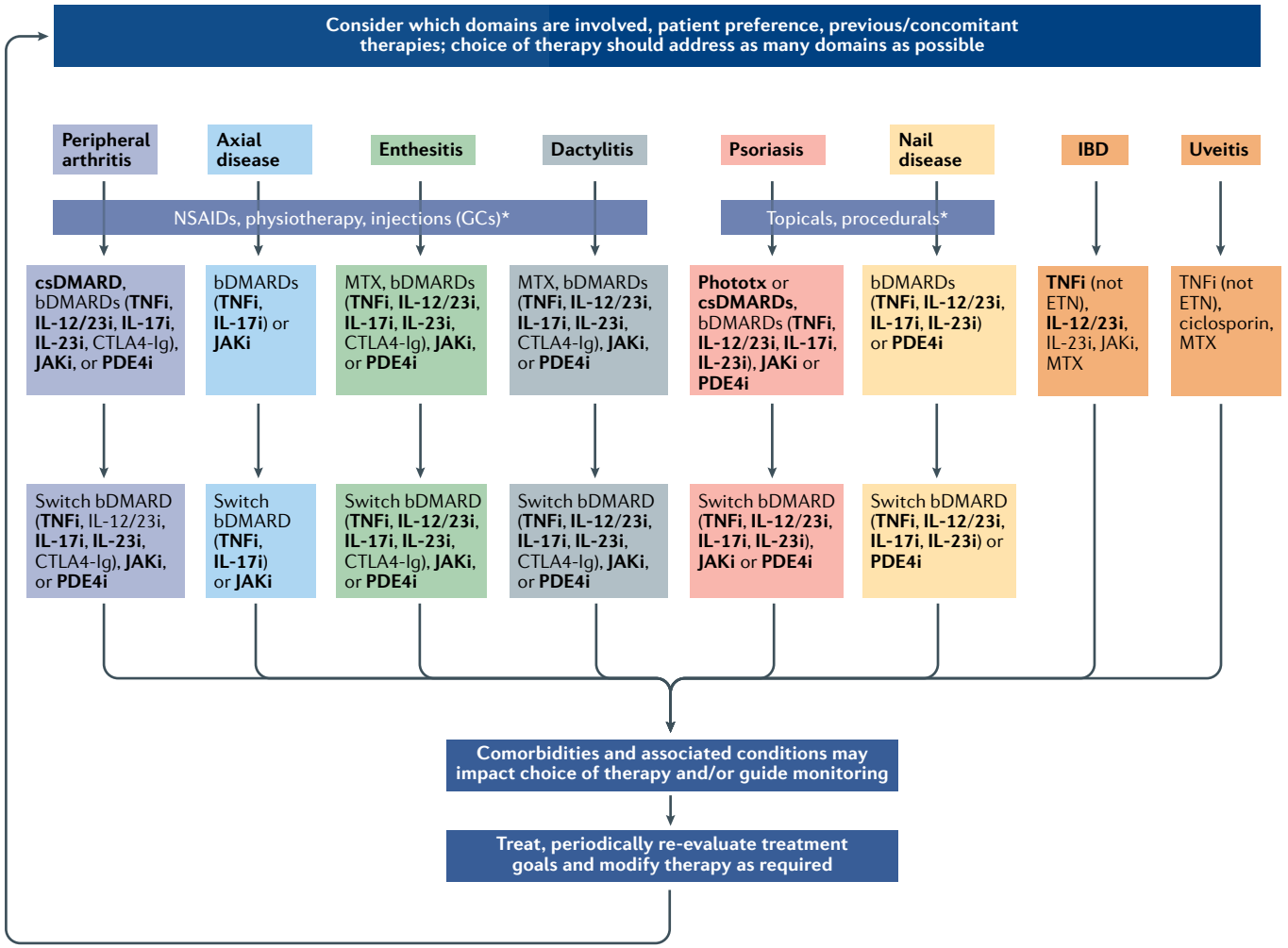


Fig. 2 | **GRAPPA 2021 treatment schema.** The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) 2021 treatment recommendations for psoriatic arthritis (PsA) use a domain-based approach, but, considering that most patients present with disease in multiple domains, this treatment schema combines the recommendations for each domain to guide therapeutic decisions. Disease activity should be assessed in each of the domains and consideration given to comorbidities, previous therapies and patient preference. Standard 'step-up' approaches, as well as expedited treatment routes, are indicated. Treatment efficacy and tolerability should be re-evaluated periodically and treatment adjusted as appropriate. The order of the products in the boxes is sorted by mechanism of action and does not reflect guidance on relative efficacy or suggested usage. Bold text indicates a strong recommendation, standard text a conditional recommendation. The asterisks indicate a conditional recommendation based on data from abstracts only. bDMARD, biologic DMARD; CTLA4-Ig, CTLA4–immunoglobulin fusion protein; csDMARD, conventional synthetic DMARD; ETN, etanercept; GC, glucocorticoid; IBD, inflammatory bowel disease; JAKi, Janus kinase inhibitor; MTX, methotrexate; PDE4i, phosphodiesterase 4 inhibitor; TNFi, TNF inhibitor.

JAK inhibition with TNF inhibition[13]. These studies were adequately powered to inform a direct comparison between these therapies. On the basis of current evidence, the efficacies of IL-17 inhibitors and TNF inhibitors are comparable for the peripheral arthritis domain in patients with an inadequate response to csDMARDs. Superiority of a JAK inhibitor (given at the higher of two doses) over a TNF inhibitor for some, but not all, peripheral arthritis outcomes was seen in a single RCT[13]; consistent superiority of JAK inhibitors over other bDMARDs is yet to be shown. Based on the evidence, including head-to-head studies, TNF inhibitors, IL-17 inhibitors and JAK inhibitors are equally recommended. There are no current head-to-head studies comparing IL-23 inhibitors with other bDMARDs or JAK inhibitors. Although IL-23 inhibition is still strongly recommended, it might be considered slightly lower in terms of recommendations for use in patients with peripheral arthritis. One small, open-label study comparing IL-12/23 inhibition with TNF inhibition did not show the superiority of IL-12/23 inhibition over TNF inhibition in peripheral joint domains[14]. For patients with previous experience with bDMARDs, TNF inhibitors, IL-17 inhibitors, IL-23 inhibitors and JAK inhibitors are strongly recommended on the basis of moderate- to high-quality evidence. PDE4 inhibition is conditionally recommended.

