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Consensus Statements for Evaluation and Management of **Psoriatic Arthritis** in UAE

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1. Abstract

Objective: Psoriatic arthritis (PsA) is a chronic inflammatory disease characterized by diverse clinical presentations, with varied articular and dermatological manifestations. PsA adversely impacts the physical function, work productivity and social life of affected patients. In United Arab Emirates (UAE), there is an unmet need of region-specific recommendations for assessment and management of PsA. This article aims at developing consensus recommendations for the assessment, management of the various clinical manifestations of PsA in UAE population.

Methods: An extensive literature review of the current international and regional guidelines and the related literature on the assessment, management, monitoring requirements for PsA therapies and management of comorbid conditions in patients with PsA was performed. Key highlights of these guidelines and articles were reviewed by a panel of experts at an advisory board meeting to identify unmet need, bridge clinical gaps in the UAE, and develop consensus statements for evaluation and management of patients with PsA.

Results: The consensus statements were developed on the overarching principles for the management of PsA, evaluation of patients with PsA, non-pharmacological and pharmacological approaches for the management of PsA, management of comorbid conditions in patients with PsA and monitoring requirements for PsA therapies. The overarching principles included adopting a targeted, and multidisciplinary approach, along with collaboration between the rheumatologists and dermatologists in case of clinically significant skin involvement. The panel also highlighted the value of composite disease severity measures for characterizing the clinical manifestations of PsA. In terms of non-pharmacological management approaches, life-style modification comprising of dietary changes, exercise, cessation of smoking, and psychotherapy was recommended. The consensus recommendations encompassed the use of non-steroidal anti-inflammatory agents, glucocorticoids, conventional disease-modifying antirheumatic drugs, and biologics for the treatment of various domains within PsA, including peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, and nail disease. Expert panel emphasized on importance of monitoring requirements and based on international guidelines, evidence from literature and local practices, there was agreement among the experts with regard to appropriate laboratory tests for monitoring PsA therapies. Consensus statements for the management of common comorbidities associated with PsA, including cardiovascular disease, obesity, metabolic syndrome, hypercholesterolemia, hypertension, diabetes mellitus, chronic kidney disease, malignancy, osteoporosis, non-alcoholic fatty liver disease, depression, was developed.

Conclusion: This consensus recommendation can guide the physicians and healthcare professionals in UAE for making proper treatment decisions, as well as, efficiently managing comorbidities and monitoring PsA patients.

Keywords: Psoriatic arthritis, severity, assessment, non-pharmacological, pharmacological, monitoring, comorbidities, guidelines.

2. Introduction

Psoriatic arthritis (PsA) is an autoimmune disorder characterized by chronic inflammation of the skin and joints, affecting approximately 2%–3% of the general population.[1] The global prevalence of PsA varies by geographic region and ranges from 0.001% to 0.42%,[2-4] while the prevalence of PsA is 0.01% to 0.3% in Middle East countries[5, 6] Evidence of nail dystrophy, scalp lesions, intragluteal and/or perianal lesions,involvement of >3 sites, male sex, family history of PsA[7-9] are factors that contribute to an increased risk of development of PsA in patients with psoriasis. Approximately 20% of patients diagnosed with PsA may develop a more aggressive form of arthritis resulting in joint damage (Figure 1).[4] Studies have shown that in many patients, PsA may progress to erosive disease in as early as 2 years after onset.[10]

Figure 1: Prevalence of Psoriatic Arthritis: Global and Regional Data[2-6]

PsA is a **chronic, progressive inflammatory arthritis** that is common among people living with psoriasis and **may result in permanent joint damage and disability**[1].

The global prevalence of PsA varies by geographic region and ranges from 0.001% to 0.42%,[2-4] while the prevalence of PsA is 0.01% to 0.3% in Middle East countries.[5, 6]

Men and women are equally at risk[1]

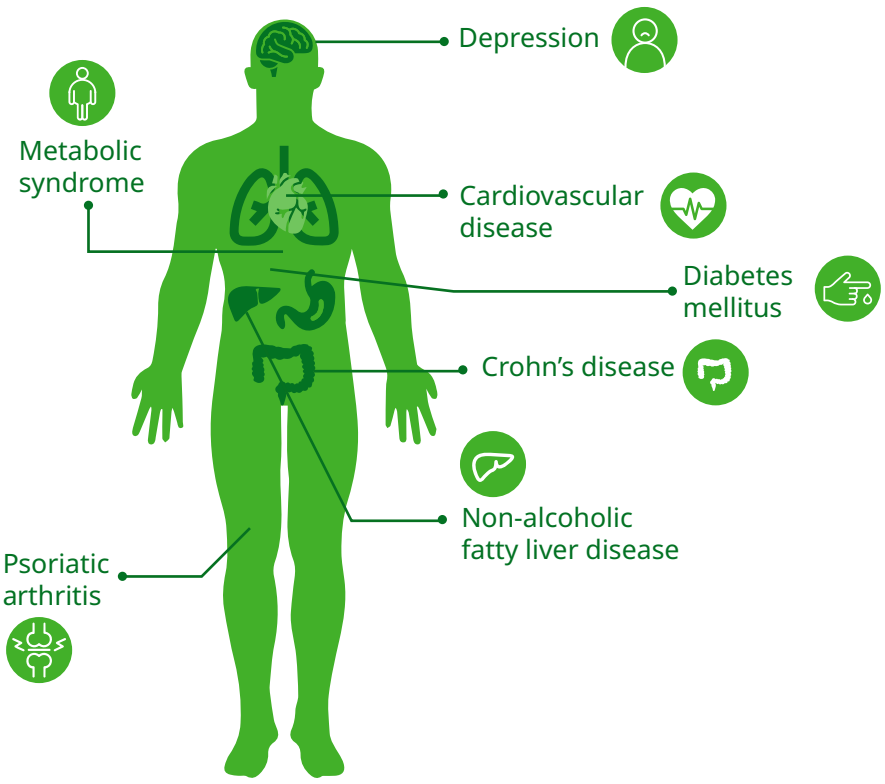
Approximately **20%** of patients diagnosed with PsA may develop a more aggressive form of arthritis resulting in joint damage.[4]

Patients with PsA are known to have a lower quality of life (QoL) as a result of stress, depression, mood changes, pain, and compromised physical functioning (Figure 2).[11, 12]

Figure 2: Effects of Psoriatic Arthritis on Quality of Life of Affected Patients[11, 12]

Additionally, inflammatory pathways linked to the development of PsA may also be associated with comorbidities such as cardiovascular disease, obesity, type 2 diabetes mellitus, metabolic syndrome, hyperlipidemia, hypertension, nonalcoholic fatty liver disease (NAFLD), hyperuricemia, gout, Crohn's disease, among others (Figure 3).[11-15]

Figure 3: Common Comorbid Conditions Associated with Psoriatic Arthritis[11-15]



Therapeutic decisions in PsA are guided by a patient-centric approach in collaboration with dermatologists, primarily aimed at addressing disease activity, comorbidities, structural damage, and patient-reported outcomes.[16, 17] Considering the heterogeneity in the clinical manifestations of PsA, it is important to ensure standardized treatment practices to assist practicing physicians, rheumatologists, and dermatologists.

Nearly all the current treatment recommendations in place for PsA are reflective of the treatment and disease landscape in developed countries, particularly Europe and the United States.[18-20] Currently, not much is known about the epidemiology and treatment practices specific to PsA in the Middle East. There are several local challenges that may not be adequately accounted for in currently available treatment recommendations for PsA.[21]

Multiple factors necessitate national recommendations for the management of PsA specific to the United Arab Emirates (UAE), including wide variability in healthcare systems, patient access to advanced care, affordability of treatment, practicing rheumatologists trained in different countries and implementing different approaches to treatment, and ethnic diversities among patients from almost 200 countries in the UAE. Many of the newer approved therapies such as biological disease-modifying antirheumatic drugs (DMARDs) may not be accessible to patients who do not have insurance coverage, given their prohibitive cost. Other factors that preclude the implementation of global treatment recommendations in local clinical practice are lack of disease awareness among both patients and health care providers, shortage of health care resources, and lack of multidisciplinary health care clinics.[22]

The objectives of this article are to address the gaps in clinical practice recommendations for the assessment and treatment of PsA in the UAE and to develop consensus statements for the evaluation, non-pharmacological and pharmacological management of PsA and associated comorbidities and monitoring requirements of PsA therapies, to assist practicing physicians in the UAE.

3. Methods

Six experts from the Emirates Society for Rheumatology representing different health care sectors of the UAE set up advisory board meetings to develop the consensus guidelines. The panel reviewed international and regional guidelines to determine clinical gaps in the evaluation and management of patients with PsA, and development of consensus statements centered around the identified gaps for the UAE.

3.1 Targeted literature review

For the development of the consensus guidelines, 6 experts with international board-certifications, and more than 15 years' experience in rheumatology and an interest in psoriatic arthritis representing different healthcare sectors (government and private) of the UAE were chosen from the Emirates Society for Rheumatology and convened in several meetings.

A targeted literature review was conducted. Current international and local treatment guidelines for PsA were identified through an extensive literature search and reviewed by members of the panel to identify unmet needs in local treatment practices in the UAE.[23]

Regional guidelines were compared with the latest international guidelines from the American College of Rheumatology/National Psoriasis Foundation Guideline (ACR/NPF) for the Treatment of Psoriatic Arthritis 2018, EULAR 2019, GRAPPA 2020, GRAPPA 2015 (Figure 4), and 2014 Saudi Practical Guidelines on Biologic Treatment of Psoriasis.[18-20, 23, 24]

As of August 2021, there is a dearth for guidelines on management of PsA specific to Arab region.

Based on a review of international and regional guidelines, consensus statements were developed focusing on pharmacological treatment options, screening and monitoring requirements for PsA therapies, and management of comorbidities associated with PsA. The results were discussed with all the members of Emirates Society of Rheumatology meeting to arrive at the final consensus statements. Key findings from the review were presented as statements.

