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**ABSTRACT. Objective.** Psoriatic arthritis (PsA) is chronic disease that compromises multiple domains and might be associated with progressive joint damage, increased mortality, functional limitation, and considerably impaired quality of life. Our objective was to generate evidence-based recommendations on the management of PsA in Pan American League of Associations for Rheumatology (PANLAR) countries.

**Methods.** We used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)-ADOLPMENT approach to adapt the 2019 recommendations of the European Alliance of Associations for Rheumatology. A working group consisting of rheumatologists from various countries in Latin America identified relevant topics for the treatment of PsA in the region. The methodology team updated the evidence and synthesized the information used to generate the final recommendations. These were then discussed and defined by a panel of 31 rheumatologists from 15 countries.

**Results.** These guidelines report 15 recommendations addressing therapeutic targets, use of antiinflammatory agents and corticosteroids, treatment with disease-modifying antirheumatic drugs (conventional synthetic, biologic, and targeted synthetic), therapeutic failure, optimization of biologic therapy, non-pharmacological interventions, assessment tools, and follow-up of patients with PsA.

**Conclusion.** Here we present a set of recommendations to guide decision making in the treatment of PsA in Latin America, based on the best evidence available, considering resources, medical expertise, and the patient's values and preferences. The successful implementation of these recommendations should be based on clinical practice conditions, healthcare settings in each country, and a tailored evaluation of patients.

*Key Indexing Terms:* practice guideline, psoriatic arthritis, treatment

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Psoriatic arthritis (PsA) is a chronic inflammatory heterogeneous disease characterized by the involvement of different domains including the skin, nails, peripheral joints, digits, entheses, axial skeleton, eyes, and bowel. The incidence of PsA is approximately 6 per 100,000 individuals per year, and the prevalence is approximately 1 per 1000 in the general population.<sup>1-3</sup> The annual incidence of PsA in patients with psoriasis (PsO) is approximately 2.7%,<sup>4-8</sup> and the reported prevalence in this group ranges from 6% to 41%.<sup>9,10</sup>

PsA is associated with poor health-related quality of life, and more active disease leads to progressive joint damage, higher mortality, and limitations in the activities of daily living. The clinical burden increases direct costs through the use of care resources and indirect costs through disability and lost productivity. Delay in diagnosis and treatment are associated with damage progression and poorer quality of life.<sup>11,12</sup> Therefore, timely identification of PsA and early initiation of treatment play a key role in improving long-term outcomes, as does the need to improve the information provided to patients with respect to their treatment options.<sup>13</sup>

In the last few years, many new drugs and new mechanisms of action have been incorporated into the treatment of PsO and

PsA, and new long-term information on older drugs has become available.<sup>14</sup> These new treatment options and new long-term information require frequent evaluation of their role in the effective management of PsA. Many countries in Latin America have developed national recommendations on the management of PsA,<sup>15-20</sup> and in the context of regions with limited resources, an international working group led by the International League of Associations for Rheumatology (ILAR) adapted existing recommendations from other groups.<sup>21</sup> All these issues clearly highlight the relevance of these recommendations from Pan American League of Associations for Rheumatology (PANLAR), considering the need to incorporate viewpoints from several countries in the region to ensure a joint vision that will enable us to harmonize therapy. These recommendations are evidence-based and were developed with the aim to inform decisions on therapy in PsA for physicians, healthcare professionals, rheumatologists, and policy decision makers in PANLAR countries.

## METHODS

*Objectives.* To provide an evidence-based framework to guide healthcare professionals treating patients > 18 years with PsA in Latin America. The scope of the guidelines is limited to recommendations regarding the use of

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pharmacological and nonpharmacological treatment for arthritis, enthesitis, dactylitis, and axial involvement.

*Areas not covered by these recommendations.* Diagnosis and other aspects of the management of patients with PsA (eg, immunizations, clinical monitoring, prognosis, pregnancy) are not covered. Because these guidelines were developed by rheumatologists without the involvement of dermatologists, treatment of the skin was not specifically addressed but rather was mentioned only when related to musculoskeletal involvement.

*Target audience.* The target audience of these guidelines are healthcare providers who are involved in the management of patients with PsA. This may include rheumatologists, dermatologists, internists, primary care providers or general practitioners, specialty pharmacists, and physicians in other specialties who may find this information useful.

*Stakeholder involvement.* These guidelines were drawn up and endorsed by PANLAR and were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)-ADOLOPMENT framework,<sup>22</sup> in a process led by a GRADE working group. The working group was divided into different teams (Supplementary Material, Section A, available with the online version of this article).

A systematic literature review was performed to update the evidence supporting the “EULAR recommendations for the management of PsA with pharmacological therapies: 2019 update”<sup>23</sup> (Supplementary Material, Sections B and C, available with the online version of this article; Table 1).<sup>23-25</sup>

A multidisciplinary panel of 31 experts comprising rheumatologists and epidemiologists defined the scope of these guidelines, generated the PICO (Patient/Population – Intervention – Comparison/Comparator – Outcome) questions (Supplementary Material, Section D, available with the online version of this article), and voted on the recommendations.

The multidisciplinary panel including 3 patient representatives discussed the recommendation. Patients were invited to attend recommendation voting meetings. They contributed their points of view, values, and preferences, thus enriching the discussion by the experts, as is done in the GRADE-ADOLOPMENT methodology (Supplementary Material, Section E, available with the online version of this article). A central review

committee comprising 6 experts and/or methodological experts verified and validated the specific processes of the development of the guidelines to ensure their proper implementation.

*Literature search.* A systematic literature search for published randomized controlled trials (RCTs), nonrandomized trials, cohort studies, posthoc analyses, and pooled analyses was conducted in MEDLINE/PubMed and the Cochrane Library, from the beginning of each database to November 2021. The grey literature, materials, and research produced by organizations outside of the traditional commercial or academic publishing and distribution channels were also evaluated (Supplementary Material, Section B, available with the online version of this article).