The limitations for these recommendations include the issue that the evidence was derived from patients with PsA who predominantly had polyarthritis, with this evidence then extrapolated to oligoarthritis and other phenotypes. For inadequate responders, there are insufficient data for specific recommendations based on primary versus secondary failure of prior treatment.

Axial disease. For patients with axial symptoms who have not responded to treatment with NSAIDs, physiotherapy and/or sacroiliac joint glucocorticoid injections (when appropriate), initiation of a targeted therapy is strongly recommended. TNF inhibition and IL-17 inhibition have demonstrated efficacy in both radiographic and non-radiographic axSpA and were recommended for axial PsA in the previous GRAPPA recommendations[2].

Since the 2015 recommendations[2], several phase II and phase II–III RCTs have demonstrated the efficacy of the JAK inhibitors tofacitinib[15], upadacitinib[16] and filgotinib[17] in ankylosing spondylitis. Data from a phase III study of tofacitinib in ankylosing spondylitis published in 2021 confirm this efficacy[18]. Extrapolating from the evidence in axSpA, we recommend these agents for axial PsA as well.

Only one study was designed specifically to assess axial PsA[19]. In this phase IIIb RCT, the IL-17 inhibitor secukinumab demonstrated significant improvement in the signs and symptoms of axial disease compared with placebo in patients with PsA who had an inadequate response to NSAIDs; a reduction in MRI scores was also noted[19]. As IL-17 inhibitors have shown efficacy and have been approved for use in the treatment of axSpA, these agents are strongly recommended for axial PsA.

Although IL-12/23 inhibitors and IL-23 inhibitors have not demonstrated efficacy in ankylosing spondylitis[20], post hoc analyses from the trials of ustekinumab and guselkumab in patients who have had axial symptoms suggest that these agents might be effective in axial PsA[19,20]. However, it is also possible that improvement in the outcome measures used (for example, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)) could reflect disease activity in other PsA domains. Because these studies included primarily patients with active PsA, and these agents did not prove effective in axSpA, the evidence is currently too limited and conflicting such that these medications cannot be recommended for axial PsA at this time.