Figure 4: International Guidelines for Assessment and Management of Psoriatic Arthritis[18-20,23]

Several meetings were held to generate consensus statements regarding pharmacological management of psoriatic arthritis. The first expert panel meeting was conducted on 23 September 2020 and the meeting lasted for 2 hours. The second expert panel meeting was conducted on 7 October 2020 and the meeting lasted for 3 hours. Third expert panel meeting was held on 16 December 2020 and lasted for 2 hours. The fourth and fifth meetings were held in the presence of Emirates Society for Rheumatology members on 18 December 2020 and 22 May 2021 respectively; each meeting lasted for almost 2 hours. The final meeting was held on 10 August 2021 and lasted for 2 hours when the consensus statements were approved.

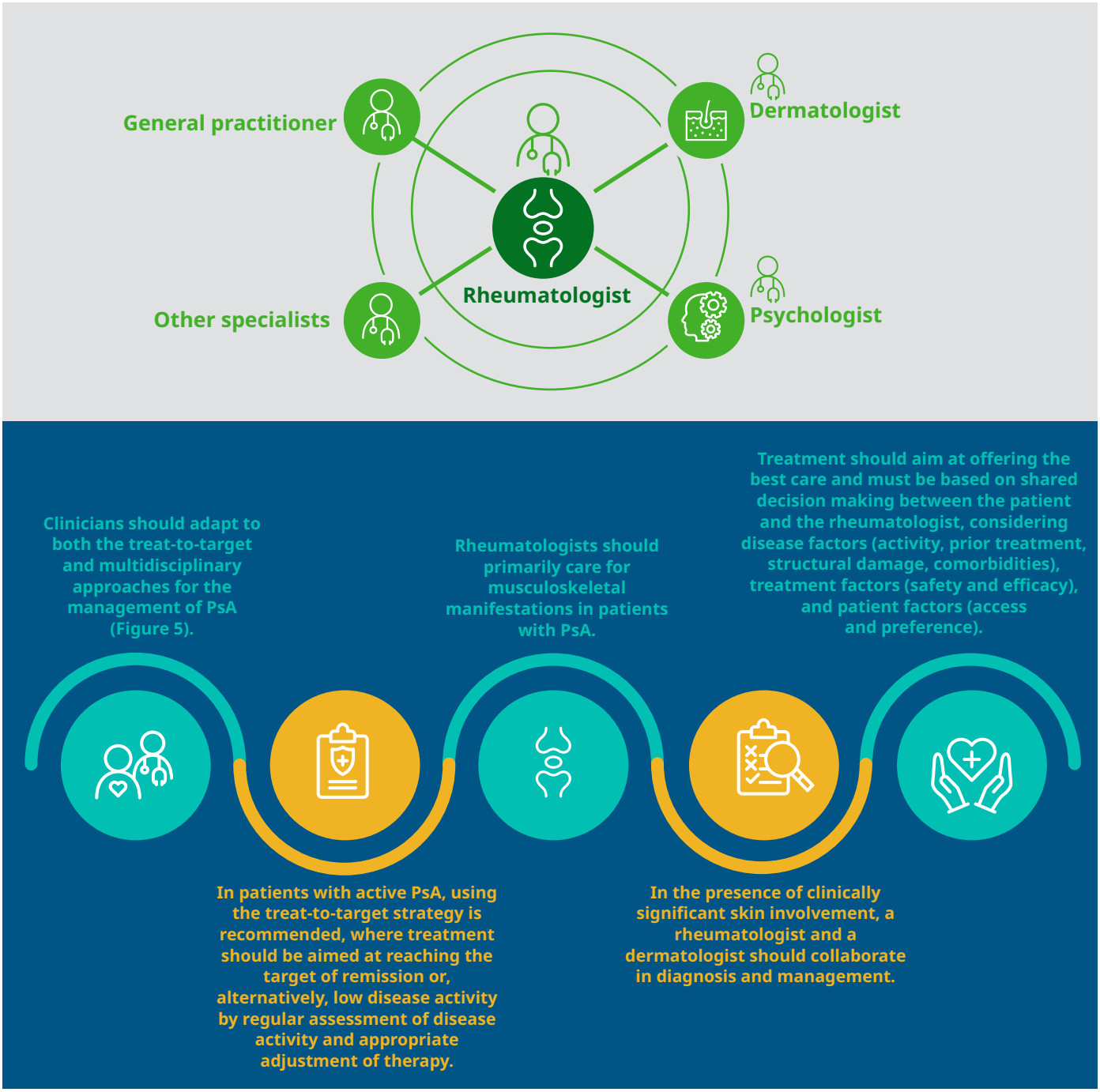
The key objectives of the meeting were:

1. To review similarities/differences in recommendations between the selected PsA guidelines
2. To identify and discuss gaps and unmet needs in current clinical practice for the evaluation and nonpharmacological management of PsA in the UAE
3. To identify and discuss the gaps present in various aspects related to PsA treatment
4. To tailor international guidelines to suit local needs in PsA management

4. Results

4.1 Overarching principles

Figure 5: Multidisciplinary Treatment Approach in Management of Psoriatic Arthritis[17,18,24]



4.2 Evaluation of patients with PsA

A key aspect of PsA treatment is comprehensive understanding of disease severity. **Due to the complex clinical presentation of PsA, there is a lack of acceptable diagnostic criteria and outcome measures for severity assessment. Several measures have been adopted to standardize the classification of patients based on disease severity.**

The 2009 GRAPPA recommendations state that patients can be stratified into 'mild,' 'moderate,' and 'severe' categories for each of the clinical manifestations of PsA (peripheral arthritis, skin disease, spinal disease, enthesitis, and dactylitis).[25] However, it was understood that patients may present with different levels of disease activity and different clinical manifestations, and therefore, the 2015 updated GRAPPA statements removed these rigid categorizations and designed treatment approaches based on disease activity, prognostic factors, comorbidities, and local access to therapies for the individual domains of PsA, namely peripheral arthritis, axial disease, enthesitis, dactylitis, skin psoriasis, psoriatic nail disease, uveitis, and inflammatory bowel disease (IBD).[18, 19]

The expert panel acknowledged the value of composite disease severity measures for characterizing the clinical manifestations of PsA.

The Psoriatic Arthritis Disease Activity Score (PASDAS) is a widely adopted weighted index measure that incorporates evaluator and patient assessments of visual analog scale (VAS) scores, tender and swollen joint counts, dactylitis, enthesitis, health-related quality of life (HRQoL), and C-reactive protein (CRP) levels.

The Disease Activity for Psoriatic Arthritis (DAPSA) is a composite activity measure adapted from the disease activity index for the assessment of reactive arthritis (DAREA).[26] DAPSA has been clinically validated[27] and performs well in arthritis domains,[28, 29] but was found to be less powerful than the Composite Psoriatic Disease Activity Index (CPDAI) in other clinical domains of PsA.[29, 30] The CPDAI is a composite measure that includes assessments for 6 domains of PsA: peripheral arthritis, functional disability, skin, dactylitis, enthesitis, and spinal manifestations.[31] Unlike DAPSA, the CPDAI composite measure evaluates the extent of disease activity, as well as the effects of particular domains on physical function and HRQoL, which includes the mental, emotional, and social functioning domains.[32] Overall, PASDAS has been shown to perform better than the DAPSA and CPDAI measures, specifically for estimating high and low disease activity.[29, 33, 34] The expert panel urges that PASDAS scoring assessment should be performed by a trained physician, since rheumatologists do not routinely use this tool.

For assessment of peripheral joint involvement, the Psoriatic Arthritis Response Criteria (PsARC) is an easy tool that can be used in clinical practice. The PsARC evaluates tender and swollen joint scores, and physician and patient global assessment of disease activity.[35] The PsARC was able to distinguish between outcomes in the treated and placebo groups in several trials.[36-38]

The Minimal Disease Activity (MDA) scoring instrument is a clinically validated, reliable indicator of a patient's disease activity at a given point.[39, 40] The MDA consists of 7 outcome measures including evaluation of tender joints, swollen joints, Psoriasis Area and Severity Index (PASI) or body surface area (BSA) patient pain VAS, Patient Global Assessment, Health Assessment Questionnaire (HAQ) and tender entheseal points. The MDA can be widely adopted in routine rheumatology clinics, owing to the ease of evaluating individual component measures and the absence of blood tests.[41] Very low disease activity (VLDA), a modified MDA, has been developed and validated in recent studies. It represents the most stringent target for remission in PsA. The VLDA state is achieved when seven out of seven criteria are met.[42]

The Ankylosing Spondylitis Disease Activity Score (ASDAS) is a recently developed composite disease activity score endorsed by Assessment of SpondyloArthritis International Society (ASAS). The preferred version selected by the ASAS is the ASDAS-CRP, and ASDAS-Erythrocyte sedimentation rate (ESR) is the alternative. ASDAS score correlated well with disease activity and showed good discriminative power, both in terms of physician and patient global

assessments of disease severity.[43, 44] For PsA with axial involvement, expert panel suggests the use of the ASAS criteria.[45, 46]

The important disease activity measures routinely used in clinical practice are detailed in Table 1, along with their components.

Experts emphasized on consistent use of scoring method in clinical practice based on physician's discretion and domain of the disease.

Table 1: Components in Calculation of Disease Activity Measures in Psoriatic Arthritis[36, 47-50]

COMPONENTS	DAPSA	CPDAI	PASDAS	MDA	PsARC	ASDAS
CLINICAL ASSESSMENT						
Tender joint count	68	68	68	68	68	
Swollen joint count	66	66	66	66	66	
PASI		X	X	X		
Enthesitis (LEI)		X	X	X		
Dactylitis count		X	X			
VAS physician			X		X	X
PATIENT QUESTIONNAIRE						
VAS global	X		X	X	X	X
VAS skin						
VAS joints						
VAS pain	X			X		
HAQ		X		X		
DLQI		X				
BASDAI		X				X
ASQoL		X				
SF-36 PCS			X			
PsAQoL						
LABORATORY ASSESSMENT						
CRP	X		X			X
ESR						X

ASDAS: Ankylosing Spondylitis Disease Activity Score; ASQoL: Ankylosing Spondylitis quality of Life; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; CPDAI: Composite Psoriatic Disease Activity Index; CRP: C-reactive protein;DAPSA: Disease Activity index for PSoriatic Arthritis; DAS28: Disease Activity Score 28; DLQI: Dermatology Life Quality Index; ESR: Erythrocyte sedimentation rate;LEI: Leeds Enthesitis Index; MDA: Minimal Disease Activity; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI: Psoriasis Area and Severity Index; PsAQoL: Psoriatic Arthritis-specific Quality of Life; SF-36 PCS: Short Form 36 Physical Component Scale; VAS: Visual analog scale; PsARC: Psoriatic Arthritis Response Criteria.