*Study selection.* We performed duplicate screening of each title and abstract using 2 independent reviewers, with a third reviewer resolving potential conflicts. Eligible articles underwent full-text screening by 2 independent reviewers. Selected manuscripts were matched to PICO questions (Supplementary Material, Section D, available with the online version of this article).

*Data extraction and analysis.* Data for the statistical analysis were pooled using Stata 16 software (StataCorp). The quality of RCTs was assessed using the Cochrane risk-of-bias tool (<http://handbook.cochrane.org/>). For non-RCTs, the assessment was performed using the Newcastle-Ottawa scale.<sup>26</sup>

*Rigor of development.* These guidelines were developed following GRADE-ADOLOPMENT methodology and are consistent with the Application of the Appraisal of Guidelines for Research and Evaluation (AGREE) Reporting Checklist to ensure the completeness and transparency of reporting in practice guidelines.<sup>27</sup>

In keeping with the GRADE methodology, 4 members of the panel of experts (ERS, DFGA, WBM, and MLB) drafted the recommendations for the different clinical questions. Recommendations were presented to the panel of experts, modified if needed, and voted upon (using a 1-9 scale, where 1 indicated strong disagreement and 9 strong agreement). All recommendations required  $\geq 70\%$  level of agreement at the voting stage (agreement was considered as a score  $\geq 7$ ). Each recommendation was developed

Table 1. Definition of terms.

Term	Definition
Mild disease <sup>a</sup>	$\leq 4$ joints (oligoarticular disease), reduced disease activity according to composite scores, and/or limited skin involvement
Polyarticular disease <sup>a</sup>	$\geq 5$ active joints (swollen)
Relevant cutaneous involvement <sup>a</sup>	Extensive involvement based on body surface ( $> 10\%$ ) or patient perspective (eg, more limited psoriasis with a significant impact on quality of life, such as in face/hands/feet/genitals) Corresponds with moderate-to-severe psoriasis
Factors indicating poor prognosis in PsA <sup>a</sup>	Structural damage, high ESR/CRP, dactylitis, or nail involvement
csDMARDs	Leflunomide, methotrexate, sulfasalazine
tsDMARDs	JAKi (tofacitinib, upadacitinib), apremilast
Biologics	TNFi (adalimumab, certolizumab, golimumab, etanercept, infliximab) IL inhibitors (ixekizumab, secukinumab, ustekinumab, risankizumab, guselkumab) Others (abatacept, rituximab, tocilizumab)
Biosimilars	A biologic product that, despite small differences in clinically inactive components, is <i>very similar</i> to the existing approved reference product, with no <i>clinically significant differences</i> in terms of <i>safety, purity, and potency</i> <sup>24,25</sup>

<sup>a</sup> Definitions taken from the EULAR 2019 guidelines.<sup>23</sup> CRP: C-reactive protein; csDMARD: conventional synthetic DMARD; DMARD: disease-modifying antirheumatic drug; ESR: erythrocyte sedimentation rate; EULAR: European Alliance of Associations for Rheumatology; IL: interleukin; JAKi: Janus kinase inhibitor; PsA: psoriatic arthritis; TNFi: tumor necrosis factor inhibitor; tsDMARD: targeted synthetic DMARD.

taking into account the risk-benefit ratio and the quality of the evidence available for each intervention was considered. A recommendation could be either in favor of or against the proposed intervention and be qualified as being either strong or conditional (ie, weak).

*Disclosures and conflicts of interest.* Relevant conflicts of interest were those occurring within 12 months prior to and during the development of these guidelines.

*Data sharing.* Information about these guidelines will be available on the PANLAR website (<https://www.panlar.org/>). Upon request, explanatory tables will be available free of charge to any physician. Materials for patients will be developed and made available on the PANLAR website.

*Guidelines updates.* PANLAR plans to update these guidelines on regular basis. Initially, an online update on PANLAR's website is planned in 2 years.

## RESULTS

The literature search flow chart is in the Supplementary Material, Section C (available with the online version of this article). A definition of terminology regarding disease concepts is shown in Table 1, and all current recommendations are provided in Table 2. In addition, an algorithm for pharmacological management of patients with a diagnosis of PsA is proposed in the Figure.

### Therapeutic targets in PsA

*Recommendation 1.* It is strongly recommended that treatment of PsA should aim to achieve the lowest level of activity in all disease domains by means of regular, multidisciplinary evaluation and appropriate adjustments of treatment. This recommendation is in accordance with the treat-to-target principle<sup>28</sup> and is supported by the Tight Control of Psoriatic Arthritis (TICOPA) study.<sup>29</sup> Two important points in this recommendation are the aim to achieve the target in all disease domains and the recommendation of multidisciplinary assessment. As there is no consensus on a definition of remission or low disease activity (LDA) in PsA,<sup>30</sup> the panel decided not to recommend any measurement in particular. To date, the 2 most frequently used tools are minimal disease activity (MDA) and Disease Activity Index for Psoriatic Arthritis (DAPSA), which have also been recommended by a consensus document of the Spanish Society of Rheumatology and the Mexican College of Rheumatology.<sup>31</sup> The patient's expectations and needs should be considered when setting treatment goals in PsA.

### Nonsteroidal antiinflammatory drugs (NSAIDs) in PsA

*Recommendation 2.* NSAIDs are strongly recommended in adults with PsA only to alleviate musculoskeletal signs and symptoms at any stage of the disease. This recommendation was adapted from the EULAR source guideline.<sup>23</sup> Available evidence has shown the efficacy of nonsteroidal antiinflammatory drugs (NSAIDs) in the treatment of pain, morning stiffness, and joint inflammation in patients with PsA. They have proven neither to be efficacious for other manifestations of the disease nor to reduce disease progression. Consequently, the expert panel strongly recommends the use of NSAIDs in PsA solely for management of symptoms and emphasizes that treatment with NSAIDs should be accompanied by disease-modifying antirheumatic drugs (DMARDs) to control joint disease damage and other domains of the disease.