Enthesitis. Classes of advanced therapies found to be effective and thus strongly recommended as treatment options for active enthesitis in patients with PsA include TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, JAK inhibitors and PDE4 inhibitors. Despite novel information about the comparative efficacy of different classes of medications emerging from head-to-head studies, including comparisons of IL-17 inhibitors with TNF inhibitors[11,12], methotrexate with TNF inhibitors[8,9], and IL-12/23 inhibitors with TNF inhibitors[14], none of the evaluated classes of medications was found to have clear and consistent superiority over the other. Therefore, none of the medication classes detailed above was prioritized for the treatment of enthesitis in the recommendations.

Methotrexate received a conditional recommendation for the treatment of active enthesitis. This is a change from previous guidelines, in which methotrexate was not recommended owing to a lack of evidence[1,2]. The change was made on the basis of expert opinion and data emerging from the SEAM-PsA trial, which suggested efficacy of methotrexate for enthesitis that was similar to that observed for etanercept[8]. It should be noted that the SEAM-PsA trial did not include a placebo arm, so the evidence is limited and therefore the recommendation is conditional.

The use of NSAIDs, local glucocorticoid injections and physiotherapy was conditionally recommended, despite the lack of high-quality studies that investigated their efficacy for enthesitis in PsA or SpA. These modes of treatment, which are commonly used as first-line therapies for enthesitis, provide a relatively safe and affordable option, especially for localized enthesitis.

Dactylitis. Meaningful advances have been made in the treatment of dactylitis since the last GRAPPA recommendations[2]. In the SEAM-PsA RCT[8], no statistically significant difference was found between methotrexate monotherapy, etanercept monotherapy and methotrexate–etanercept combination therapy, neither in the change from baseline in the Leeds Dactylitis Index (LDI) nor in the proportion of patients achieving complete resolution of dactylitis[8]. However, no definite conclusion regarding effect size could be drawn owing to the lack of a placebo control group[8].

The therapeutic armamentarium for dactylitis has increased considerably. The IL-17 inhibitors secukinumab[21–23], ixekizumab[24] and brodalumab[25] demonstrated superior efficacy compared with placebo for improving dactylitis signs and symptoms in RCTs; another IL-17 inhibitor, bimekizumab, is being studied. In RCTs the IL-23 inhibitors guselkumab and risankizumab were found to be effective for dactylitis as assessed by the proportion of patients with total resolution of dactylitis at week 24 (REFS[26,27]); another IL-23 inhibitor, tildrakizumab, decreased mean LDI at week 52 compared with baseline in a phase II trial[28].

The T cell modulator abatacept (CTLA4-Ig) numerically improved the proportion of patients achieving resolution of dactylitis at week 24 compared with placebo[29]. Head-to-head trials comparing TNF inhibitors and IL-17 inhibitors[11,12] assessed the proportion of patients achieving resolution of dactylitis at week 24 and did not find a statistically significant difference between the two classes of biologic agents.

Dactylitis-related outcomes were assessed as secondary outcomes in trials of JAK inhibitors, and these drugs were considered statistically superior to placebo in most of these studies[13,30,31]. In a head-to-head trial comparing JAK inhibition with TNF inhibition, the improvements in dactylitis disease activity of upadacitinib and adalimumab at week 24 were similar[13].

Considering the evidence, the group made a conditional recommendation for the use of methotrexate and against the use of other csDMARDs in the treatment of dactylitis. The use of NSAIDs and local glucocorticoid injections was also conditionally recommended for the treatment of dactylitis. A strong recommendation was established for the use of TNF inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, IL-17 inhibitors, JAK inhibitors and PDE4 inhibitors, and a conditional recommendation was established for the use of CTLA4-Ig in the treatment of dactylitis in PsA.