Considering the paucity of information on diagnostic instruments for the screening of patients with PsA, the severity assessment of PsA should be performed on a case-by-case basis[20] and should account for the following factors: involvement of joints and damage based on imaging modalities, loss of physical function, impact on QoL and patient-reported outcomes.

Patient-reported outcomes used for PsA including the Short Form (SF)-12/36, Health Assessment Questionnaire Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scales are used to capture disease activity, pain, physical function, fatigue, and productivity, among others.[51]

The expert panel acknowledged the pivotal role of rheumatologists in the care of patients with PsA and, therefore, agreed that stratification of disease severity should primarily be based on rheumatologic assessment.[18] Severe PsA should be established in accordance with ACR/NPF criteria: poor prognostic factors (erosive disease, dactylitis, elevated levels of inflammatory markers such as ESR and CRP attributable to PsA), long-term damage that interferes with joint function (e.g. joint deformities), and highly active disease that causes major impairment to QoL, and rapidly progressive disease.[20]

Consensus statements on assessing PsA disease severity are presented in Table 2.

Table 2: Consensus Statements on Assessing Psoriatic Arthritis Disease Severity

1. **Assessment of PsA requires consideration of major disease domains, including peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, nail disease, uveitis, and IBD.**
2. **Instruments that could be considered for measuring severity in patients with PsA include: PASDAS,DAPSA scores, PsARC, MDS score, and the ASDAS.**

- PsARC is an easy instrument that can be considered for assessment of severity of disease in patients with PsA in clinical practice.
  Although PsARC is no longer part of the OMERACT core domain set, some insurance companies mandate it for approval of immunosuppressive therapy
- MDA score can be considered a valid and reliable instrument for the assessment of disease severity in patients with PsA.
- The ASDAS score can be considered in the assessment of PsA with axial involvement despite the lack of validation studies.
- A combination of 2–3 most preferred instruments can be used to assess the disease activity, and the practitioner should be able to choose an instrument based on patient characteristics and disease involvement.
- Stratification of severity of PsA should be assessed considering one or more of the following parameters:
  - » Involvement of joints
  - » Damage on imaging modalities
  - » Loss of physical function
  - » QoL impact
  - » Patient-reported outcomes (e.g. SF-12/36, HAQ-DI, FACIT-F scale)
  - » Axial involvement
- For stratification of the severity of PsA, only rheumatological assessment instruments should be considered.
- Severe PsA disease includes the presence of one or more of the following (ACR/NPF):
  - » Poor prognostic factor (erosive disease, dactylitis, extensive skin disease)
  - » Long-term damage that interferes with function (e.g. joint deformities)
  - » Highly active disease that causes major impairment to quality of life
  - » Rapidly progressive disease

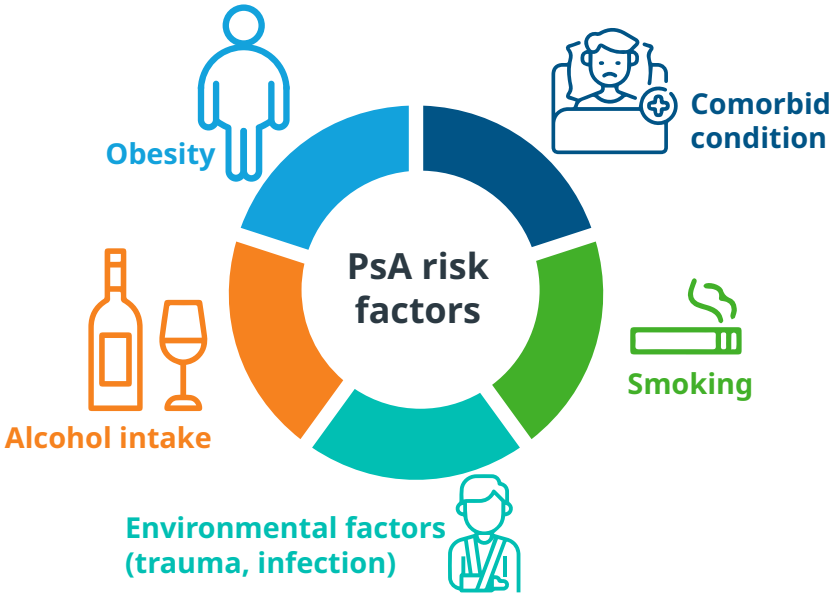
3. **Regular assessment of:**
   - » pain,
   - » functional limitation,
   - » QoL, and
   - » structural damage (e.g. X-ray, ultrasound, MRI) is recommended.
4. **Assessment and timely referral of comorbidities and related conditions, such as metabolic syndrome, obesity, cardiovascular disease, psychiatric disease, fibromyalgia, fatty liver disease, malignancies, chronic infections (e.g. HBV/HCV), and bone health is recommended.**

ACR: American College of Rheumatology; ASDAS: Ankylosing Spondylitis Disease Activity Score; DAPSA: Disease Activity in Psoriatic Arthritis; FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; MDA: Minimal disease activity;MRI: Magnetic resonance imaging;NPF: National Psoriasis Foundation; PASDAS: Psoriatic Disease Activity Score; PsA: Psoriatic arthritis; PsARC: Psoriatic Arthritis Response Criteria; QoL: Quality of life; SF-12/36: Short Form-12/36.

5. Nonpharmacological therapies

It is known that comorbid medical conditions and lifestyle factors such as obesity, smoking, alcohol intake, and environmental triggers are risk factors for the development of PsA (Figure 9).[52-54]

Figure 9: Risk Factors of Psoriatic Arthritis[55-57]

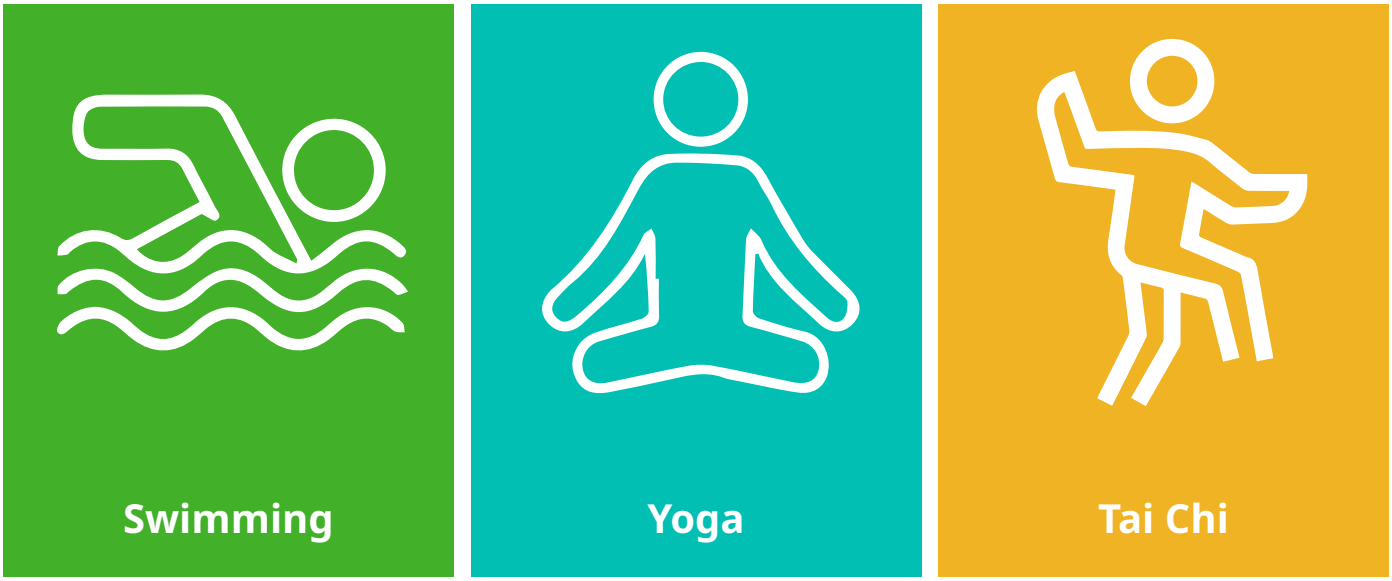


Obese patients with PsA are likely to experience chronic inflammation and have more severe disease activity when compared with patients with a normal body mass index (BMI). While obesity is an independent risk factor for PsA, it is also true that patients with obesity have poorer outcomes and response to pharmacological therapies.[58, 59] Although the evidence is limited to draw definitive conclusions,[60] weight-loss interventions can be particularly effective in improving disease activity in this population.[61, 62] These patients may directly benefit from the use of a hypocaloric diet plan, either alone or in combination with aerobic physical exercise.[63] There is evidence that intermittent fasting, such as the circadian system of fasting observed during Ramadan, is associated with improved disease activity in patients with PsA, regardless of the pharmacological therapy they receive.[64]

In accordance with the recommendations of ACR/NPF,[20] the expert panel agrees that any form of physical exercise is preferable to none in patients with active PsA.[65] Despite limited evidence, physical exercise has been shown to improve cardiorespiratory function and improve health-related QoL in patients with active PsA.[66] Patients with active PsA may also benefit from the use of nonpharmacological interventions, such as physical exercise, occupational therapy, massage therapy, and acupuncture.[67]

The expert panel opined that low-impact physical exercises such as tai chi, swimming, and yoga (Figure 7) should be encouraged in patients who cannot tolerate high-impact exercises such as running.