Of note, the risk-benefit ratio of NSAIDs must also be carefully evaluated, especially in patients with renal and cardiovascular (CV) comorbidity.

### Corticosteroids (CS) in PsA

*Recommendation 3.* Local CS injections are conditionally recommended as adjuvant therapy in patients with PsA, and systemic CS are conditionally recommended to be used with caution at the lowest effective dose and for as short a period as possible. Evidence on the use of local corticosteroid (CS) injections in patients with PsA is scarce. A reduction in pain for up to 3 months is generally observed with intraarticular injection in patients with monoarthritis/oligoarthritis, dactylitis (tendon sheath injection),<sup>32,33</sup> and enthesitis<sup>34</sup> (eg, in the elbow or retrocalcaneal bursa in Achilles tendon enthesitis).<sup>35</sup> The panel conditionally recommends its use in these cases.

No RCTs on the use of systemic CS in PsA were identified. However, a systematic review of observational studies reported that approximately 35% of patients with PsA are treated with systemic CS, showing a clinical benefit and low rates of exacerbation of PsO.<sup>36</sup> In some areas of the region, there are barriers to access to biologic therapy. Therefore, the expert panel considers that systemic CS can be used at low doses and for short periods when it is necessary to achieve a rapid antiinflammatory effect or as bridging therapy until the patient can be prescribed biologic therapy.

### Conventional synthetic DMARDs in PsA

*Recommendation 4.* In patients with active PsA and polyarthritis, the panel strongly recommends the use of methotrexate (MTX) or leflunomide (LEF). MTX should be preferred in cases of relevant cutaneous involvement. Also, MTX or LEF are strongly recommended in adults with PsA with monoarthritis or oligoarthritis, especially in those whose prognosis is poor. Evidence for the use of conventional synthetic DMARDs (csDMARDs) in PsA is scarce and of poor quality. Evidence for the efficacy of methotrexate (MTX) in PsA comes from a few RCTs,<sup>37,38</sup> with small samples and observational studies.<sup>39-44</sup> The results of the RCTs<sup>37,38</sup> and of the observational studies<sup>39-44</sup> suggest that MTX can provide a clinically significant benefit in terms of function, pain, and patient and physician global assessment in all disease domains, including enthesitis and dactylitis.

Leflunomide (LEF) has proven efficacious for PsA in RCTs and observational studies.<sup>45,46</sup> Comparative evidence, which is of poor quality, indicates that this agent can be as efficacious as MTX and more efficacious than cyclosporine A (CSA).<sup>47-49</sup>

Evidence for other csDMARDs is scarce and inconsistent. An open-label, prospective randomized study comparing the efficacy of sulfasalazine (SSZ) and CSA for treatment of PsA<sup>50</sup> found a statistically significant difference in favor of CSA in pain scores (main outcome), although no significant differences were reported for the remaining disease activity outcome measures.

Although evidence in favor of csDMARDs is scarce, the experts strongly recommend initial treatment with MTX or LEF based on the widespread use of these agents in clinical practice, their low cost, and their availability throughout the region.

Table 2. PANLAR 2022 recommendations for the treatment of PsA.

Category	Recommendation	Strength and Direction	Level of Evidence	Level of Agreement (1-9), mean
Therapeutic targets	1. It is strongly recommended that treatment of PsA should aim to achieve the lowest level of activity in all disease domains by means of regular, multidisciplinary evaluation and appropriate adjustments of treatment.	Strong in favor	Moderate	8.8
NSAID use	2. NSAIDs are strongly recommended in adults with PsA only to alleviate musculoskeletal signs and symptoms at any stage of the disease.	Strong in favor	Moderate	8.4
CS use	3. Local CS injections are conditionally recommended as adjuvant therapy in patients with PsA, and systemic CS are conditionally recommended to be used with caution at the lowest effective dose and for as short a period as possible.	Conditional in favor	Very low	8.3
csDMARD use	4. In patients with active PsA and polyarthritis, the panel strongly recommends the use of MTX or LEF. MTX should be preferred in cases of relevant cutaneous involvement. Also, MTX or LEF are strongly recommended in adults with PsA with monoarthritis or oligoarthritis, especially in those whose prognosis is poor.	Strong in favor	Very low/low	8.7
bDMARD and tsDMARD use	5. Combination of MTX and LEF is conditionally recommended in adults with active peripheral arthritis in whom biologic, JAKi, and apremilast therapy are contraindicated or not available.	Conditional in favor	Low	8.2
	6. A bDMARD, JAKi, or PDE4i are strongly recommended in patients with PsA and peripheral involvement (arthritis and/or dactylitis) and an inadequate response to at least 1 csDMARD.	Strong in favor	Moderate	8.7
	7. A bDMARD, JAKi, or PDE4i is strongly recommended in patients with PsA and enthesitis and an insufficient response to NSAIDs or CS injections.	Strong in favor	Moderate	8.5
	8. A bDMARD (TNFi or IL-17i) or a JAKi is strongly recommended in patients with PsA and predominantly active axial disease and an insufficient response to NSAIDs. An IL-17i should be preferred in cases of relevant cutaneous involvement.	Strong in favor	Moderate	8.8
	9. Monotherapy with biologics is strongly recommended. It is also strongly recommended to suspend csDMARDs in patients on combination therapy.	Strong in favor	Low	8.4
Biosimilar use	10. Switching to another biologic or cycling to another biologic of the same class, a JAKi, or a PDE4i is strongly recommended in adults with PsA and peripheral arthritis, enthesitis, and/or dactylitis and intolerance or incomplete response to a bDMARD.	Strong in favor	Low	8.6
	11. Biosimilars are strongly recommended as an option in adults with PsA requiring biologic therapy.	Strong in favor	Low	8.8
Optimization of biologic therapy	12. It is strongly recommended that gradual dose reduction or extension of the dosing interval should be considered in adults with PsA in remission or MDA receiving biologics and in whom all domains of the disease have been adequately controlled for at least 1 year.	Strong in favor	Low	8.4
Exercise and rehabilitation	13. Tailored physical exercise should be encouraged throughout the disease course as part of the integrated care provided to patients with PsA.	Strong in favor	Low	8.7
Assessment tools	14. It is conditionally recommended that disease activity in PsA should be assessed using the DAPSA score and MDA, and when axial involvement is present ASDAS score should be used.	Conditional in favor	Low	8.8
Imaging	15. Conventional radiography, ultrasound, and MRI are the conditionally recommended tools for follow-up of disease activity and structural damage in PsA.	Conditional in favor	Low	8.1

