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REVIEW

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Brazilian Society of Rheumatology 2020 guidelines for psoriatic arthritis

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Abstract

Psoriatic arthritis (PsA) is a chronic and systemic immune disease characterized by inflammation of peripheral and/or axial joints and entheses in patients with psoriasis (PsO). Extra-articular and extracutaneous manifestations and numerous comorbidities can also be present. These recommendations replace the previous version published in May 2013. A systematic review of the literature retrieved 191 articles that were used to formulate 12 recommendations in response to 12 clinical questions, divided into 4 sections: diagnosis, non-pharmacological treatment, conventional drug therapy and biologic therapy. These guidelines provide evidence-based information on the clinical management for PsA patients. For each recommendation, the level of evidence (highest available), degree of strength (Oxford) and degree of expert agreement (interrater reliability) are reported.

Keywords: Psoriatic arthritis, Spondyloarthropathies, Inflammation, Treatment, Guideline

Introduction

Psoriatic arthritis (PsA) is defined as chronic inflammatory arthropathy associated with psoriasis (PsO), with an equal distribution between men and women. A meta-analysis of 28 studies regarding the frequency of PsA in the general population of several countries found an incidence of 83 cases per 100.000 person-years and an estimated prevalence of 133 cases per 100.000 people [1].

It is estimated that one in 3 or 4 patients with Pso will also have PsA [2, 3].

The diagnosis of PsA is clinical, based on anamnesis, physical examination and imaging tests. Classification criteria can be used to homogenize patients and are valuable for scientific communication and clinical studies.

Regarding anamnesis and physical examination, some findings suggest the presence of PsA even in the absence of PsO: inflammatory arthropathy with involvement of the distal interphalangeal joints (DIP), asymmetric arthritis, nail lesions such as pitting and onycholysis, dactylitis and family history of PsO [4].

Bone and cartilage destruction with the pathological formation of new bone is one of the most striking aspects of PsA. Radiographs of peripheral joints may show bone loss with eccentric erosions and decreased joint space as well as new bone formation characterized by periostitis,

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enthesophytes or bone ankylosis [5]. In the axial skeleton, the changes associated with PsA include unilateral or bilateral sacroiliitis and bulky paramarginal vertical syndesmophytes (or parasyndesmophytes). Magnetic resonance imaging (MRI) may reveal focal erosions, synovitis and bone marrow edema in the peripheral and/or axial skeleton, particularly in entheses. Ultrasound (US) can identify synovitis, tenosynovitis, increased blood flow, enthesophytes and early erosive disease [5].

The treatment of PsA aims to achieve a state of remission, defined as complete resolution of signs and symptoms of inflammatory activity depending on the clinical judgment of the specialist or a Disease Activity index for PSoriatic Arthritis (DAPSA) score £ 4 or fulfillment the 7 Minimal Disease Activity (MDA) criteria, also called very low disease activity (VLDA). When remission cannot be achieved, a state of minimal disease activity may be acceptable and is defined as a DAPSA score between 4 and 14 points or fulfillment of at least 5 of the 7 MDA criteria. When there is axial involvement, metrics proposed for axial spondyloarthritis, i.e., Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) £ 4 or Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS-CRP) £ 1.3, are recommended [6–8]. These strategies are expected to optimize the function and improve the well-being of patients, prevent structural damage and minimize disease and treatment complications [9] (Tables 1, 2, 3 and 4).

The impact of the disease on pain, function, quality of life and structural damage should be evaluated. In addition, inflammation may influence other commonly related clinical conditions, such as cardiovascular disease, uveitis, inflammatory bowel disease and others.

Therapeutic decisions must be individualized and shared between the patient and physician, reflecting patient preferences based on adequate information [6, 9].

Table 2 MDA criteria for the evaluation of inflammatory disease activity [7, 198]

When meeting at least 5 of the 7 criteria	
1. Painful joint count	≤ 1
2. Swollen joint count	≤ 1
3. PASI ≤ 1 or BSA	≤ 3
4. VAS for pain by the patient	≤ 15
5. VAS for overall activity by the patient	≤ 20
6. HAQ	≤ 0.5
7. Pain points in entheses	≤ 1

MDA: minimal disease activity; BSA: body surface area; HAQ: health assessment questionnaire; PASI: psoriasis area severity index; VAS: visual analog scale

* Patients who meet 7 of the 7 criteria are considered to have very low inflammatory activity and are considered to be in remission

Drug choice may be influenced by factors such as disease activity, structural damage, concomitant clinical conditions and previously used therapies [6–10].