Figure 10: Low-impact Physical Exercises



Despite the fact that there have been few studies examining the effect of smoking on treatment outcomes in patients with PsA,[68] it is well established that smoking is strongly linked to radiographic progression and poor prognosis in RA.[69-72] Smoking cessation is associated with lower disease activity and improved cardiovascular outcomes in patients with RA.[73] Therefore, in accordance with ACR/NPF, smoking cessation is recommended (cigarettes or tobacco) in patients with PsA.[20]

A significantly high proportion of patients with PsA report poor QoL, depressive symptoms, anxiety, mood disturbances, and changes in sleep quality.[74-76] It has been reported that higher disease activity and pain scores are correlated with the presence of a comorbid mental condition.[77] Psychological interventions, therefore, are an important part of the multidisciplinary care plan for the management of PsA. Although studies are lacking for PsA, psychological interventions such as cognitive behavioral therapy, biofeedback, counseling, mindfulness, relaxation (e.g., tai chi and yoga), and patient education have been shown to have a positive effect on the physical and psychological distress associated with RA.[78] Considering the value of these interventions in improving QoL, which can ultimately have a positive impact on disease outcomes, the experts recommend the use of psychotherapy in the routine clinical management of PsA.

Consensus recommendations for the use of nonpharmacological therapies for PsA are presented in Table 3.

Table 3: Consensus Recommendations for Use of Nonpharmacological Therapies for Psoriatic Arthritis

Diet

- Patients with PsA should be provided diet counseling.
- Intermittent fasting can have beneficial effects on PsA disease activity, including PsA-related disorders such as enthesitis and dactylitis, regardless of the implicated drug therapy.
- In patients with overweight and obesity, weight loss should be emphasized.
- Limited intake of alcohol should be encouraged.

Exercise

- In patients with PsA, some form or combination of physical therapy, exercise, occupational therapy, acupuncture, and massage therapy should be considered.
- Low-impact exercises such as yoga, tai chi, swimming should be encouraged.
- High-impact exercise such as running can be considered in patients who have no contraindication to these exercises.

Smoking and psychotherapy recommendations

Cessation of smoking (cigarettes and tobacco) should be emphasized.

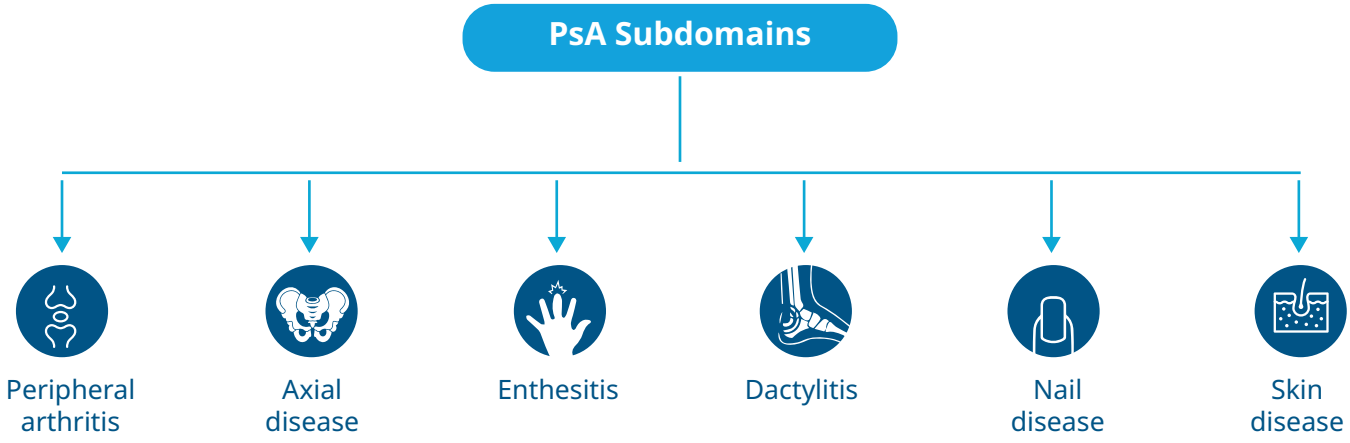
Psychotherapy should be considered in patients with PsA, as depression is prevalent in these patients.

6. Treatment options

6.1 Pharmacological therapies

GRAPPA recommendations (2015) are centered around major domains within PsA, including peripheral arthritis, axial disease, enthesitis, dactylitis, psoriasis, and nail disease (Figure 8).[18]

Figure 6: Major Domains of Psoriatic arthritis[18]



In accordance with the overarching principles outlined in the GRAPPA recommendations, the expert panel agreed that treatment selection should be based on shared decision making between the physician and patient. The current treatment recommendations were developed to align with the core recommendations from GRAPPA.[18]

Pharmacological therapies for the management of PsA include:[18,19,25, 79-84]

- Symptomatic treatments: non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCCs)[18]
- Disease-modifying antirheumatic drugs (DMARDs):
  - » Conventional synthetic DMARDs (csDMARDs): methotrexate, sulfasalazine, leflunomide[18]
  - » Targeted synthetic DMARDs (tsDMARDs): phosphodiesterase-4 inhibitors (PDE-4i)(apremilast), Janus kinase inhibitors (JAKi) (tofacitinib, upadacitinib) [18,19,79]
- Biologic DMARDs:
  - » Tumor necrosis factor inhibitors (TNFi): adalimumab, etanercept, infliximab, certolizumab pegol, golimumab[18]
  - » Interleukin -12/23 inhibitors (IL-12/23i): ustekinumab[18]
  - » Interleukin-23 inhibitors. (IL-23i): guselkumab[80]
  - » Interleukin-17 inhibitors (IL-17i): secukinumab, ixekizumab[19]
  - » Cytotoxic T-lymphocyte-associated protein 4-Immunoglobulin (CTLA4-Ig): abatacept[19]
  - » Upcoming therapies: filgotinib, risankizumab, brodalumab, bimekizumab, deucravacitinib[25, 81-84]

6.2 Dosage and Administration:

6.2.1 NSAIDs

The expert panel urged that a thorough safety evaluation should precede their use in patients with comorbid medical conditions (e.g. peptic ulcer disease, chronic kidney disease [CKD)], cardiovascular disease [CVD]).

6.2.2 GCCs

In the treatment of peripheral arthritis, GCCs is recommended conditionally, and the lowest effective doses should be administered to reduce the risk of side effects.[18]

6.2.3 csDMARDs

Conventional DMARDs are indicated for the treatment of moderate-to-severe PsA and in patients who

have failed to respond to short-term NSAID therapy. Methotrexate has been shown to improve disease activity and health-related QoL in patients with PsA. Methotrexate has a broad therapeutic dose range (7.5–30 mg/week) and different administration forms (oral, or subcutaneous).[85] Evidence suggests that monotherapy with methotrexate offers moderate improvement in joint and skin disease in patients with PsA, and doses >15 mg per week are associated with greater clinical efficacy compared to lower doses.[86, 87]

In patients with mild-to-moderate peripheral arthritis, use of sulfasalazine at a dose of 2–3 g/day may improve functional outcomes.[36, 88]

Leflunomide monotherapy with a daily loading dose of 100 mg for 3 days, followed by 20 mg/day is effective in the management of patients with mild-to-moderate PsA.[38] In an ongoing randomized, placebo-controlled, double-blind trial, the effectiveness of combination therapy of methotrexate and leflunomide in the treatment of patients with PsA is being evaluated, and the outcomes of the study are expected to provide key information for treatment strategies in PsA.[89]

6.2.4 tsDMARDs

- PDE-4i

Apremilast at a dose of 30 mg twice daily (BID) improves signs and symptoms and physical function in patients with active PsA.[90-94]

- JAKi

The recommended dosage of upadacitinib, a selective JAK inhibitor is 15 mg once daily orally in patients with active PsA, who have not adequately responded or intolerant to one or more DMARDs.[79]

According to EULAR 2019 recommendations, tofacitinib should be administered after inadequate response or intolerance to at least one bDMARD, or in case bDMARDs are not considered appropriate (due to patient preference for oral therapy or adherence issues to injectable formulations).[19] The recommended dose of tofacitinib is 5 mg twice daily (immediate release) or 11 mg once daily (extended release) in combination with nonbiologic DMARDs.[95]

6.2.5 Biological agents

- TNFi

TNFi agents approved by the US Food and Drug Administration (FDA) and other health authorities worldwide for PsA treatment include etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. They are recommended for use in PsA after inadequate response to at least one synthetic DMARD, although they may also be used as initial therapy.[96] TNFi agents are recommended in peripheral arthritis, and are also the first choice of therapy in enthesitis, dactylitis, and nail psoriasis.[97] The dosage recommendations for TNFi (adalimumab, etanercept, infliximab, certolizumab pegol, and golimumab are shown in Table 4.

- IL-12/23i

The IL-12/23i ustekinumab has been recommended alongside other biologics such as TNFi and IL-17i agents after DMARD therapy in patients with active PsA.[18, 19] The recommended dose of ustekinumab is 45 mg or 90 mg (SC)at 0 and 4 weeks and every 12 weeks thereafter.[98]

- IL-17i

The recommended dose of IL-17i ixekizumab in patients with active PsA and inadequate respons to TNFi agents is starting dose of 160 mg followed by 80 mg every 2 or 4 weeks for the safe and effective management of PsA.[99] Subcutaneous administration of IL-17i secukinumab is recommended at doses of 300 mg in patients with concomitant moderate-to-severe plaque psoriasis or who are TNFi inadequate responders at week 0,1,2,3 and 4 and every 4 weeks thereafter. The loading dose can be 150 mg in other patients at Weeks 1, 2, 3, and 4 and every week thereafter and based on the clinical response the dose can be increased to 300 mg.[100]

- IL-23i

Guselkumab, a specific IL-23i, has been recently approved for the treatment of PsA by the US FDA and EMA.[80] The recommended dose of guselkumab is 100 mg at Week 0, Week 4, and every 8 weeks thereafter.[101] Risankizumab was not approved for PsA by FDA and European Medicines Agency (EMA) when

our consensus statements were drafted. However, the EMA and FDA approved it on 22 November 2021 and 21 January 2022 respectively for treatment of active psoriatic arthritis.[102, 103]

- CTLA4-Ig

Abatacept is a biologic agent that targets T-cell costimulatory signals selectively and is approved for the treatment of PsA patients with inadequate response to csDMARDs, excluding those with uncontrolled skin lesions and axial disease.[104]

6.2.6 Biosimilars

In recent years, biosimilars of infliximab, etanercept, and adalimumab have been approved by regulatory bodies in Europe and the United States of America (USA) for the treatment of PsA. These agents have been approved for the treatment of PsA based on similar efficacy to the reference product in psoriasis and/or RA, by the extrapolation principle.[105-107] Biosimilars are more cost-effective compared to biologics, and thereby represent a solution for better patient accessibility to therapy and reduction in associated healthcare costs.[108]