ASDAS: Ankylosing Spondylitis Disease Activity Score; bDMARD: biologic DMARD; CS: corticosteroid; csDMARD: conventional synthetic DMARD; DAPSA: Disease Activity Index for Psoriatic Arthritis; DMARD: disease-modifying antirheumatic drug; IL-17i: interleukin 17 inhibitor; JAKi: Janus kinase inhibitor; LEF: leflunomide; MDA: minimal disease activity; MRI: magnetic resonance imaging; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug; PANLAR: Pan American League of Associations for Rheumatology; PDE4i: phosphodiesterase-4 inhibitor; PsA: psoriatic arthritis; tsDMARD: targeted synthetic DMARD.

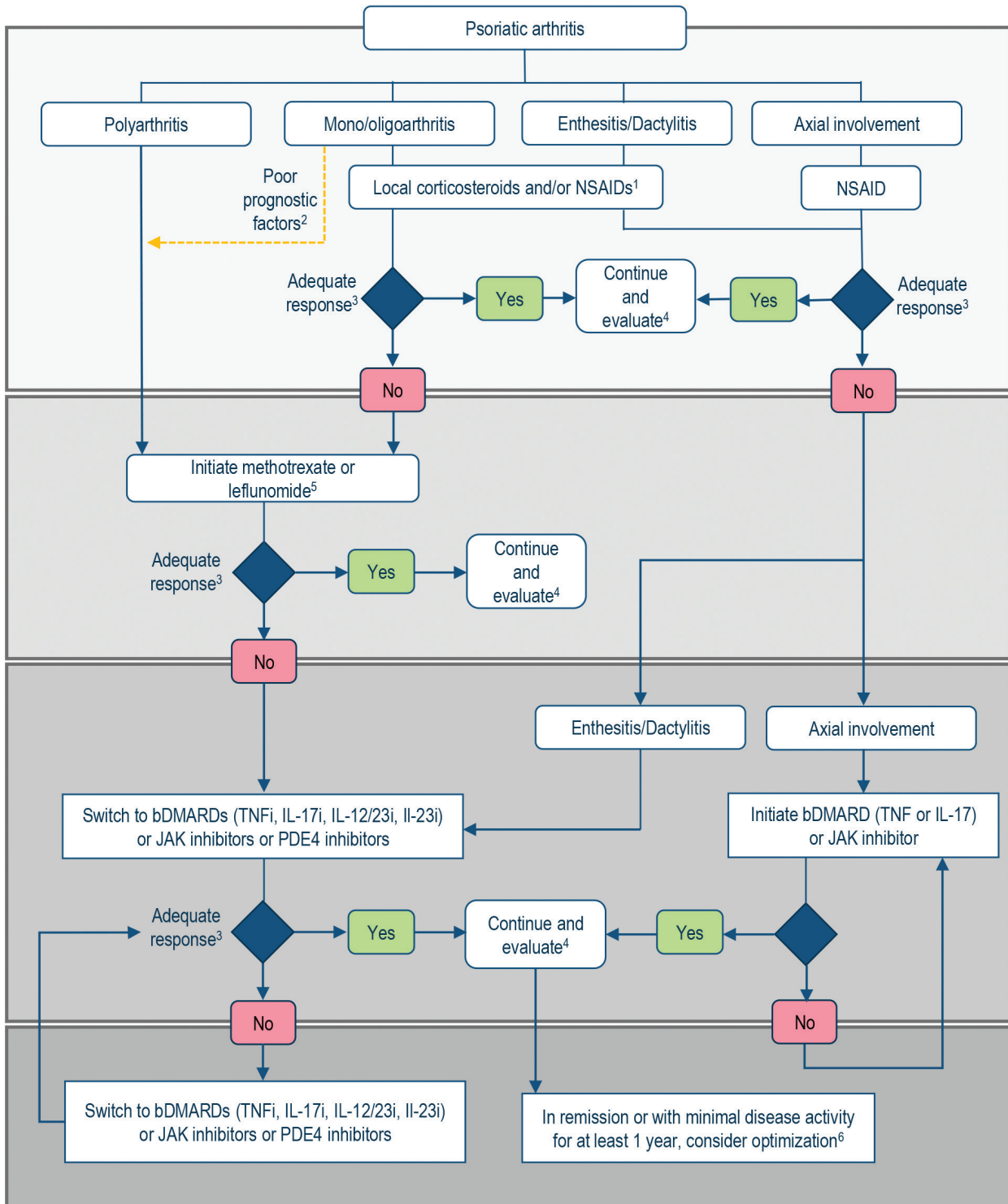


Figure. Algorithm for management of pharmacologic therapy in psoriatic arthritis. <sup>1</sup> Use systemic corticosteroids with caution at the lowest effective dose and for as short a period as possible. <sup>2</sup> Poor prognostic factors in PsA include structural damage, high erythrocyte sedimentation rate/C-reactive protein value, dactylitis, and nail involvement. <sup>3</sup> Remission or low disease activity. <sup>4</sup> Regular monitoring with DAPSA and MDA; use ASDAS in cases of mainly axial involvement. <sup>5</sup> Preferred in cases of relevant cutaneous involvement (moderate-to-severe psoriasis). <sup>6</sup> Consider gradual reduction in the dose of the biologic or extending the dosing interval. ASDAS: Ankylosing Spondylitis Disease Activity Score; bDMARD: biologic disease-modifying antirheumatic drug; DAPSA: Disease Activity Index for Psoriatic Arthritis; IL-17i: interleukin 17 inhibitor; JAK: Janus kinase; MDA: minimal disease activity; NSAID: nonsteroidal antiinflammatory drug; PDE4: phosphodiesterase-4; TNFi: tumor necrosis factor inhibitor.

The experts do not consider SSZ to be sufficiently efficacious for treatment of PsA. The panel considers CSA to have an unfavorable risk-benefit ratio, primarily due to its potential to cause hypertension and kidney failure, requiring more frequent monitoring. Therefore, it should only be used if MTX or LEF cannot be used and for a limited period of 12 to 24 months.

For patients with monoarthritis or oligoarthritis who have not responded to local treatment, the panel suggests initiating treatment with csDMARDs. This is especially recommended for patients who exhibit poor prognostic factors, such as elevated acute-phase reactants, dactylitis, and/or nail involvement. Without proper treatment, these patients may develop polyarthritis over time.

*Recommendation 5. Combination of MTX and LEF is conditionally recommended in adults with active peripheral arthritis in whom biologic, Janus kinase inhibitor, and apremilast therapy are contraindicated or not available.* The evidence for this recommendation comes mainly from 3 RCTs.<sup>29,48,51</sup> An open-label controlled trial performed at 2 centers compared the combination of MTX and LEF with both agents in monotherapy at 24 weeks. At the end of follow-up, tender joint count, swollen joint count, patient global assessment, and physician global assessment improved significantly compared with baseline ( $P < 0.05$ ). The percentage of patients who fulfilled the Psoriatic Arthritis Response Criteria (PsARC) in the MTX, LEF, and combination group was 75%, 68.8%, and 83.3%, respectively, and the percentage of patients who achieved American College of Rheumatology 20% improvement (ACR20) was 66.7%, 50%, and 83.3%, respectively. The improvement in pain and Health Assessment Questionnaire (HAQ) score was better in the combination group than in the group taking LEF only. The incidence of treatment-related adverse events was 38.5% for MTX, 38.9% for LEF, and 35% for the combination group.<sup>48</sup>