Ideally, patients should be evaluated regularly, with treatment adjusted as needed.

The objective of these guidelines is to provide evidence-based information on the clinical management of patients with PsA, including diagnosis, treatment and prognosis for rheumatologists, specialists in related fields, clinicians and other health professionals who deal directly with these patients.

This version replaces the previous guidelines published on May 26, 2013 [11].

Methods

A systematic literature review was conducted by a group of experts of the Brazilian Medical Association. Keywords defined according to the PICO strategy (Patient | Intervention | Comparison | Result) were used to search for records in the following databases: MEDLINE,

Table 1 DAPSA criteria for the evaluation of inflammatory disease activity [7, 197]

Domain	Rating
VAS Pain	0 to 10
GDA (Pt)	0 to 10
Painful joints	68
Swollen joints	66
CRP	mg/dL
DAPSA	**Simple sum**
DAPSA ≤ 4	Activity = Remission
DAPSA > 4–14	Activity = Low
DAPSA > 14–28	Activity = Moderate
DAPSA > 28	Activity = High

DAPSA: Disease Activity index for Psoriatic Arthritis; VAS: visual analog scale; GDA (Pt): patient global disease assessment; CRP: C-reactive protein

Table 3 BASDAI assessment criteria for axial inflammatory activity in spondyloarthritis [8, 199]

BASDAI	
1. How would you describe the overall level of fatigue/tiredness you have experienced?	0 to 10 (none to intense)
2. How would you describe the overall level of AS neck, back or hip pain you have had?	0 to 10 (none to intense)
3. How would you describe the overall level of pain/swelling in joints other than neck, back, hips you have had?	0 to 10 (none to intense)
4. How would you describe the overall level of discomfort you have had in any areas tender to touch or pressure?	0 to 10 (none to intense)
5. How would you describe the overall level of morning stiffness you have had from the time you wake up?	0 to 10 (none to intense)
6. How long does your morning stiffness last from the time you wake up?	0 to 10 (0 to 2 or more hours)
BASDAI = [(Q5 + Q6)/2 + (Q1 + Q2 + Q3 + Q4)]/5	
BASDAI < 4	Inactive or low-activity disease
BASDAI from 4 to 10	Active disease

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index = mean of the values of questions 5 and 6 plus the values of questions 1 to 4, divided by 5

Table 4 ASDAS-CRP evaluation criteria for axial inflammatory activity in spondyloarthritis [8, 200, 201]

ASDAS-CRP							
1. Overall back pain (BASDAI question 2)							
2. Global patient assessment							
3. Peripheral pain/inflammation (BASDAI question 3)							
4. Duration of morning stiffness (BASDAI question 6)							
5. C-reactive protein (CRP) in mg/l [or erythrocyte sedimentation rate (ESR)]							
$ASDAS_{CRP}$	**0.12 X overall back pain**	+	**0.06 X duration of morning stiffness**	+	**0.07 X Peripheral pain/ inflammation**	+	**0.58 X Ln(CRP + 1)**
$ASDAS_{CRP} < 1.3$	Activity = Inactive						
$1.3 \leq ASDAS_{CRP} < 2.1$	Activity = Low disease activity						
$2.1 \leq ASDAS_{CRP} < 3.5$	Activity = High						
$ASDAS_{CRP} > 3.5$	Activity = Very high						

ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein

EMBASE, SciELO/LILACS and the Cochrane Library, from March 1st, 2012, to December 31st, 2019.

After conducting the systematic literature review there were added some relevant studies published until December 31st 2020, including the validation study of the Portuguese version of the TOronto Psoriatic Arthritis Screen II (TOPAS-II), two pivotal randomized clinical trial that approved guselkumab and upadacitinib for the treatment of PsA, and two other head-to-head clinical trials studies comparing IL-17 inhibitors (secukinumab and ixekizumab) with adalimumab.