Table 4: Dosage Recommendations for Pharmacological Therapies for Psoriatic Arthritis

THERAPEUTIC CLASS	DOSAGE	ROUTE OF ADMINISTRATION
NSAIDs*	-	Oral and IM
GCCs**	Lowest effective dose	IM and IA
csDMARDs		
Methotrexate[85]	7.5–30 mg/week	Oral, SC
Sulfasalazine[88, 109]	2 to 3 g/day	Oral
Leflunomide[38]	Daily loading dose of 100 mg for 3 days followed by 20 mg/day	Oral
tsDMARDs		
Apremilast[90, 91, 93, 94]	20 mg twice daily or 30 mg twice daily	Oral
Tofacitinib[95]	5 mg twice daily (immediate release) or 11 mg once daily (extended release) in combination with non-biologic DMARDs	Oral
Upadacitinib[79]	15 mg once daily	Oral
TNFi**		
Adalimumab[110]	40 mg every 2 weeks in patients with PsA with inadequate response to DMARDs	SC
Etanercept[37, 111, 112]	50 mg once weekly	SC
Infliximab[113, 114]	5mg/kg at 0, 2, 6 weeks, and every 8 weeks thereafter.	IV
Certolizumab pegol[115, 116]	400 mg at Weeks 0, 2, 4 Maintenance dose:200 mg every 2 weeks, or 400 mg every 4 weeks once clinical response is confirmed	SC
Golimumab[117]	SC: 50 mg monthly IV: 2 mg/kg over 30 minutes at Weeks 0 and 4 (loading dose), thereafter every 8 weeks (maintenance)	SC, IV
IL-12/23i***		
Ustekinumab[98]	45 mg or 90 mg (based on weight) at 0 and 4 weeks, and every 12 weeks thereafter	SC
IL-17i		
Secukinumab[118]	300 mg in patients with concomitant moderate-to- severe plaque psoriasis or who are TNFi inadequate responders at Weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter. 150 mg in other patients at Weeks 0, 1, 3, 4 and every 4 weeks thereafter and based on clinical response the dose can be increased to 300 mg.	SC
Ixekizumab[99, 119]	160 mg followed by 80 mg every 2 or 4 weeks in patients who previously had inadequate response to TNFi; For patients with arthritis and moderate-to-severe plaque psoriasis, using the dosing regimen for plaque psoriasis;160 mg SC at week 0, then 80 mg SC at week 2, 4, 6, 8,10 and 12, then 80 mg SC every 4 weeks, starting week 16.	SC
IL-23i		
Guselkumab[101]	100 mg at Weeks 0 and 4, and every 8 weeks thereafter (maintenance)	SC
CTLA4-IG		
Abatacept (CTLA4-Ig) T-Cell co-stimulation inhibitor[104, 120]	1) 500 mg, 750 mg, or 1000 mg (based on weight range); following initial IV infusion, subsequent infusions should be administered at 2 and 4 weeks and every 4 weeks thereafter 2) 125 mg of abatacept injection should be administered subcutaneously once weekly	IV, SC

* Mentioning the doses of all available NSAIDs is beyond the scope of this paper.

**EULAR 2019 and GRAPPA 2015 guidelines recommend administering the lowest effective doses of GCC.

***Loading dosage might vary according to the severity of psoriasis and other domains of the disease.

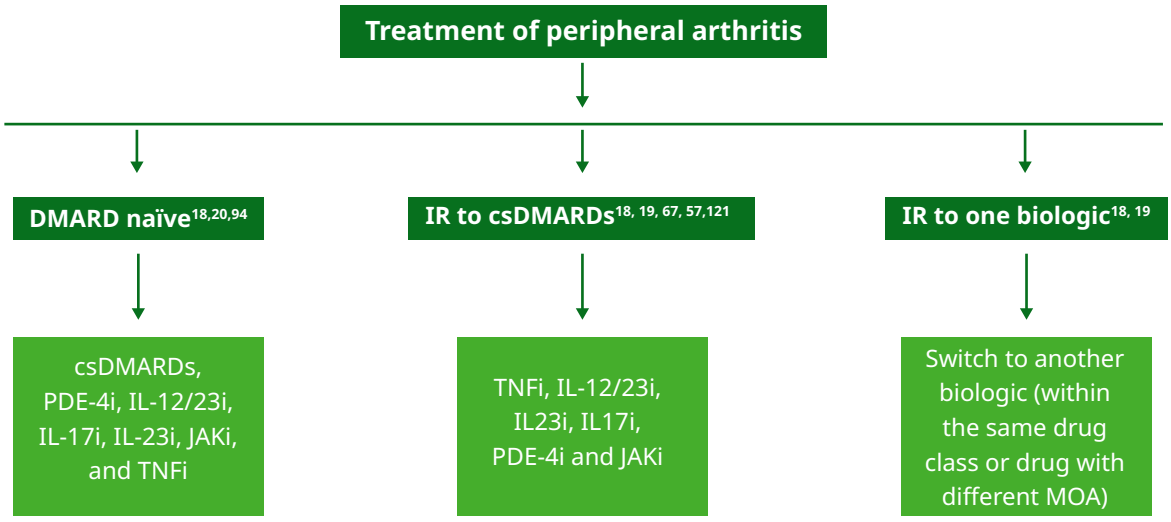
csDMARD: Conventional synthetic disease-modifying antirheumatic drug; CTLA4-Ig: Cytotoxic T-lymphocyte-associated antigen4-immunoglobulin; IA: Intra-articular; IL: Interleukin; IM: Intramuscular; IV: Intravenous; JAK: Janus kinase; NSAIDs: Non-steroidal anti-inflammatory drugs; PsA: Psoriatic arthritis; PDE-4i: Phosphodiesterase-4 inhibitor; SC: Subcutaneous; TNFi: Tumor necrosis factor inhibitor; tsDMARD: Targeted systemic disease-modifying antirheumatic drug.

6.3 Treatment recommendations based on PsA domains

6.3.1 Peripheral arthritis

In DMARD-naïve patients with peripheral arthritis, csDMARDs (methotrexate, sulfasalazine, and leflunomide), PDE-4i, IL-12/23i, IL-17i, IL-23i, JAKi, and TNFi are recommended.[18, 20, 92] In patients with monoarthritis or oligoarthritis accompanied by factors such as dactylitis or joint damage, the use of csDMARD and intraarticular (IA) GCC should be considered.18 In patients with polyarticular disease, csDMARDs should be administered either as first-line treatment or after a short course of NSAIDs.In patients with inadequate response to csDMARDs, TNFi, IL-12/23i, IL23i, IL17i, PDE-4i and JAKi are recommended therapeutic options.[18, 19, 95, 121, 122] In patients with inadequate response to one biologic treatment, switching to another biologic within the same drug class, or to a drug with a different mode of action, should be considered.[18, 19] In all patients with peripheral arthritis, intra-articular and systemic GCC are conditionally recommended at the lowest dosages and for a short duration (Figure 9).

Figure 7: Treatment Schema for Peripheral Arthritis



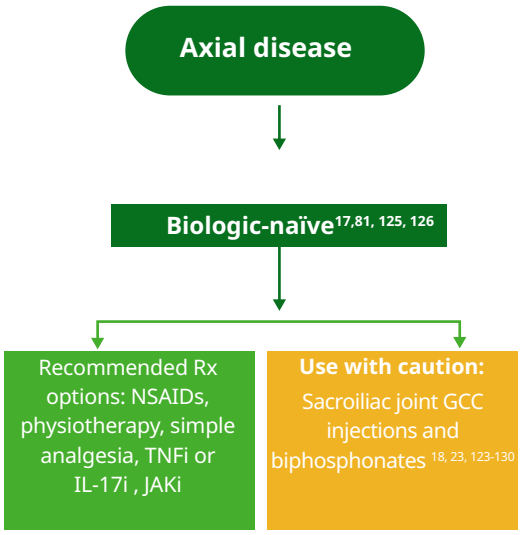
Intra-articular and systemic GCC are conditionally recommended at lowest dosages in all patients with peripheral arthritis

csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs; DMARD: Disease-modifying antirheumatic drugs;IL-17i: Interleukin-17 inhibitors; IL-12/23I:Interleukin-12/23 inhibitors; IL-23i:Interleukin-23 inhibitors; IR:Inadequate response;JAKi: Janus kinase inhibitors; MOA:Mechanism of action; PDE-4i:Phosphodiesterase-4 inhibitors; TNFi: Tumor necrosis factor inhibitors

6.4.2 Axial disease

At the time of drafting consensus statements, there were no studies on management of psoriatic spondylitis. Therefore, management of this condition depends on current treatment modalities in ankylosing spondylitis. In patients with psoriatic spondylitis/ axial disease who are biologic-naïve, NSAIDs, physiotherapy, simple analgesia, TNFi or IL-17i, JAKi are recommended therapeutic options. Tofacitinib was not approved for PsA by FDA and European Medicines Agency (EMA) when the consensus statements were drafted. However, FDA and EMA approved it on 18 November 2021 and 14 December 2021 respectively for treatment of ankylosing spondylitis. Other therapeutic options such as sacroiliac joint GCCs injections and bisphosphonates can be used, but with caution.[18, 23, 123-129]

Figure 8: Treatment Schema for Axial Disease



GCCs:Glucocorticoids; IL-17i: Interleukin-17 inhibitors; IR: Inadequate response; JAKi:Janus kinase inhibitors; NSAIDs: Non-steroidal anti-inflammatory drugs; Rx: Medical prescription; TNFi: Tumor necrosis factor inhibitors

6.3.3 Enthesitis

For the management of PsA patients with enthesitis (inflammation at the sites of attachment of ligaments, tendons, and joint capsules to bone),131 treatment with TNFi, IL-17i, JAKi, IL-23i, and IL-12/23i are recommended therapeutic options. Other therapeutic include NSAIDs, physiotherapy, methotrexate, CTLA-4 Ig, and PDE-4 inhibitors.[18, 19, 121, 132-136]