In the Canadian Humira Post Marketing Observational Epidemiological Study Assessing Effectiveness in Psoriatic Arthritis (COMPLETE-PsA) trial, MTX plus LEF combination therapy was superior to MTX monotherapy at week 16 (Psoriatic Arthritis Disease Activity Score [PASDAS] 3.1 [SD 1.4] vs 3.7 [SD 1.3]), although combination therapy was less tolerated than MTX monotherapy.<sup>51</sup>

Indirect evidence from the TICOPA trial points to the efficacy of the combination of both MTX and LEF. However, the strength of the evidence is low owing to factors such as uncontrolled bias between the groups in the treatment administered.<sup>29</sup>

The panel believes that, despite the low degree of evidence, combination therapy with csDMARDs (MTX and LEF) is justified in patients for whom biologics and/or Janus kinase inhibitors (JAKi) and/or apremilast are contraindicated or not available.

### **Biologic DMARDs (bDMARDs) and targeted synthetic DMARDs in PsA**

*Recommendation 6. A bDMARD, JAKi, or phosphodiesterase-4 inhibitor are strongly recommended in patients with PsA and peripheral involvement (arthritis and/or dactylitis) and an inadequate response to at least 1 csDMARD. JAKi are condition-*

*ally recommended after csDMARD failure when bDMARDs are contraindicated or unavailable in patients aged > 65 years with a history of smoking or risk factors for CV disease or malignancy.* Compared with placebo, tumor necrosis factor inhibitors (TNFi), interleukin-12/23 inhibitors (IL-12/23i), IL-23i, IL-17i, and phosphodiesterase-4 inhibitors (PDE4i) have shown to be efficacious and safe for the treatment of peripheral arthritis in patients with PsA in RCTs and observational studies, and showed favorable long-term safety.<sup>52</sup> Head-to-head trials of IL-17i vs TNFi showed similar efficacy of ixekizumab (IXE) and secukinumab (SEC) with adalimumab (ADA) for musculoskeletal manifestations.<sup>53-55</sup> Due to the lack of head-to-head trials among treatment options, the panel intentionally refrained from recommending an order between these treatments that have different targets.

Although the JAKi tofacitinib was reported to have a higher risk of CV events, as well as increased risk for malignancies, compared with a TNFi in patients with rheumatoid arthritis aged  $\geq 50$  years and with at least 1 CV risk factor,<sup>56</sup> the panel strongly recommends JAKi after csDMARD failure. This recommendation is made considering that PsA is a different disease, and no increased incidence has been observed in the long-term follow-up of RCT and observational studies with JAKi. However, we also conditionally recommend (expert opinion) that in patients  $\geq 65$  years old with a history of smoking or risk factors for CV disease or malignancy, JAKi should be used only if no suitable alternatives exist. The treating physician should also consider warnings by some regulatory agencies in the Americas.