The target population included patients with joint, axial and entheseal musculoskeletal inflammatory pain according to the 2006 Classification of Psoriatic Arthritis (CASPAR) criteria [12] (Table 5). Studies were selected and used to formulate 12 recommendations, answering 12 clinical questions, which were divided into 4 sections: diagnosis, nonpharmacological treatment, conventional therapy and biologic therapy. For each recommendation, the level of evidence (highest available) and the degree of strength (Oxford Center for Evidence-Based Medicine Level of Evidence) [12–16] were reported. The degree of expert agreement

Table 5 Classification criteria for psoriatic arthritis [12]

Presence of established inflammatory joint disease	
(arthritis, enthesitis, axial) and at least 3 points	Points
Current skin psoriasis OR	2 or
History of psoriasis OR	1 or
Family history of psoriasis	1
Dactylitis	1
Nail dystrophy	1
Negative rheumatoid factor	1
Juxta-articular bone neoformation	1

Sensitivity 0.914; Specificity 0.987

Table 6 Guidelines of the Brazilian Society of Rheumatology for the diagnosis and treatment of psoriatic arthritis with their respective level of evidence, strength of recommendation and degree of agreement among experts (interrater reliability), 2020

	Question/Recommendation	Level of evidence	Strength of recommendation	Degree of agreement
1	What are the criteria for considering that an individual has psoriatic arthritis?			
	The diagnosis of PsA should be based on clinical and imaging criteria, and the CASPAR should be used for disease classification	1A	A	0.97
	The use of PsA screening questionnaires in patients with PsO is recommended, with preference for those that have already been validated in the Brazilian population, such as the PASE, PEST and TOPAS-II	1A	A	0.94
2	Is there a correlation between skin, nail and osteoarticular manifestations in psoriatic arthritis?			
	All patients with PsO should be evaluated for the presence of musculoskeletal manifestations, and those with involvement of the nails, intergluteal region, scalp or of extensive areas are at higher risk for musculoskeletal involvement	2B	B	0.94
3	What are the comorbidities most associated with psoriatic arthritis?			
	The most frequent comorbidities in patients with PsA, such as metabolic syndrome, atherosclerosis, cardiovascular disease, mood disorders, inflammatory bowel disease, osteoporosis and uveitis, should be screened and managed	2B	B	0.96
4	Is there evidence of benefits of exercise in the treatment of psoriatic arthritis?			
	Aerobic and resistance exercises should be individually prescribed to improve functional capacity, pain and quality of life	1B	A	0.97
5	What is the evidence for the use of corticosteroids in patients with psoriatic arthritis?			
	The use of intra-articular corticosteroid injection is recommended for localized, mono- or oligoarticular disease, especially in patients who are unresponsive to systemic treatment	2C	B	0.95
	Due to the lack of quality data on the efficacy of the use of systemic corticosteroids in PsA and the known adverse effects, their long-term use is not recommended	5	D	0.94
6	What is the evidence for the use of nonsteroidal antiinflammatory drugs (NSAIDs) in patients with psoriatic arthritis?			
	The use of NSAIDs is recommended as a symptomatic treatment in patients with peripheral arthritis	1B	A	0.95
	The use of NSAIDs is recommended as a symptomatic treatment in patients with enthesitis, dactylitis and axial manifestations	5	D	0.96
	As there is no evidence of a difference in efficacy among NSAIDs*, the choice of the drug should be based on the physician's familiarity with the drug and individual patient preference, respecting the concomitant clinical conditions**	*1B**5	B	0.96
7	What is the evidence for the use of conventional DMARDs in the treatment of psoriatic arthritis?			
	The use of methotrexate (MTX) is recommended as the first option among cDMARDs for the treatment of peripheral articular and skin involvement in PsA*, preferably at doses higher than 15 mg/week and subcutaneously**.	*1B **5	B	0.93
	If MTX is not available, cyclosporine, leflunomide or sulfasalazine should be used in patients with peripheral arthritis	2B	B	0.93
	There is NO scientific evidence of the use of cDMARDs in axial disease and limited evidence for enthesitis	5	D	0.89
8	When are biologic DMARDs or targeted synthetic DMARDs indicated for the treatment of PsA?			
	A bDMARD should be initiated in patients with PsA and peripheral arthritis who remain with active disease despite the use of a cDMARD, preferably MTX, for at least 3 months	1B	A	0.95
	In the case of failure or inability to use a bDMARD, a tsDMARD can be used	1B	B	0.95
	The use of a bDMARD is recommended for patients with PsA and axial manifestations who remain with active disease despite the use of 2 classes of NSAIDs, in full dose, for at least 30 days each	1B	B	0.92
9	Is there a difference in the efficacy of biologic DMARDs and targeted synthetic DMARDs in the treatment of PsA?			
	For the treatment of peripheral arthritis, dactylitis and enthesitis, the use of any of the following drugs is recommended: anti-TNFs (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), anti-IL-17 (ixekizumab and secukinumab), anti-IL-12/23 (ustekinumab) and anti-IL-23 (guselkumab)	1B	A	0.98