6.3.4 Dactylitis

The recommended therapies for the management of PsA patients with dactylitis include TNFi therapies (infliximab, adalimumab, golimumab, and certolizumab pegol), IL-17i, IL-12/23i, IL-23i, JAKi, and PDE-4i.[18, 101, 105, 106] Other therapeutic options include NSAIDs, GCCs injections, and methotrexate.[18]

6 .3.5 Nail disease

The recommended therapies for the management of PsA patients with dactylitis include TNFi therapies (infliximab, adalimumab, golimumab, and certolizumab pegol), IL-17i, IL-12/23i, IL-23i, JAKi, and PDE-4i.[18, 132, 136, 137]

[106]Other therapeutic options include NSAIDs, GCCs injections, and methotrexate.[18]

6.3.6 Skin disease

The expert panel recommends the use of topical therapies, phototherapy, acitretin and csDMARDs (methotrexate, leflunomide, cyclosporine) as first-line therapeutic options especially for PsA patients with milder skin disease.[18] TNFi, IL-17i, IL12/23i, IL-23i, JAKi and PDE-4i are recommended therapeutic options for treatment of PsA patients with significant skin involvement.[18] Furthermore, biologic agents such as IL-17i are preferred to TNFi, with or without topical treatments and DMARDs, in PsA patients with active psoriasis (≥ 3% of body surface area of skin involvement).[56] In accordance with GRAPPA 2015 recommendations, the expert panel recommends switching from one DMARD to another, or to biologic treatment, or from one biologic treatment to another.[18]

Consensus recommendations for the treatment of PsA domains were based on GRAPPA 2015, GRAPPA 2020, EULAR 2019 recommendations and literature review, and are presented in Table 5.

Table 5: Consensus Recommendations for Treatment of Psoriatic Arthritis Domains

DOMAIN	RECOMMENDED THERAPEUTIC OPTIONS (STRONGLY RECOMMENDED)	OTHER THERAPEUTIC OPTIONS (CONDITIONALLY RECOMMENDED)	TO BE AVOIDED (STRONGLY NOT RECOMMENDED)
• **Peripheral Arthritis DMARD-naïve**[18,20,94]	• csDMARD • TNFi • PDE-4i • IL-12/23i • IL-17i • IL-23i • JAKi	• NSAIDs • GCCs (oral or IA) • CTLA-4 lg	
• **Peripheral Arthritis DMARD inadequate response**[18,19,57,95,121]	• TNFi • PDE-4i • IL-12/23i • IL-17i • IL-23i • JAKi	• NSAIDs • GCCs (oral or IA) • csDMARD • CTLA-4 lg	
• **Peripheral Arthritis, inadequate response to biological treatment**[18,123]	• TNFi • IL-17i • IL-12/23i • IL-23i • JAKi	• NSAID • GCC (oral and IA) • CTLA-4 Ig • PDE-4i	
• **Axial PsA**[18,81, 125, 126]	• NSAIDs and simple analgesia • Physiotherapy • TNFi • IL-17i • JAKi	• GCC injection for sacroiliac joints • Bisphosphonate	• csDMARD • IL-12/23i
• **Enthesitis**[18,19,57, 132-136]	• TNFi • IL-17i • JAKi • IL-23i • IL-12/23i	• NSAIDs • physiotherapy • MTX • CTLA-4 IgG, and PDE-4i	
• **Dactylitis**[18, 123, 132, 136, 137]	• TNFi • IL-17i • IL12-23i • IL-23i • JAKi • PDE-4i	• NSAIDs, • GCCs injections • MTX • CTLA-4 Ig	
• **Nail disease**[18, 19, 55, 138-140, 142]	• TNFi • IL-17i • PDE-4i • IL-12/23i • IL-23i		
• **Skin disease (Plaque)**[18, 93, 143-146]	• Topical therapies, phototherapy • acitretin, • csDMARDs (MTX,LEF,CSA) • TNFi • IL-12/23i • IL-17i • IL-23i • JAKi • PDE-4i		

CS: Corticosteroids; CSA: Cyclosporine; CTLA-4 Ig: Cytotoxic T lymphocyte-associated antigen-4 immunoglobulin; DMARD: Disease-modifying antirheumatic drug; GCC: Glucocorticoids; IA: Intra-articular; IL-12/23i: Interleukin-12/23 inhibitor; IL-17i: Interleukin-17 inhibitor; IL-23i: Interleukin-23 inhibitor; IV: Intravenous; JAKi: Janus kinase inhibitor; LEF: Leflunomide; MTX: Methotrexate; NSAIDs: Non-steroidal anti-inflammatory drugs; PsA: Psoriatic arthritis; PDE-4i Phosphodiesterase-4 inhibitor (apremilast); SC: Subcutaneous; TNFi: Tumor necrosis factor inhibitor.

7. Efficacy and safety PsA therapies

7.1 Treatment response

Evaluating response to therapy in patients with PsA can be difficult due to its complex nature, which encompasses a multitude of clinical manifestations. To date, there is no standardized outcome measure for PsA. In terms of efficacy and safety profile, experts agreed to adhere to the recommendations from guidelines, latest literature evidence and prescription label. Accordingly, consensus statements were developed for efficacy and safety of non-biologic and biologic therapies.

7.2 Efficacy and safety of non-biologic pharmacological therapies

For relieving musculoskeletal signs and symptoms, the efficacy and safety of available nonbiologic pharmacological therapies is detailed below.

Consensus statements on the efficacy and safety of non-biologic pharmacological therapies are presented in Table 6.

Table 6: Consensus Statements on Efficacy/Safety Profile of Nonbiologic-pharmacological Therapies

SYMPTOMATIC TREATMENTS	
NSAIDs	In PsA patients with peripheral arthritis, NSAID monotherapy without DMARDs should not exceed 1 month if disease activity persists.[19]
	In the case of axial or entheseal involvement, NSAID therapy may be continued for up to 12 weeks if relief has already been achieved after 4 weeks.[19]
	Because of the potential for side effects (eg gastrointestinal complications, hepatic complications, allergic complications, cardiovascular complications and chronic kidney disease), NSAIDs should be used with caution.
	NSAIDs such as celecoxib are contraindicated in patients with hypersensitivity to celecoxib, patients with history of asthma, urticaria, or other allergic type of reactions after taking NSAIDs. NSAID use should be avoided during the perioperative period in the setting of coronary artery bypass surgery.
GCCs	Systemic GCC use may be associated with skin flares, and GCCs should be used with caution, especially when treatment is being tapered for the potential worsening of skin symptoms. Intra-articular injection of GCCs may rarely result in depigmentation.[147]
	Intra-articular injection of GCCs may rarely result in depigmentation.[147]

csDMARDs	
Methotrexate	MTX should be prescribed at an optimal dose of 25 mg per week and with folate supplementation.
	If improvement does not exceed 50% of a composite measure for PsA within 3 months or the treatment target is not reached within 6 months, JAKi or bDMARD can be added to MTX treatment.
	Gastrointestinal manifestations, hepatotoxicity, dizziness, photosensitivity are common adverse effects associated with MTX treatment.
	MTX should be used with caution in patients with impaired renal function, ascites pleural effusion should be avoided in pregnant women due to its teratogenic effects. Other contraindications for use of MTX include liver disease, immunodeficiency syndrome, preexisting blood dyscrasias and in patients with hypersensitivity to MTX.
Leflunomide	Leflunomide is effective and safe in the management of PsA, particularly in reducing tenderness, pain, fatigue, dactylitis, and skin disease in patients with PsA.[148]
	Common adverse effects of leflunomide include diarrhea, nausea, headache, rash, respiratory infection, abnormal liver enzymes.
	Leflunomide should be used with caution in patients with severe infections.
	Caution should be taken for its use in pregnant women and in patients with severe hepatic impairment.
Sulfasalazine	Sulfasalazine shows greater improvement in patients with symmetrical polyarticular peripheral arthritis.
	Sulfasalazine shows significant improvement in joint scores and reduction in disease activity as early as the fourth week of treatment.[149]
	Sulfasalazine is well tolerated and safe in patients with PsA at a dose of 2.0g/day.
	Patients with PsA who are known or suspected to have COVID-19, should continue to use sulfasalazine.[150, 151]
	Common adverse events associated with sulfasalazine include gastric upset, skin rashes, headache, and liver disorders. Should be used with caution in patients with severe allergy, bronchial asthma, and glucose-6-phosphate dehydrogenase deficiency (G6PD). Sulfasalazine should be avoided in patients with intestinal or urinary obstruction, porphyria, and hypersensitivity to sulfasalazine.
tsDMARDs	
Apremilast	Apremilast is effective in the treatment of biologic-naïve patients with PsA and has a tolerable safety profile.
	Diarrhea and nausea are the 2 most common adverse events associated with the use of apremilast.
	Apremilast should be used with caution in PsA patients with depression.
	Apremilast does not require routine therapeutic monitoring.
	Apremilast is a safe and effective therapeutic option in the HIV-infected population with psoriatic arthritis.
Tofacitinib	Tofacitinib is safe and effective in the management of csDMARD-IR/TNFi-naïve and TNFi-IR patients and is effective in PsA patients with enthesitis and dactylitis.
	Patients with recurrent deep-vein thrombosis and those at high risk of shingles infection should exercise caution.
	Tofacitinib has an acceptable safety profile with a low incidence of serious infections, malignancies, cardiovascular events, and gastrointestinal complications.

Upadacitinib	Upadacitinib is safe and effective in the management of patients with active ankylosing spondylitis.
	Upper respiratory tract infections, nausea, cough, and pyrexia are common adverse effects associated with the use of upadacitinib.
	Caution should be taken in patients with active and serious infections, malignancy, thrombosis, and gastrointestinal perforation.

bDMARD: Biologic disease-modifying antirheumatic drug; csDMARD: Conventional synthetic disease-modifying antirheumatic drug; COVID-19: Coronavirus disease-2019; GCC: Glucocorticoids; HIV: Human immunodeficiency virus; IR: Inadequate response; JAKi: Janus kinase inhibitor; MTX: Methotrexate; NSAIDs: Non-steroidal anti-inflammatory drugs; PsA: Psoriatic arthritis; TNF: Tumor necrosis factor; tsDMARD: Targeted synthetic disease-modifying antirheumatic drug.