*Recommendation 7. A bDMARD, JAKi, or PDE4i is strongly recommended in patients with PsA and enthesitis and an insufficient response to NSAIDs or CS injections.* Indirect evidence did not reveal differences between IXE and SEC vs ADA for the resolution of enthesitis and dactylitis in patients with PsA.<sup>53-55</sup> A study comparing ustekinumab (UST) with TNFi reported favorable results for UST; however, since the data are from a low-quality study with a small sample size, the results should be interpreted with caution.<sup>57</sup> Based on data from a classic meta-analysis, it was found that the relative risk (RR) for resolution of enthesitis compared with placebo was 2.31 (95% CI 1.60-3.34) for IL-17i, 1.99 (95% CI 1.36-2.90) for TNFi, and 1.41 (95% CI 1.02-1.95) for UST.<sup>58</sup> The same caution should be exercised with JAKi in patients with enthesitis and high CV or cancer risk, as recommended in patients with peripheral disease.

*Recommendation 8. A bDMARD (TNFi or IL-17i) or a JAKi is strongly recommended in patients with PsA and predominantly active axial disease and an insufficient response to NSAIDs. An IL-17i should be preferred in cases of relevant cutaneous involvement.* Data on the efficacy of biologics in axial disease in patients with PsA are scarce. Only 1 study to date has addressed these patients specifically. The Managing Axial Manifestations in Psoriatic Arthritis With Secukinumab (MAXIMIZE) trial, which evaluated the efficacy and safety of SEC in this population, recorded a significant improvement in the signs and symptoms of axial disease compared with placebo.<sup>59</sup>

Evidence for TNFi and JAKi comes mainly from studies in axial spondyloarthritis. IL-23i are not recommended as risankizumab failed in ankylosing spondylitis.<sup>60</sup> However, they were not recommended against, as a posthoc analysis of pivotal trials in PsA showed that they might work in this domain.<sup>61</sup> As IL-17i have shown superior efficacy in skin than TNFi in a head-to-head RCT in PsO and PsA,<sup>54</sup> IL-17i are strongly recommended when the skin involvement is extensive.

The same caution should be exercised in patients with axial disease and high CV or cancer risk, as suggested in recommendations 6 and 7 regarding JAKi.

*Recommendation 9. Monotherapy with biologics is strongly recommended. It is also strongly recommended to suspend csDMARDs in patients on combination therapy.* The panel identified 4 clinical trials that evaluated the combination of csDMARDs with TNFi agents,<sup>42,62-64</sup> 3 with IXE,<sup>62,65,66</sup> 1 with SEC,<sup>55</sup> and 2 with UST.<sup>67,68</sup> Biologics combined with csDMARDs do not generally imply an increase in the ACR20, ACR50, or ACR70 response rates at 24 and 48 weeks. However, the studies were highly heterogeneous.

As for safety, the risk of adverse events was higher in patients receiving combination therapy than in those receiving monotherapy.<sup>69</sup> Three clinical trials reported development of anti-drug antibodies for infliximab (IFX), ADA, and etanercept (ETN).<sup>42,64,70</sup> The results indicate that combination therapy can decrease the risk of developing antidrug antibodies. It is noteworthy that evidence for this outcome is indirect, since the studies selected included patients with plaque PsO.<sup>42,64,68-73</sup>

Based on the scarce evidence available, there is no reason to combine csDMARDs and bDMARDs, since the clinical effect of reducing immunogenicity remains uncertain, and no clear additional benefits have been shown beyond monotherapy with bDMARDs.

*Recommendation 10. Switching to another biologic or cycling to another biologic of the same class, a JAKi, or a PDE4i is strongly recommended in adults with PsA and peripheral arthritis, enthesitis, and/or dactylitis and intolerance or incomplete response to a bDMARD.* In patients with PsA whose first TNFi agent failed, placebo-controlled clinical trials reported biologics and JAKi to be efficacious. Despite there being no RCT with TNFi in patients failing a first TNFi, observational data suggest that TNFi are still efficacious in patients with an inadequate response or intolerance to TNFi, although with a lower level of efficacy.

Upadacitinib showed similar efficacy in TNFi-naïve and TNFi-experienced patients.<sup>74</sup> An observational study<sup>75</sup> of the clinical efficacy of intraclass switching (ie, to a drug with the same mechanism of action) and interclass cycling (ie, to a drug with a different mechanism of action) in 180 patients treated with the biologics apremilast or tofacitinib found no differences in the retention rate between the 2 strategies (low quality of evidence). Comparisons from a network metaanalysis revealed response rates (ACR20) for tofacitinib 5 mg and 10 mg to be similar to those of other biologic drugs and apremilast. As for the change in HAQ Disability Index (HAQ-DI), all treatments were associated with improvements compared to placebo.<sup>76</sup>

Current data reveal that the response to JAKi and bDMARDs is similar for most outcomes, especially in the case of upadacitinib. In line with the experience of some experts, JAKi can be used before biologics in specific cases and on an individual basis when a bDMARD is not considered appropriate.

### **Biosimilars in PsA**

*Recommendation 11. Biosimilars are strongly recommended as an option in adults with PsA requiring biologic therapy.* The results presented were retrieved from clinical trials in various inflammatory rheumatic diseases that included subgroups of patients with PsA.

We found data on biosimilars of ADA (SDZ-ADL<sup>77</sup> and ZRC 3197<sup>78</sup>), IFX (CT-P13<sup>79</sup>), and ETN (SB4<sup>80</sup>).

In line with the PANLAR consensus statement on biosimilars,<sup>25</sup> the panel considers biosimilars to be an option in patients with PsA who must start biologic therapy. Their use depends on availability and on the criteria of the attending rheumatologist.

### **Optimization of biologic therapy in PsA**

*Recommendation 12. It is strongly recommended that gradual dose reduction or extension of the dosing interval should be considered in adults with PsA in remission or MDA receiving biologics and in whom all domains of the disease have been adequately controlled for at least 1 year.* That biologics should not be suspended in adults with PsA in remission or with MDA who are receiving biologic therapy and in whom all domains of the disease are adequately controlled is also strongly recommended, although both recommendations have low levels of evidence.