Skin. The evidence reviewed for the update of the recommendations for the treatment of skin psoriasis was limited to that presented in RCTs for PsA and interpreted in the context of the large body of psoriasis literature and previous GRAPPA recommendations. Topical agents are strongly recommended as first-line treatment for patients with limited body surface area involvement. For patients with more widespread psoriasis or psoriasis unresponsive to topicals, phototherapy, oral therapies (methotrexate, ciclosporin, PDE4 inhibitors and JAK inhibitors) and bDMARDs (TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors and IL-23 inhibitors) are strongly recommended. Phototherapy is efficacious for psoriasis affecting the trunk and extremities. Acitretin, an oral retinoid, is conditionally recommended for psoriasis in patients with PsA owing to its limited efficacy as monotherapy for plaque psoriasis and scarce evidence from the PsA population; however, this agent can be efficacious for pustular psoriasis.

Strong recommendations were made for TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors and IL-23 inhibitors; newer mode of action drugs (inhibitors of IL-17, IL-12/23 and IL-23) show higher efficacy for skin involvement than TNF inhibitors in studies of psoriasis and/or PsA. The selection of one drug over another should be influenced by the results of head-to-head studies in psoriasis populations, the presence of comorbidities, and disease activity in other PsA domains.

It should be noted that some csDMARDS (leflunomide and sulfasalazine) have limited evidence for efficacy in skin disease and were graded in the context of other available therapies as having limited evidence for cutaneous psoriasis. CTLA4-Ig (abatacept) also has limited evidence for efficacy in skin disease.

Nails. As with psoriatic skin disease, the evidence reviewed for the update of the treatment of nail psoriasis was limited to that presented in RCTs for PsA and interpreted in the context of the large body of psoriasis literature and previous GRAPPA recommendations. As in the previous recommendations[2], strong recommendations were made for bDMARDs given the rigorous evidence from RCTs. bDMARDs, including TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors and IL-23 inhibitors, are strongly recommended for the treatment of psoriatic nail disease; the selection of one of these agents over another should be informed by head-to-head studies in psoriasis, comorbidities and activity in other PsA domains.

Conditional recommendations were made for a number of topical and/or local therapies as well as systemic medications. Topical therapies that can be considered include calcipotriol and glucocorticoid preparations, topical tacrolimus, topical ciclosporin, intralesional glucocorticoids and pulsed dye laser. Systemic medications that should also be considered are ciclosporin, methotrexate, acitretin, JAK inhibitors and PDE4 inhibitors. In many cases, evidence specifically for nail psoriasis remains insufficient. Agents with limited evidence preventing recommendations include topical glucocorticoids, topical tazarotene, dimethyl fumarates/fumaric acid esters, phototherapy and alitretinoin.

Related conditions. The related conditions included two subtypes of IBD — namely, Crohn's disease and ulcerative colitis — and non-infectious anterior uveitis. Several high-quality RCTs have demonstrated the efficacy of TNF inhibitors (with the exception of etanercept, which did not show efficacy) and IL-12/23 inhibitors for Crohn's disease and ulcerative colitis. For JAK inhibition, although tofacitinib has been effective in ulcerative colitis, a single phase II RCT in Crohn's disease did not reach its primary end point. However, promising results are emerging from phase II RCTs for the efficacy and safety of other JAK inhibitors (upadacitinib and filgotinib) and IL-23 inhibitors in both Crohn's disease and ulcerative colitis. Phase III RCTs of these agents are in progress. For methotrexate, which is used in clinical practice, data from some RCTs has shown efficacy in Crohn's disease and ulcerative colitis. IL-17 inhibitors (secukinumab and brodalumab) exacerbated Crohn's disease in RCTs of patients with known Crohn's disease and should therefore be avoided[32].

For the treatment of uveitis, methotrexate is currently a commonly prescribed non-biologic therapy and was conditionally recommended. TNF inhibitors (excluding etanercept) were also conditionally recommended for treatment of uveitis. Recent RCTs have shown strong evidence for the use of adalimumab, albeit in types of uveitis not typically associated with SpA. Two multicentre, phase III RCTs demonstrated strong evidence of the efficacy of adalimumab (TNF inhibitor) in the treatment of uveitis[32]. The TNF inhibitor etanercept is strongly recommended against, owing to its relatively inferior efficacy and the potential for exacerbation of uveitis compared with monoclonal antibodies.