Table 6 (continued)

	Question/Recommendation	Level of evidence	Strength of recommendation	Degree of agreement
	The choice of drug should take into account patient preference (in regard to the route of administration and frequency of use, for example), concomitant clinical conditions, medical history (e.g., history of tuberculosis, fungal infections, and herpes zoster), cost, availability in the health system and presence of extra-articular manifestations of PsA	5	D	0.99
	In patients with axial manifestations, the use of anti-TNF and anti-IL-17 drugs is preferentially recommended	1B	B	0.98
	In patients with PsA and severe PsO, anti-IL-23, anti-IL-17, and anti-IL-12/23 drugs are preferentially recommended over anti-TNFs	1B	A	0.95
	In patients with recurrent uveitis, the use of anti-TNF monoclonal antibodies is recommended	1B	B	0.99
	In patients with concomitant active Crohn's disease, the use of IFX, ADA, CTZ, and UST is preferentially recommended	1B	B	0.98
	In patients with concomitant active ulcerative colitis, the use of IFX, ADA, GOL, UST or TOF is preferentially recommended	1B	B	0.98
10	Is there a difference in the safety of biologic DMARDs in the treatment of PsA?			
	Screening and treatment of latent tuberculosis infection (LTBI) or disease is recommended before the use of any immunobiologic and JAK inhibitor	2B	B	0.98
	In general, the biologics used for the treatment of PsA have similar safety profiles, and the particularities inherent to the cytokine to be inhibited should be considered	1B	B	0.96
	The use of anti-TNFs in patients with demyelinating disease or class III or IV heart failure is not recommended	4	C	0.99
	The use of JAK inhibitors in patients with disseminated or recurrent herpes zoster is not recommended	1B	A	0.99
	The use of IL-17 inhibitors in patients with a history of severe or recurrent fungal infections is not recommended	1B	A	0.98
11	Is there evidence for the use of conventional DMARDs combined with biologic DMARDs or target synthetic DMARDs?			
	Regarding monoclonal anti-TNF biologics, the concomitant use of MTX is recommended to increase survival, although there is no evidence of increased efficacy	*2B **1B	B	0.88
	Regarding non-anti-TNF biologics or tsDMARDs, there is no evidence of increased efficacy or survival with the concomitant use of cDMARDs	1B	A	0.97
12	Is there evidence for switching biologic and small-molecule DMARDs in patients with psoriatic arthritis?			
	In patients with PsA and bDMARD failure, switching to any other immunobiologic agent or to JAK inhibitors is recommended, with no differences between drugs, and the most relevant manifestations of the disease and concomitant clinical conditions should be considered	*1B **5	B	0.96
	When the therapeutic failure of an anti-TNF agent is attributed to skin inflammatory activity, switching to drugs with another mechanism of action, such as anti-IL23, anti-IL17 or anti-IL-12/23 agents, can be evaluated	1B	B	0.95
	When the therapeutic failure of an anti-TNF agent is attributed to serious adverse events, especially infections, switching to drugs with another mechanism of action, such as anti-IL-17, anti-IL-12/23, and anti-IL23 drugs or CTLA4 inhibitors	2B	B	0.98
	If there is a preference for oral medication or contraindications to injectable medications, the use of tofacitinib may be considered	5	D	0.96

(interrater reliability) was determined by the Delphi method [17] through an anonymous online survey. Table 6 summarizes these recommendations, and Fig. 1 shows a guidance algorithm for the management of PsA.

The results are presented, whenever possible, in absolute values, followed by a measure of the effect size to highlight the clinical significance or practical relevance. In the comparisons between treated and untreated individuals (placebo), the number needed to treat (NNT) or the number needed to harm (NNH) and the respective confidence intervals (95% CI) were calculated using a normal approximation, which is the most accepted statistical method. The data from each study used to define these intervals are available from the authors. In comparisons between paired means (before and after treatment),

the effect size was calculated using the Cohen method (difference between the means divided by the standard deviation) [18]. Effect sizes were considered small when they ranged from 0.2 to 0.4, medium when they ranged from 0.4 to 0.8 and large when they were greater than 0.8 [19].

Clinical questions

What are the criteria for considering that an individual has psoriatic arthritis?