7.3. Biologic pharmacological therapies

Consensus statements on the efficacy and safety of biologic pharmacological therapy are presented in Table 7.

Table 7: Consensus statements on Efficacy/Safety Profile of Biologic Pharmacological Therapies

TNFi THERAPY
• Adalimumab at a dose of 40 mg (at baseline, Weeks 2 and 4, and every 4 weeks thereafter) can significantly improve joint and skin manifestations and reduce radiographic progression in patients with active PsA by achieving clinical response by 6 months.[152, 153]
• Etanercept (25 mg twice weekly) can significantly reduce the signs and symptoms of PsA and achieve clinical response by Week 12, sustaining its efficacy from 48 weeks to 2 years.[111, 112]
• Use of infliximab, at a dose of 5 mg/kg (at Weeks 0, 2, and 6, and every 8 weeks thereafter) significantly inhibits the progression of radiographic damage in patients with active PsA as early as 6 months after starting treatment, and the beneficial effect continues through 1 year of treatment.[154]
• Treatment with infliximab at a dose of 5 mg/kg significantly improves the signs and symptoms of arthritis, psoriasis, dactylitis, and enthesitis in patients with active PsA that is resistant to DMARD therapy.[155, 156]
• Certolizumab pegol (200 mg every 2 weeks or 400 mg every 4 weeks) provides rapid improvement in the signs and symptoms of PsA, including joints, skin, enthesitis, dactylitis, and nail disease. It can reduce the progression of structural damage until 2 years in PsA patients with/without prior anti-TNF exposure.[157, 158]
• Golimumab (100 mg) has also been shown to inhibit radiographic progression as early as 6 months and is effective in maintaining clinical improvement for 5 years.[159]
• TNFi therapy should not be initiated or continued in the presence of serious active infection but can be recommenced once the infection has resolved clinically.
• TNFi therapy should be used with caution in patients at high infection risk: » Active mycobacterial infection should be adequately treated before TNFi therapy is started. » HIV or HCV infection should not preclude treatment with TNFi therapy, although treatment should only be commenced in those with well-controlled disease and with appropriate monitoring under the care of a hepatologist or HIV specialist, although etanercept has been shown to be safe in PsA patients with HCV. » TNFi therapy in those with chronic HBV should be approached with caution, given the potential risk of reactivation and fulminant hepatitis.
• TNFi therapy should be avoided in patients with a current or prior history of malignancy.
• Caution should be taken in patients with serious infections and demyelinating diseases or in patients with systemic lupus erythematosus.

IL-12/23 INHIBITORS
• Ustekinumab (SC) at a dose of 45 mg or 90 mg (weight dependent) reduces signs and symptoms of articular and dermatological manifestations in PsA patients with and without TNFi therapy exposure and is well tolerated through 16 weeks of therapy.[160]
• Adverse effects of IL-12/23i include upper respiratory tract infections, nasopharyngitis, back pain, headache, injection-site reactions, myalgia, fatigue, and rarely severe infection and malignancy.
• Caution should be taken in patients with serious infections and malignancy.
• Ustekinumab is contraindicated in patients with clinically significant hypersensitivity to ustekinumab or to any of its excipients.
IL-17 INHIBITORS
• Secukinumab (SC) provides sustained improvement in signs and symptoms and multiple clinical domains in active PsA patients and is well tolerated through 5 years of therapy.[161]
• Secukinumab (150–300 mg) is well tolerated for long-term treatment.
• Ixekizumab is a highly effective treatment for active PsA patients, especially those previously exposed to csDMARDs and TNFi therapies.[99, 162]
• The most common adverse effects associated IL-17i include upper respiratory tract infections and injection-site reactions.
• IL-17i should be used with caution in patients with concomitant IBD and severe infections.
• IL-17i are contraindicated in patients with serious allergic reactions to the molecule or its recipients.
IL-23 INHIBITORS
• Guselkumab has shown significant improvement in joint symptoms with more than one-third of patients achieving ACR50 by Week 24.[114]
• Guselkumab shows significant improvement in inhibition of radiographic progression of joint structural damage and resolving enthesitis, dactylitis in patients with active PsA at 24 weeks.[57, 163]
• Common adverse events with guselkumab include hypersensitivity reactions, including anaphylaxis and upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex infections.
CTLA-4 Ig
• Abatacept can be effective in patients with PsA refractory to DMARDs.[121]
• The most common adverse effects associated with abatacept include headache, upper respiratory tract infection, nasopharyngitis, and nausea.

ACR: American College of Rheumatology; CTLA4-Ig: Cytotoxic T-lymphocyte-associated protein4 -immunoglobulin; DMARD: Disease-modifying antirheumatic drug; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; IBD: Inflammatory bowel disease; IL: Interleukin; PsA: Psoriatic arthritis; SC: Subcutaneous; TNFi: Tumor necrosis factor inhibitor.

7.4 Treatment failure and switching therapy

The expert panel agreed that transitioning to alternative TNFi therapy should be considered in PsA patients with primary or secondary failure of TNFi therapy. The response to alternative treatment should be assessed with the same criteria as those used for the first TNFi agent. Furthermore, possible consequences for control of skin disease should be considered and referral to a dermatologist also considered, if required.[20]

Similarly, switching within a class or between a class (bDMARD to tsDMARD) can also be considered in case of primary or secondary failure of a bDMARD. However, it is more advisable to change class after a second failure within a given class.[20]

8. Monitoring

Expert panel suggested that before initiation of any systemic therapy, a practical approach should be adopted to monitor PsA patients on the basis of medical history, physical examination, and tests (laboratory and imaging). Expert panel opined that monitoring of systemic therapies aids is crucial to maximize the benefits and minimize the risks associated with these drugs.

Owing to an increased risk of hepatotoxicity and renal toxicity associated with most systemic DMARDs, experts recommended monitoring tests including complete blood count, comprehensive liver function tests, renal function test, erythrocyte sedimentation rate (ESR), CRP, and serum creatinine levels.

As most bDMARDs are immunomodulators, there is a high risk of serious infections, including tuberculosis, hepatitis, and HIV. Therefore, it is important that patients are routinely screened for tuberculosis (QuantiFERON), hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV prior to initiating any biologic therapy.

Furthermore, patients should be assessed for their vaccination status before initiating any systemic therapy. Routine vaccination for pertussis and inactivated influenza, pneumococcal, and HBV is recommended in high-risk patients and in highly prevalent regions at baseline. Varicella-zoster antibody (IgG) test, especially in patients taking JAKi inhibitors, should be conducted at baseline. Live vaccines should be avoided during treatment with biologics.

Patients on TNFi should be regularly screened for skin cancers (including melanoma), especially if they are at high risk. A general screening questionnaire for malignancy should also be considered on a case-by-case basis. Given the increased prevalence and incidence of CVD and diabetes among PsA patients, appropriate screening is recommended. Framingham risk score or atherosclerotic cardiovascular disease (ASCVD) should be used regularly for CVD risk assessment in patients with PsA. All patients with PsA should be encouraged to achieve and maintain a healthy body weight. This is of specific relevance to PsA, as the likelihood of reduction in disease activity with TNFi treatment appears to be higher among patients with normal body weight than among patients with PsA who are overweight. Depression and anxiety are highly prevalent among patients with PsA. It is necessary to weigh the risks and benefits of treatment in patients with a history of depression and/or suicidal thoughts/behavior, before initiating therapy. Patients at high risk should be regularly screened for any psychotic symptoms and suicide ideation. Due to the increased risk of ophthalmic disease and IBD in patients with PsA, the experts also agreed that prior to initiating PsA therapy, it is important to obtain a baseline evaluation of the patient for eye disease and gastrointestinal disease and if needed, patients should be referred to appropriate specialists. Also, pregnancy test should be considered as an important screening test prior to initiation of any biologic. Although all approved biologics for psoriasis belong to pregnancy category B, these drugs should be used with caution with strong consideration of the specific clinical scenario. All tests should be conducted periodically every 1–3 months during treatment and be based on clinical judgment.

In accordance with the recommendations provided by the Saudi guideline and GRAPPA 2015 and evidence from literature, consensus statements on monitoring requirements for PsA therapies are presented in Table 8.

Table 8: Consensus Statements on Monitoring Requirements for Psoriatic Arthritis Therapies

RECOMMENDATIONS
• Recommended laboratory tests prior to initiation of a biologic treatment include:[18, 24] » Complete blood count: Hemoglobin, hematocrit, white blood cell count, white blood cell differentiation, and platelet count » Comprehensive liver function tests: Direct bilirubin, total bilirubin, ALP, ALT and GGT » Renal function test
• Other important tests include ESR, CRP, and serum creatinine.
• Screening for HIV, HBV, HCV, and tuberculosis (QuantiFERON preferable) should be strongly considered, in accordance with local guidelines and standards of medical practice, before initiation of therapies that may potentially alter normal immune response.[18]
• Inclusion of varicella-zoster antibody (IgG) test, especially in patients taking JAKi, for baseline tests, should be considered.[164]
• Chest X-ray as a baseline monitoring test for all drugs should be strongly considered.
• A general screening questionnaire for malignancy should be considered on a case-by-case basis.
• Given the increased prevalence and incidence of CVD and diabetes among patients with PsA, regular screening is recommended (e.g. Framingham risk score or ASCVD for CVD risk assessment).[18]
• Screening for depression and anxiety among patients with PsA should also be considered.[18]
• Given the association of ophthalmic disease with the spondylarthritis and an increased risk of IBD among patients with PsA, consideration of screening for eye disease and gastrointestinal disease is recommended as a part of the review of systems, as well as consideration of appropriate referral, as applicable.[18]
• Monitoring tests should be conducted every 1–3 months during treatment and based on clinical judgment.

ALP: Alkaline phosphatase; ALT: Alanine transaminase; ASCVD: Atherosclerotic cardiovascular disease; CRP: C-reactive protein; CVD: Cardiovascular disease; ESR: Erythrocyte sedimentation rate; GGT: G-glutamyl transferase; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency viruses; IBD: Inflammatory bowel disease; IgG: Immunoglobulin G; JAK: Janus kinase; PsA: Psoriatic arthritis.