Studies in PsA cohorts investigating clinical screening strategies for related conditions and for an association between the presence of concomitant related conditions and phenotype and/or prognosis were reviewed. Patients with PsA, especially those with axial disease, seem to have a higher incidence and prevalence of IBD and uveitis compared with the general population. Methods of screening for IBD in patients with PsA have not been evaluated in RCTs. Criteria that might prompt the referral of patients with PsA or SpA for evaluation of possible IBD include: chronic diarrhoea (≥3 months' duration); nocturnal bowel symptoms causing waking from sleep; rectal bleeding (non-haemorrhoidal); chronic abdominal pain; perianal fistula or abscess; and weight loss.

Two studies have examined the pattern of peripheral SpA and/or axSpA in patients with concomitant IBD and found no association with phenotypes of IBD or SpA[33,34]. Two retrospective studies investigated phenotype of PsA and uveitis. Women with PsA were more likely to have uveitis than men. Compared with patients with peripheral PsA, those with axial PsA more commonly had early-onset unilateral uveitis[35]. The prevalence of uveitis was higher in patients with axial PsA than oligoarticular or polyarticular PsA[36]. No studies have reported on the prognosis of patients with PsA with and without concomitant IBD or uveitis. One study reported poorer ophthalmic prognosis in PsA compared with patients with only skin psoriasis and uveitis[35].

Table 4 | **Summary of recommendations for the treatment of PsA in the case of comorbidities**

Comorbidity	NSAIDs	GCs	MTX and/or LEF	TNF inhibitor	IL-17 inhibitor	IL-12/23 inhibitor, IL-23 inhibitor	JAK inhibitor	PDE4 inhibitor
Elevated risk of CVD	Caution	–	–	–	–	–	Caution	–
Congestive heart failure[a]	–	Caution	–	Avoid	–	–	–	–
Elevated risk for VTE	–	–	–	–	–	–	Caution	–
Obesity	–	–	Caution	–	–	–	–	–
Fatty liver disease	–	–	Avoid	–	–	–	–	–
Active hepatitis B or C	–	–	Avoid	Caution	Caution	Caution	Caution	Caution
HIV	–	–	–	Caution	Caution	Caution	Caution	Caution
Tuberculosis	–	–	–	Caution	Caution	Caution	Caution	Caution
History of recent malignancy	–	–	–	Caution	Caution	Caution	Caution	Caution
MS and/or demyelinating disease	–	–	–	Avoid	–	–	–	–
Depression and/or anxiety	–	–	–	–	–	–	–	Caution

CVD, cardiovascular disease; GC, glucocorticoid; JAK, Janus kinase; LEF, leflunomide; MS, multiple sclerosis; MTX, methotrexate; PDE4, phosphodiesterase 4; PsA, psoriatic arthritis; VTE, venous thromboembolism. [a]Severe or advanced; class III or IV according to the New York Heart Association (NYHA) Functional Classification.

Comorbidities. Psoriasis and PsA are both associated with several chronic conditions that can influence treatment choice, response to treatment, quality of life and mortality. The comorbidities sub-committee considered diseases with a specific link to PsA. Comorbidities of particular importance in PsA include cardiovascular disease (CVD), obesity, metabolic syndrome, liver disease (fatty liver disease in particular), mood disorders including depression and anxiety, chronic infections (hepatitis B, hepatitis C, HIV, tuberculosis and fungal infections), malignancy (for example, skin cancer and lymphoma), osteoporosis and fibromyalgia and/or central sensitization[37]. Recommendations around these key comorbidities are listed below and are also shown in TABLE 4.