Diagnosis

The CASPAR is internationally accepted and has a sensitivity of 91% and specificity of 99% [12]. In this classification, individuals with established inflammatory joint disease (peripheral, axial or entheseal) are classified as having PsA if their points add up to 3 or more from the following categories (Table 5):

- PsO skin lesions: present/current (2 points) or previous (1 point) or family history of PsO (1 point);
- Nail lesions (onycholysis or pitting): 1 point;
- Current dactylitis, defined as whole-digit edema or a history of dactylitis: 1 point;
- Negative rheumatoid factor: 1 point; and
- Juxta-articular new bone neoformation: defined as poorly defined ossification near the joint margins (but excluding osteophyte formation) on plain radiographs of the hands or feet: 1 point.

Questionnaires and survey instruments were developed to assist clinicians and dermatologists in the early identification of cases of PsA among patients with PsO: CONTEST [20, 21], TOPAS-II [22, 23], PURE-4 (Psoriatic arthritis UnclutteRed screening Evaluation-4) [24], SiPAS (Simple Psoriatic Arthritis Screening) [25], PASE (Psoriatic Arthritis Screening Evaluation) [23, 26–28], PEST (Psoriasis Epidemiology Screening Tool) [23, 28, 29], and EARP (Early Psoriatic Arthritis Screening Questionnaire) [23, 28, 30, 31].

The CONTEST instrument was developed from the PASE, PEST and TOPAS. Studies comparing the CONTEST and PEST questionnaires found no significant differences in efficacy between them [20, 32]. Considering that the PEST is shorter and simpler than the CONTEST, the use of the latter has become unfeasible in clinical practice [20, 32]. However, a recent systematic review with meta-analysis showed the EARP had better accuracy (sensitivity and specificity = 0.85 each) for PsA screening among psoriasis patients when compared to other self-administered tools (PASE, TOPAS, PEST) including 2280 references and 130 for the final analysis [31].

The TOPAS-II considers images of PsO, joint inflammation and dactylitis, improving doctor-patient agreement, being a useful tool to identify PsA in patients with PsO and to track PsO in the general population [22, 23, 33].

Further evidence is needed to recommend the routine use of the SiPAS and PURE-4 questionnaires [24, 25].

To date, only the PASE, PEST and TOPAS-II questionnaires have been translated into Portuguese and validated in the Brazilian population [33–35]. The Portuguese version of the PEST is available free of charge through the app of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) [35].

The sensitivity and specificity of the instruments vary according to the studied population (Table 7).

Recommendation

The diagnosis of PsA should be based on clinical and imaging criteria, and the CASPAR criteria should be used for disease classification. **Level of evidence: 1A; Strength of recommendation: A; Degree of agreement: 0.97.**

The use of PsA screening questionnaires in patients with PsO is recommended, with preference for those

(See figure on next page.)

Fig. 1 Algorithm proposed by the Brazilian Society of Rheumatology for the management of psoriatic arthritis patients, 2020. **cDMARDs**: conventional disease-modifying antirheumatic drugs; **MTX**: methotrexate; **LFN**: leflunomide; **SSZ**: sulfasalazine; **CSP**: cyclosporine; **NSAIDs**: nonstreroidal antiinflammatory drugs; **DAPSA**: Disease Activity Index for Psoriatic Arthritis; **MDA**: minimal disease activity; **VLDA**: very low disease activity; **BASDAI**: Bath Ankylosing Spondylitis Disease Activity Index; **ASDAS**: Ankylosing Spondylitis Disease Activity Score; **bDMARDs**: biologic disease-modifying antirheumatic drugs; **tsDMARDs** targeted synthetic disease modifying antirheumatic drugs; **TNFi:** TNF-alpha inhibitor; **ADA**: adalimumab, **CTZ**: certolizumab pegol; **ETN**: etanercept; **GOL**: golimumab; **IFX**: infliximab; **IL-17i**: IL-17 inhibitor; **IXE**: ixekizumab; **SEC**: secukinumab; **IL-12/23i:** IL-12/23 inhibitors; **UST**: ustekinumab; **IL-23i**: IL-23 inhibitor; **GUS**: guselkumab; **ABA**: abatacept; **TOF**: tofacitinib. **1**. Analgesics, NSAIDs and intra-articular corticosteroid infiltrations can be used in all stages, when necessary. **2**. Preferably use TNFi or IL-17i if there are axial manifestations; IL-23i or IL-17i or IL-12/23i if significant psoriasis; monoclonal TNFi if recurrent uveitis; TNFi (IFX, ADA, CTZ) or IL-12/23i if concomitant active Crohn's disease; TNFi (IFX, ADA, GOL) or IL-12/23i or JAKi (TOF) if concomitant active ulcerative colitis. **3**. Preferably use IL-17i if significant psoriasis; monoclonal TNFi if recurrent uveitis; TNFi (IFX, ADA, CTZ) if concomitant active Crohn's disease; TNFi (IFX, ADA, GOL) if concomitant active ulcerative colitis