Optimization of biologic therapy was addressed in 5 studies: 3 case-control studies,<sup>81-83</sup> 1 cross-sectional study,<sup>84</sup> and 1 open-label longitudinal study.<sup>85</sup> Findings for TNFi agents show that remission was maintained in 35-88% of patients, mainly with ADA and ETN. In those studies where disease activity was evaluated, no differences were reported between the groups that reduced and maintained doses. The patients evaluated had generally been in remission or had MDA for 6-12 months. Interruption of therapy was addressed by 6 observational studies.<sup>86-91</sup> The results include TNFi agents (ADA, ETN, and IFX) and MTX, with remission reported in 11.8-48.5% of cases. Relapses were generally reported within the first 2-5 months after discontinuation.

Based on the information available, the experts consider that gradually reducing bDMARDs seems feasible in patients with PsA in remission or LDA in all domains. In contrast, interrupting bDMARDs seems to be associated with a major risk of relapse. Further, the rheumatologists agreed that a period of > 1 year in remission or LDA would be necessary before considering reducing the dose or dosing interval.

### **Exercise and rehabilitation in PsA**

*Recommendation 13. Tailored physical exercise should be encouraged throughout the disease course as part of the integrated care provided to patients with PsA. Joint management with physical medicine and rehabilitation should be considered for prescription of physical therapy and exercise in adults with PsA.* These recommen-



dations were based on the evidence obtained from a systematic review<sup>92</sup> including 3 clinical trials<sup>93-95</sup> that evaluated the effects of physical activity on joint disease, additional joint symptoms, and general well-being. Exercise improved the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), general symptoms (pain and fatigue), and quality of life. Improvements were also recorded for muscular strength and some CV comorbid conditions. Whereas studies on the risk of enthesitis or flare-ups triggered by physical activity report contradictory evidence, recent clinical trials reported no adverse events.<sup>94-96</sup>

The experts consider that physical activity is part of the integrated and interdisciplinary management of PsA and should be prescribed by a specialist in physical medicine and rehabilitation. Frequency and intensity will depend on the patient's characteristics and disease activity.

### Assessment tools in PsA

*Recommendation 14. It is conditionally recommended that disease activity in PsA should be assessed using the DAPSA score and MDA, and when axial involvement is present, Ankylosing Spondylitis Disease Activity Score should be used.* Several validated tools can be used to measure the different domains of PsA. The most common include MDA<sup>97</sup> and the DAPSA<sup>98</sup> score. The data supporting these recommendations come from clinical trials, observational studies, and posthoc analyses.

Consensus on the best indices for measuring disease activity in PsA is lacking, since no single instrument covers all the dimensions of the disease. The experts agree that DAPSA is useful for evaluating the degree of disease activity in terms of joint involvement. MDA can be used to define remission status and/or LDA. However, its application in clinical practice is not always feasible. The Ankylosing Spondylitis Disease Activity Score (ASDAS) is considered the best instrument for evaluating axial involvement.

### Imaging in PsA

*Recommendation 15. Conventional radiography, ultrasound, and magnetic resonance imaging are conditionally recommended tools for follow-up of disease activity and structural damage in PsA.* Conventional radiography makes it possible to evaluate disease progression in PsA. The presence of erosions and reduced joint space on plain radiographs of the hands and feet of patients with PsA is associated with a greater probability of progression and worse scores on the HAQ.<sup>99,100</sup> Available scoring systems have proven to be moderately sensitive, although highly specific for detecting changes.<sup>101-103</sup>

The role of ultrasound in the follow-up of patients with PsA was assessed using a review of the literature including 15 studies with heterogeneous evaluation criteria. In general, power Doppler ultrasound was able to monitor the response to therapy at 6 months in patients with PsA.<sup>104</sup>

Magnetic resonance imaging (MRI) has been used to monitor disease activity in some clinical studies.<sup>105-107</sup> The Outcome Measures in Rheumatology (OMERACT) working group developed and validated the PsA MRI scoring system (PsAMRIS) for the hand and forefoot. The system includes scores for synovitis, erosions, bone marrow edema, tenosyno-

vititis, periarticular inflammation, and bony proliferation.<sup>107-111</sup> The PsAMRIS has been shown to be sensitive to change, and there is abundant information on its validity.<sup>108,109,112,113</sup>

### DISCUSSION

The first PANLAR PsA treatment guidelines provide an evidence-based framework to guide healthcare professionals (eg, rheumatologists, dermatologists, internists, primary care physicians, specialty pharmacists) treating adults with PsA in Latin America. We specifically address pharmacological therapy for arthritis, enthesitis, dactylitis, and axial involvement. The text brings together a series of recommendations drawn up and endorsed by PANLAR and addresses factors for the implementation of optimal disease management in the region. Our guideline makes recommendations on therapeutic targets, use of antiinflammatory agents and CS, treatment with DMARDs (conventional synthetic, biologic, and targeted synthetic), therapeutic failure, optimization of biologic therapy, nonpharmacological interventions, assessment tools, and follow-up of patients with PsA. Local recommendations on management stress the importance of considering the perspective of several countries to ensure a joint vision that will make it possible to harmonize therapy.

We used the GRADE-ADOLPMENT approach to adapt the 2019 EULAR recommendations based on the opinions of a group of experts from various countries in Latin America. The experts identified priority areas that were relevant for the region. We performed a systematic literature review to update the evidence supporting the "EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update."<sup>23</sup> Application of the AGREE Reporting Checklist<sup>27</sup> ensured the completeness and transparency of reporting in the practice guidelines. The recommendations cover local implementation issues such as access, use of resources, and patient preferences and values.