- Cardiovascular risk is elevated in patients with PsA compared with the age- and sex-matched general population[38]. Patients should be screened for cardiovascular risk factors and modifiable risk factors should be managed to improve cardiovascular outcomes in this patient population. Screening for cardiovascular risk and risk factors can be accomplished by any of the health-care providers caring for the patient (that is, rheumatologist, dermatologist, cardiologist or primary care provider).
- Several studies have demonstrated that obesity is associated with reduced functional ability, greater psoriasis severity and disease activity, and reduced response to therapy. Patients should be encouraged to maintain a healthy weight in order to improve disease activity and minimize disease impact.
- Fatty liver disease is common in patients with PsA, and is often related to obesity and/or diabetes mellitus. This condition should be considered when monitoring liver function on medication and when selecting therapies that could affect the liver.
- Immunomodulatory therapies used in PsA can affect untreated hepatitis B virus (HBV), hepatitis C virus (HCV) or HIV. Patients should be screened for active HBV and HCV prior to initiating therapy. Input from a gastroenterologist or hepatologist should be sought regarding the use of antivirals when initiating treatment of patients with active HCV or active or past HBV. Patients should likewise be screened for HIV and, if present, treatment decisions should be made in collaboration with an infectious disease specialist.
- Tuberculosis is a serious infection and is common in some parts of the world. bDMARDs, particularly TNF inhibitors, can increase the risk of developing active tuberculosis. Screening for active or latent tuberculosis infection is recommended prior to initiation of therapy.
- Herpes zoster can be a complication of immunomodulatory therapies, although this risk seems to be higher with JAK inhibitors than with other immunomodulatory therapies. Rheumatologists should counsel patients about this risk and encourage vaccination prior to starting therapy when accessible.
- Some of the immunomodulatory therapies and previous phototherapy are associated with an increased risk of non-melanoma skin cancer. Patients should be counselled about this risk and, if exposed to these therapies, should be encouraged to undergo full skin assessment annually.

- Surveillance and treatment of osteoporosis should be the same in patients with PsA as in the general population.
- Fibromyalgia and/or central sensitization are associated with poor quality of life and diminished response to therapy. Identification and management of fibromyalgia and/or central sensitization could improve a patient's overall quality of life and diminish treatment 'cycling'.
- Depression and anxiety have a high prevalence in PsA and are strong negative predictors of joint remission in patients with PsA. Screening for mood disorders should be part of the standard clinic review and patients should be referred for diagnosis and for psychological support as appropriate.

PsA remains a complex condition requiring tailoring of therapy for individual patients dependent on multiple factors outlined above. To further demonstrate the application of these recommendations in practice, example cases are given in BOX 1 alongside discussion points related to the evidence tables (TABLE 3), treatment schema (FIG. 2) and recommendations related to comorbidities (TABLE 4). These cases represent composites of actual PsA cases encountered in the clinic, with attributes combined into these three cases to illustrate common therapeutic decision pathways and to reflect how the treatment recommendations support them.

Box 1 | **Case studies and discussion of recommendations**

Case 1

A 33-year-old woman was diagnosed with psoriatic arthritis (PsA) 6 months ago. PsA activity includes: 12 swollen and tender peripheral joints; psoriasis affecting 2% of the body surface area (BSA) despite topical steroids; knee enthesitis bilaterally. She struggles to get laboratory tests regularly. She is nulliparous, not using contraception; she says, "my husband and I would rather wait a year, but if pregnancy happens, that's fine".

What treatment should be chosen?

Given the domains involved, efficacy might be achieved with conventional synthetic DMARDs (csDMARDs), TNF inhibitors, IL-17 inhibitors, IL-12–IL-23 inhibitors, IL-23 inhibitors, PDE4 inhibitors, or Janus kinase (JAK) inhibitors. The inability to monitor bloods precludes csDMARDs and JAK inhibitors. Reproductive health issues would strongly favour TNF inhibition, with other agents considered. After discussion, the patient chose TNF inhibition.

Case 2

A 30-year-old man has had PsA for 2 years. He was intolerant of methotrexate and had no benefit after 12 weeks on a TNF inhibitor. PsA activity includes: three swollen and five tender peripheral joints; psoriasis affecting 15% BSA, including face and nails; inflammatory back pain with insufficient response to NSAIDs. Serum concentrations of acute phase reactants are elevated.

What treatment should be chosen?

Given the domains involved, efficacy might be achieved with another TNF inhibitor, IL-17 inhibitor or JAK inhibitor. After discussion, considering the skin activity, the patient decides to initiate treatment with an IL-17 inhibitor.