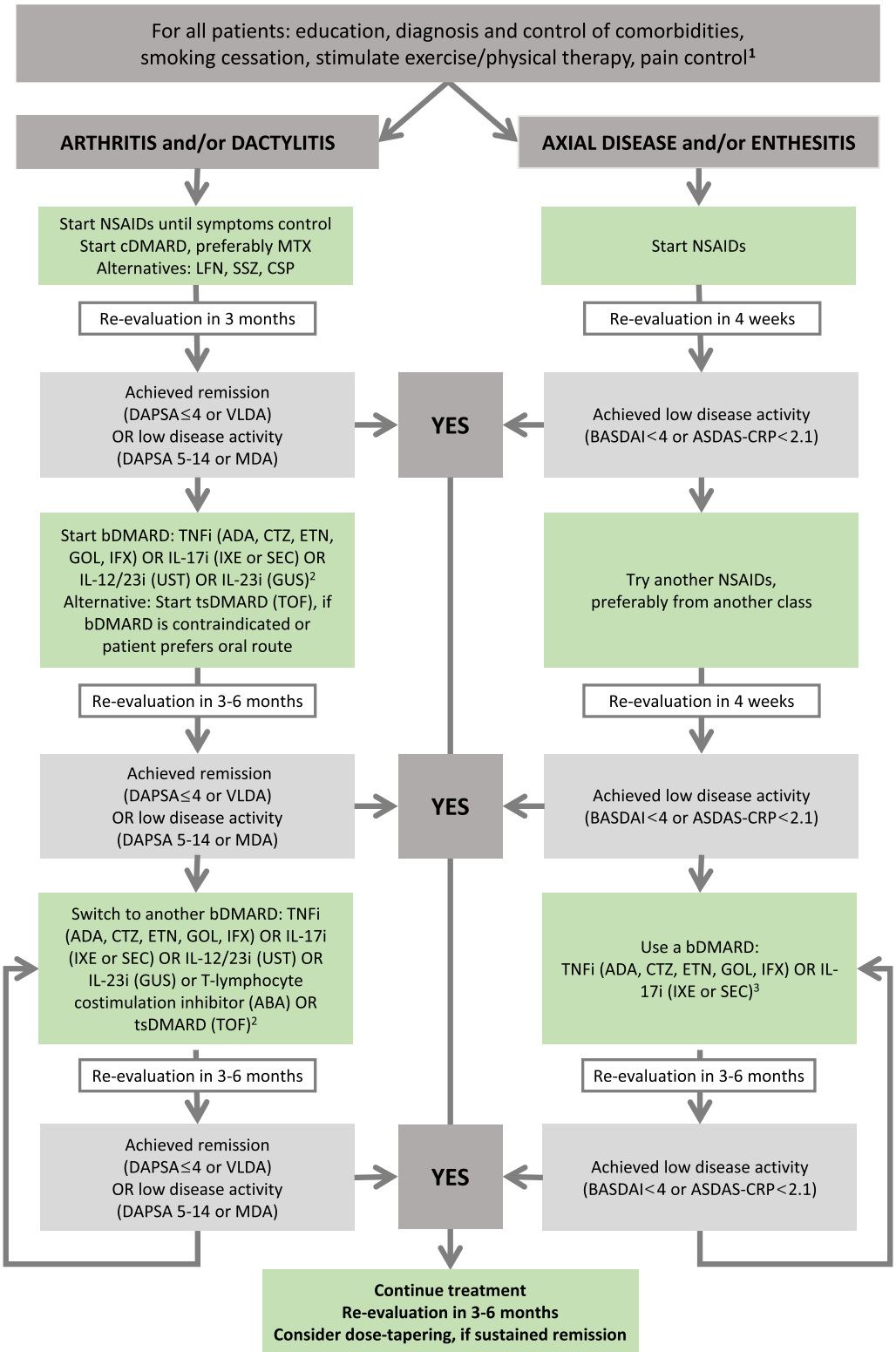

Fig. 1 (See legend on previous page.)