The evidence was summarized based on a series of questions covering areas such as therapeutic goals, efficacy and safety profile of the various treatment options (alone and in combination), approaches in cases of nonresponse, and optimization when therapeutic objectives are met. Nonpharmacologic options (rehabilitation, directed exercise), clinimetric indices (eg, DAPSA, ASDAS), and imaging evaluation of disease activity were also evaluated. The patient's perspective was assessed by means of conversations in which they discussed therapeutic objectives, pharmacological management, nonpharmacological management, and follow-up. Our findings are limited by the generally low quality of the evidence on which the recommendations were based. Consequently, every attempt should be made to update the recommendations as new evidence and treatment options become available.

Pharmacologic therapy for PsA can be managed using various options (NSAIDs, intraarticular CS, and immunomodulatory agents) and various countries in the region have developed national management recommendations,<sup>15-20</sup> thus highlighting the need to take local needs into consideration. As part of the present review, we have developed a treatment algorithm for

P<sub>s</sub>A (Figure). Our algorithm covers various domains of P<sub>s</sub>A and guides physicians on the different options before prescribing DMARDs or inhibitors (JAK, PDE4, TNF, IL-17, IL-12/23, or IL-23) or, in cases of remission or MDA, considering optimization of therapy.

The EULAR<sup>23</sup> and the PANLAR recommendations have several similarities, as the EULAR guidelines were used as a source document. However, there are some differences between them. For instance, PANLAR guidelines recommend combination therapy with MTX and LEF, whereas EULAR includes only csDMARD combination in their research agenda section. Moreover, PANLAR strongly recommends bDMARD monotherapy, whereas EULAR suggests continuing combination therapy with MTX for patients who are already taking MTX at the time of adding bDMARDs. Additionally, whereas PANLAR has defined a time frame to determine remission before tapering, the EULAR guidelines do not include such a time frame, which is similar to that of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). Further, PANLAR has included recommendations on the use of imaging for follow-up, whereas EULAR has not.

In 2022, the GRAPPA treatment guidelines were published,<sup>114</sup> wherein recommendations are presented for all domains of psoriatic disease, including peripheral arthritis, axial disease, enthesitis, dactylitis, PsO, nail involvement, inflammatory bowel disease, and uveitis, unlike in the PANLAR guidelines. The panel decided to restrict the recommendations to those domains commonly managed by rheumatologists. Regarding the joint involvement, enthesitis, dactylitis, and axial disease, our recommendations are similar to those presented by GRAPPA, except for inclusion of SSZ. Contrary to GRAPPA guidelines, we did not include SSZ within the csDMARDs based on the insufficient evidence, especially related to skin and joint involvement.

Related to the use of JAKi, although both GRAPPA and PANLAR positioned these drugs as first-line treatment after csDMARD failure, PANLAR conditionally recommended to use them only when bDMARDs are contraindicated or unavailable in patients aged > 65 years with CV or malignancy risk factors. Another difference is that PANLAR strongly and clearly recommends the use of bDMARDs and targeted synthetic DMARDs as monotherapy, based on the large body of evidence that combination with csDMARDs adds no benefits.

PANLAR suggests that patients should be at least 1 year in remission before considering tapering, whereas GRAPPA does not provide any time frame. As there is currently no evidence to suggest the appropriate tapering regimen, we have refrained from making any definitive recommendations on this matter. It should be left up to the treating physician to decide.

Related to follow-up, PANLAR specifies the role of imaging, whereas GRAPPA does not mention follow-up. Also, whereas the GRAPPA guidelines recommend that the most widely accepted metrics validated for P<sub>s</sub>A should be used for patient follow-up, PANLAR recommends specific tools, such as DAPSA, MDA, and ASDAS, which provide valuable information for the treating physician.

Our guidelines have some limitations. Not all PANLAR countries were represented, mainly because of the lack of rheumatology experts in P<sub>s</sub>A; however, this does not undermine the importance or generalizability of these recommendations, as most countries were represented and most of the experts in the region were involved. The PANLAR guidelines do not include some important domains such as skin, eye, and bowel. We considered that we would have needed experts in each one of those fields to properly address those domains, and that was beyond the scope and resources of PANLAR. Another limitation is that time has elapsed between the literature review and the publication of these guidelines. However, there have been no new mechanisms of action approved in that time, and although some new evidence has been published, there are none that would have changed the recommendations substantially.

Additional efforts should be made for the implementation of this guideline, including educational activities as well as dissemination among national scientific societies. Similarly, monitoring of indicators and evaluation of adherence should be developed, preferably at a national level. The analysis of the effect on the use of resources was not addressed in this set of recommendations. Further adjustment of these recommendations to the economic and health system condition at country level should be performed.

The panel discussed the need for more research on topics related to P<sub>s</sub>A in Latin America, owing to the absence or scarcity of data in this region. Although several studies have been conducted in Latin America aimed at filling in the information gaps on P<sub>s</sub>A, further efforts should be made in this regard to fulfill unmet needs in the region.<sup>115</sup> As new data become available in the literature considering additional therapeutic options, the current recommendations should be updated.

In conclusion, these recommendations are the first PANLAR guidelines for P<sub>s</sub>A and were developed by an expert panel, to be used in supporting decision making in the treatment of P<sub>s</sub>A in Latin America. They will prove useful to healthcare providers who are involved in the management of patients with this condition, mainly rheumatologists, dermatologists, internists, and primary care physicians. Based on the evidence obtained, the recommendations consider available resources, medical expertise, and patient values and preferences. Successful implementation of our recommendations should be based on clinical practice conditions, the particularities of national healthcare settings, and personalized assessments of patients. We strongly believe that the current recommendations may contribute to standardizing and optimizing the treatment of patients with P<sub>s</sub>A, thereby enabling healthcare professionals to provide higher-quality management.

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## ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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