Case 3

A 65-year-old man has had PsA for 15 years. He has tried therapy with sulfasalazine, methotrexate and two different TNF inhibitors, with minimal efficacy. Medical history includes ulcerative colitis (UC) doing well on mesalamine, treated hypertension and smoking, which he says helps to control his UC. PsA activity includes: four swollen and eight tender peripheral joints, psoriasis affecting 8% BSA including the genitals; enthesitis about the right elbow and left knee.

What treatment should be chosen?

Given the domains involved, efficacy might be achieved with another TNF inhibitor, JAK inhibitor, PDE4 inhibitor, IL-17 inhibitor, IL-12–IL-23 inhibitor or IL-23 inhibitor. After discussion, including consideration of comorbidities, the patient decides to initiate treatment with an IL-23 inhibitor.

Research agenda

Research in PsA is continuously growing. The GRAPPA mission includes supporting and stimulating research in PsA and psoriasis. One way to achieve this goal is to identify gaps in psoriatic disease knowledge. Many of the research topics outlined in the previous GRAPPA recommendations[2] have been addressed in the years since their publication, such as outcome measures[39,40], more effective and better tolerated treatments[4] and treatment strategies[41]. Some of the research topics that have been identified by the experts from GRAPPA in the current update are briefly described below.

Screening and early diagnosis. The knowledge of risk factors for PsA and the transition from psoriasis to PsA has advanced greatly[42]. However, we are still unable to identify those patients with psoriasis who ultimately go on to develop PsA. It has been shown in observational studies that treatment of psoriasis might prevent the development of PsA[43,44]. Longitudinal research is needed to establish whether highly effective treatment of psoriasis can prevent or mitigate development of PsA.

Precision medicine. Much has been learned about the response of the varied domains of PsA to different specific targeted therapies[45]. Indeed, this knowledge may help to define endotypes of PsA (for example, 'IL-17-inhibition-responsive disease activity'). As more is learned, it might be possible to approach truly personalized care for individual patients with PsA.

Treatment strategy and sequencing. At present, on a group level, the selection and sequence of treatments among the various available agents is not clear for most patients with PsA. The availability of data from additional head-to-head studies might provide useful information in that regard. Another area of interest for which there is at present a paucity of data is the potential for combination therapy with agents having different mechanisms of action. For those patients achieving therapeutic goals, additional high-quality research on treatment tapering, including studies incorporating the patient perspective, is important.

Special populations. Some types of involvement in PsA are not typically evaluated in clinical trials, including oligoarticular peripheral arthritis, arthritis mutilans and types of psoriasis other than plaque psoriasis, to mention a few. Additional exploration of these types of involvement would be of relevance to patients and clinicians. Moreover, some PsA disease manifestations need better definition and more research. A unanimous definition of axial PsA and the proper outcome measure to assess it are still needed, although collaborative work is underway. Given the inherent limitation in assessing enthesitis by physical examination, further research is needed to assess the utility of imaging of the entheses in clinical trials. Available clinical trials have evaluated enthesitis

only as a secondary outcome; therefore, studies that focus on enthesitis as a primary outcome are warranted. We also need to advance our knowledge on the optimal paradigm for the screening and treatment of IBD and uveitis in patients with psoriasis and PsA.

Response to treatment. Certain patient and environmental characteristics can influence the response of PsA to treatment, including sex and/or gender, obesity, socioeconomic status, ethnicity, skin colour, health-care system and other factors. Defining how such characteristics affect assessment and therapy could help to optimize care. For some issues that impact therapeutic choices, such as reproductive health considerations, although there are limited data in PsA, extrapolation from considerations of other patient groups and the work done analysing those data could be of benefit[46].

Disease impact. Beyond disease activity, PsA has an impact on people in many ways, with pain and fatigue typically identified by patients as the highest priority issues[47]. Further research into the optimal management of pain and fatigue is likely to provide substantial benefit to patients.

Safety considerations. With the increased use of drugs with different mechanisms of action, long-term safety is a universal concern among patients and physicians. In addition to data from RCTs, information on safety from registries, longer term open-label follow-up to RCTs, claims data, and other sources can be important. Further definition of the relative safety of various agents can impact therapeutic choice.