9. Management of Comorbidities

Identifying comorbidities is critical to the optimal management and treatment of PsA. Common comorbidities in patients with PsA include CVD, obesity, metabolic syndrome, hypercholesterolemia, hypertension, diabetes mellitus, chronic kidney disease, malignancy, osteoporosis, non-alcoholic fatty liver disease (NAFLD), and depression. Moreover, some comorbidities such as IBD and ophthalmic disease (e.g. uveitis) might present as extra-articular manifestations of disease.

9.1 Cardiovascular disease

The risk of major adverse cardiovascular events is found to be higher in patients with PsA not prescribed DMARD compared to the general population or those with psoriasis only.[165, 166] Based on clinical evidence and GRAPPA 2020 recommendations, JAKi, ustekinumab, IL-17i, IL-23i, abatacept could be considered as treatment options in the management of PsA patients with comorbid CVD.[123, 167-171] GRAPPA recommends caution with the use of TNFi and GCCs and NSAIDs in patients with CHF.[18]

9.2 Obesity and metabolic syndrome

GRAPPA 2020 recommends that physicians should be cautious about prescribing glucocorticoids to patients with metabolic syndrome, and methotrexate to patients with obesity and metabolic syndrome.[123, 135]

9.3 Hypercholesterolemia

Expert panel emphasized on importance of lipid-lowering drugs and nutritionist referral in PsA patients with comorbid hypercholesterolemia. Evidence suggests that tofacitinib should be used with caution in PsA patients with comorbid hypercholesterolemia.[172]

9.4 Hypertension

Statins, angiotensin-converting enzyme inhibitors, and/or angiotensin II blockers are preferred treatment options in patients with PsA and hypertension.[18] Caution should be taken when prescribing NSAIDs, cyclo-oxygenase-2 (COX-2) inhibitors, or prednisone, as they are associated with an increased risk of CVD.[18, 173]

9.5 Diabetes Mellitus

The prevalence of type 2 diabetes mellitus in patients with PsA has been reported to be between 6.1 to 20.2% with a higher risk noted in women with more severe forms of PsA.[174] When selecting the treatment for PsA in such patients, most guidelines recommend taking caution with GCCs and methotrexate, as they could worsen glycemic homeostasis and/or influence cardiovascular risk factors such as arterial hypertension.[18, 20]

9.6 Inflammatory bowel disease

There is increased prevalence of IBD and subclinical bowel inflammation among patients with PsA.[175, 176] Sulfasalazine, TNFi, and tofacitinib (only ulcerative colitis) are approved treatments for IBD. According to 2018 ACR/NPF guidelines, for patients with active PsA and concomitant active IBD who are DMARD-naïve, monoclonal TNFi are the preferred choice.[20] In patients who are contraindicated for TNFi, IL-12/23i can be prescribed. The use of NSAIDs and IL-17i should be avoided, as they may exacerbate IBD symptoms.[177-179] Interim analysis reports from a phase II study suggests that guselkumab could be effectively used in patients with Crohn's disease.[180] A long-term study on the efficacy of adalimumab in the treatment of patients with Crohn's disease with intolerance or inadequate response to infliximab reported sustained clinical remission and response with adalimumab maintenance therapy.[180]

9.7 Uveitis

The management of concomitant uveitis in PsA patients varies depending on the severity of the disease and its impact on daily activities.[181] Both infliximab and adalimumab are effective treatment options;[182-184] certolizumab/golimumab has shown moderate success, while etanercept has demonstrated only limited success.[185] Secukinumab showed promising results in phase II clinical trials; however, it did not meet the primary efficacy endpoint in the phase III study.[186, 187]

The efficacy of IL-17i, IL-12/23i, and JAK/STAT inhibitors is currently under evaluation.[186, 187]

9.8 Depression

The prevalence of depression and anxiety among patients with PsA is 9% to 36% and 15% to 30%, respectively.[188, 189] As both depression and anxiety may affect pain perception, QoL, and treatment outcomes, it is important to take appropriate screening measures and treatment decisions in such patients. Apremilast should be used with caution in patients with PsA and comorbid depression.[190]

9.9 Hyperuricemia and gout

Hyperuricemia is common in patients with PsA, especially in those with longer CVD, metabolic syndrome, and disease duration.des It is therefore important to regularly monitor serum uric acid levels in patients with PsA.[191] Gout is an important differential diagnosis of PsA and, therefore, awareness about its increased incidence in this population is critical.[178]

9.10 Hypothyroidism

Due to increased incident cases of hypothyroidism, thyroid dysfunction, positive AbTPO, and appearance of a hypoechoic thyroid pattern in patients with PsA, especially women, it is important to evaluate AbTPO levels, thyroid function, and thyroid, with regular follow-up visits.[192, 193]

9.11 Osteoporosis

Screening for osteoporosis in psoriatic patients is performed by measuring bone mineral density through dual-energy X-ray absorptiometry (DEXA) or assessing the Fracture Risk Assessment (FRAX) score. For management, specific guidelines should be followed for patients treated with chronic systemic glucocorticoids, as it may modify bone mineral density due to bone loss.[194]

9.12 Malignancy

Given the potential risk of de novo or recurrent malignancy being associated with the use of anti-TNF, regular screening is recommended, especially in patients with a history of cancer.18 In contrast, IL-17i, abatacept have a better safety profile for malignancy and are preferred treatment options in these patients.

9.13 Fatty liver disease

Liver disease, particularly NAFLD, has an increased prevalence in patients with psoriasis and PsA.[195] Given the potential risk of liver damage with specific PsA treatments, regular monitoring of liver function abnormalities is deemed necessary. Liver biopsy should also be considered, based on the presence or absence of risk factors for hepatotoxicity and cumulative methotrexate dose.[18, 20] Furthermore, caution should be taken when prescribing methotrexate, leflunomide, sulfasalazine, and NSAIDs in patients with established liver disease due to the increased risk of hepatotoxicity.

9.14 Chronic kidney disease

Methotrexate should be avoided in patients with significant renal insufficiency or end-stage renal disease on hemodialysis, given that renal impairment is a major risk factor for developing methotrexate toxicity.[196] NSAIDs should also be avoided, given that they may increase the risk for acute kidney injury.[197]

9.15 Serious infections

There is a high risk of serious infections, including tuberculosis, hepatitis, and HIV, associated with the use of certain PsA treatments—including TNF inhibitors.18 Due to the low incidence of serious infections observed with IL-12/23i, IL-17i, and abatacept in comparison to anti-TNFs, the former are preferred treatment options for PsA.[18]

9.16 Immunization

Immunization status of the patient should be assessed. Routine vaccination for pertussis and inactivated influenza, pneumococcal, and HBV (in high-risk patients and in highly prevalent regions) should be performed at baseline.[18]

Consensus statements on the management of comorbidities in patients with PsA are presented in Table 9.

Table 9: Consensus Statements on Management of Comorbidities

COMORBID CONDITION/S	TREATMENT OPTIONS/REFERRAL/ MONITORING	TREATMENT REQUIRING CAUTION
Cardiovascular disease and congestive heart failure	JAKi, ustekinumab, IL-17i, IL-23i, abatacept[167-170]	NSAIDs, GCCs, TNFi (TNFi should be avoided in patients with severe CHF [NYHA classes III and IV] and should be used with caution in patients with mild CHF [NYHA classes I and II])[18, 123, 198, 199]
Obesity and metabolic syndrome	Weight reduction, nutritionist referral, obesity/endocrine clinic referral	MTX, GCCs[18]
Hypercholesterolemia	Lipid-lowering agents, nutritionist referral	Tofacitinib[172]
Hypertension	Statins, angiotensin-converting enzyme inhibitors, and/or angiotensin II blockers[18]	NSAIDs, GCCs[18]
Diabetes mellitus	Hypoglycemic medications	MTX, GCCs[18]
IBD	TNFi (excluding etanercept) for UC (tofacitinib, IL-12/23i) IL23i[179]	IL-17i
Uveitis	TNFi (especially adalimumab and infliximab), MTX	NSAIDs, IL-17i[200]
Depression	Psychiatry referral	Apremilast
Hyperuricemia and Gout	Monitoring serum uric acid levels Urate-lowering therapy	
Thyroid disease	Routine thyroid tests/endocrine referral	
Osteoporosis	Monitor with DEXA as indicated in non-PsA patients	GCCs
Malignancy	Oncology referral, IL-17i, abatacept	All biological agents
Fatty liver disease	GI referral, Weight loss, Dietician referral	NSAIDs, SSZ, MTX, LEF, Tofacitinib[24]
Chronic kidney disease	Nephrologist referral	NSAIDs, MTX[123]
HBV	Ustekinumab GI referral, monitor Hep B PCR (once in a month for first 3 months and every 3 months thereafter)[201]	NSAIDs, MTX, LEF, biologics (for carriers)[123]
HCV	GI referral, monitor Hep C PCR (once in every 3-6 months)[201]	NSAIDs, MTX, LEF biologics (for carriers)[123]
Tuberculosis	IL-17i, abatacept, referral to respiratory physician or infectious disease specialist	TNFi, especially infliximab

CHF: Congestive heart failure; DEXA: Dual-energy X-ray absorptiometry; HBV: Hepatitis B virus; HCV: Hepatitis C virus; GCCs: Glucocorticoids; GI: Gastrointestinal; IL-12/23i: Interleukin-12/23 inhibitor; IL-17i: Interleukin-17 inhibitor; IL-23i: Interleukin-23 inhibitor; JAKi: Janus kinase inhibitor; LEF: Leflunomide; MTX: Methotrexate; NSAIDs: Non-steroidal anti-inflammatory drugs; NHYA: New York Heart Association; SSZ: Sulfasalazine; TNFi: Tumor necrosis factor inhibitor; PCR: Polymerase chain reaction.

10. Conclusion

The present consensus statements are in corroboration to established global guidelines on the different aspects of PsA, especially highlighting the evaluation, management and monitoring of therapies in patients with PsA. There is a scarcity of such consensus-based statements in the Arab world. Furthermore, present consensus statements are aligned with the most recently published Saudi consensus recommendations.[202] This consensus recommendation can help the physicians and healthcare professionals in UAE to make informed treatment decisions, improvise treatment strategies, monitor therapies, as well as effectively manage comorbidities in patients with PsA.

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