Cardiometabolic disease. Cardiometabolic disease is of special importance in patients with psoriasis and PsA[48]. The following have been identified as areas of interest in the research agenda on cardiovascular and related comorbidities: ideal methods for cardiovascular risk screening; the impact of disease activity and therapies on cardiovascular risk; methods of modifying cardiovascular risk; the effect of dietary changes and microbiome on disease activity and metabolic alterations; the effect of fatty liver disease on disease activity; and the effect of modifying obesity and metabolic disease on response to therapy and overall disease activity.

Care delivery. The COVID pandemic has affected the mental health of patients and physicians alike, and has changed medicine service delivery worldwide[49]. Many changes, such as telehealth, seem set to stay. How such changes in care delivery impact the mental health status, disease activity and quality of life of patients with psoriasis and PsA is worth studying. There are some unresolved issues related to COVID infection and COVID vaccination that need further research, such as impact on therapy outcomes and disease activity.

Discussion

This paper summarizes the updated GRAPPA treatment recommendations for 2021, covering all six clinical domains of PsA in addition to related conditions and associated comorbidities. Considering the complexity of the disease and the rapidly evolving research landscape, up-to-date treatment recommendations can be of great relevance to clinicians and patients in managing PsA. Given the heterogeneity of disease presentation of PsA, individualization of therapy is crucial. With this update, GRAPPA has maintained a domain-based approach as well as a focus on comorbidities to guide treatment selection for individuals.

The recommendations are based on systematic searches to identify relevant evidence, which was assessed using a GRADE approach to ensure that quality of evidence was considered. All subcommittees had PRP involvement and developed their recommendations using consensus among international experts and PRPs. The subcommittees had strong representation from rheumatology and dermatology, and the related condition group also invited experts from the field of uveitis and IBD to ensure that multidisciplinary views were incorporated. All groups had worldwide representation from multiple continents and different health-care settings to ensure that the recommendations can be applied globally.

Some limitations of these recommendations relate to areas of limited evidence, including oligoarthritis, axial disease and forms of psoriasis other than plaque psoriasis. In addition, specific recommendations for the sequencing of effective therapies cannot be provided at present. Of note, the efficacy data utilized herein were taken from RCTs; clearly, patients recruited to clinical trials do not represent the broad diversity of people and PsA subtypes as seen in clinical practice. We have not attempted to give recommendations on the treatment of comorbidities, but rather advice on the general management of these conditions, as there is no clear evidence of the differential treatment of these comorbidities in people with PsA compared with the general population and this is typically beyond the scope of the rheumatologist or dermatologist treating PsA. Although the involvement of a representative, international panel increases the applicability of the recommendations, the recommendations cannot account for local health-care restrictions or guidance. We hope that clinicians can interpret the GRAPPA recommendations alongside any local or national guidance to provide further clarification.

Although these recommendations summarize the latest evidence up to 2021, research in PsA is rapidly evolving and all treatment recommendations therefore require regular updates. GRAPPA is committed to this endeavour as an ongoing process following on from successful treatment recommendations in 2009, 2015 and in 2021. We hope that future research will address some of the unmet needs reviewed here and are optimistic that future iterations of the recommendations will be able to incorporate this research in the years to come.

Conclusions

There has been tremendous progress regarding PsA over the past two decades. In addition to greater insight into the immunopathophysiology, and refinement in outcomes and assessments, novel therapeutic agents

have been introduced and newer treatment approaches developed. In order to achieve optimal outcomes for all patients with PsA, clinicians need to be aware of these important advances. These GRAPPA treatment recommendations, representing the latest update, were developed to facilitate the care of patients with PsA.

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Author contributions

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Competing interests

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the GRAPPA Treatment Recommendations domain subcommittees

Kristina Callis Duffin[5], Cristiano Campanholo[6], Lihi Eder[8], Daniel G. Fernández-Ávila[9], Oliver Fitzgerald, Amit Garg[11], Dafna Gladman[12], Philip Helliwell[14], M. Elaine Husni[15], Deepak R. Jadon[16], Dhrukumar Laheru[18], Ying-Ying Leung[20], Ennio Lubrano[22], Luis Daniel Mazzuoccolo[23], Philip J. Mease[24], Alexis Ogdie[26] and Penelope Esther Palominos[28]