Table 7 Description of sensitivity, specificity and area under the curve (AUC) of the main PsA screening questionnaires

Authors	Questionnaires evaluated	Number of participants	Sensitivity	Specificity	AUC
Coates et al., 2018 [31]	CONTEST/ PEST	159	PEST 0.72 CONTEST 0.65	PEST 0.60 CONTEST 0.53	PEST 0.76 CONTEST 0.71
Coates et al., 2016 [20]	CONTEST/CONTESTjt X PEST	191	CONTEST 0.76 CONTESTjt 0.76 PEST 0.65	CONTEST 0.56 CONTESTjt 0.53 PEST 0.53	CONTEST 0.69 CONTESTjt 0.70 PEST 0.60
Duruoz et al., 2018 [32]	TOPAS II X CASPAR	150	TOPAS II 0.95	TOPAS II 0.98	TOPAS II 0.99
You et al., 2015 [27]	PASE X Rheumatologist (based on CASPAR and Moll and Wright)	148	PASE 0.77	PASE 0.82	PASE 0.79
Karreman et al., 2017 [28]	PEST X PASE X EARP X CASPAR	420	PEST 0.68 PASE 0.59 EARP 0.87	PEST 0.71 PASE 0.66 EARP 0.34	PEST 0.71 PASE 0.64 EARP0.68
Audureau et al., 2018 [24]	PURE-4 X CASPAR	168	PURE-4 0.85	PURE-4 0.83	PURE-4 0.87
Salaffi et al., 2018 [25]	SiPAS X CASPAR	202	SiPAS 0.79	SiPAS 0.87	SiPAS 0.60
Iragorri et al., 2019 [31]	PASE X TOPAS X PEST X EARP	15,208	PASE 0.66 ToPAS 0.74 PEST 0.66 EARP 0.85	PASE 0.82 ToPAS 0.79 PEST 0.83 EARP 0.78	PASE 0.68 ToPAS 0.65 PEST 0.85 EARP 0.85

CASPAR = Classification Criteria for Psoriatic Arthritis; CONTEST = Comparison of 3 screening tools to detect psoriatic arthritis in patients with psoriasis; CONTESTjt = CONTEST with the addition of a joint manikin; EARP = Early Psoriatic Arthritis Screening Questionnaire; PASE = Psoriatic Arthritis Screening Evaluation; PAQ = Psoriasis and Arthritis Questionnaire; PASQ = Psoriasis and Arthritis Screening Questionnaire; PEST = Psoriasis Epidemiology Screening Tool; PURE-4 = Psoriatic arthritis UnclutteRed screening Evaluation; SiPAS = Simple Psoriatic Arthritis Screening; TOPAS = Toronto Psoriatic Arthritis Screen

that have already been validated in the Brazilian population, such as the PASE, PEST and TOPAS-II. **Level of evidence: 1A; Strength of recommendation: A; Degree of agreement: 0.94.**

Is there a correlation between skin, nail and osteoarticular manifestations in psoriatic arthritis?

Correlations

Musculoskeletal involvement occurs simultaneously with or after the onset of PsO skin lesions in 82–87% of cases, while arthritis precedes the skin picture in 13–18% of patients [36–38].

A retrospective cohort study that included 1593 patients with PsO showed a higher incidence rate of PsA over time in patients with scalp lesions [hazard ratio (HR) = 3.89; 95%CI 2.18–6.94] and intergluteal/perianal lesions [HR = 2.35 (95%CI 1.32–4.19)] [39]. Two other cross-sectional studies that included 1928 and 459 patients with PsO also showed an increased prevalence of PsA in patients with scalp lesions (90.2% vs. 76.4%, $p = 0.001$ and 87% vs. 72%, $p = 0.0237$, respectively) [38, 40].

The duration and extent of skin disease assessed by affected body surface area (BSA) were associated with a higher chance of developing PsA [odds ratio (OR) = 7.42 (95%CI 3.86–14.25) and OR = 3.34 (95%CI 2.40–4.65), respectively] [41]. A greater number of skin sites affected by PsO also increases the risk of PsA by 2.24 (95%CI 1.23–4.08) [39].

Nail involvement in patients with PsO predisposing to musculoskeletal involvement was demonstrated in 1 cohort study [39] and in 13 cross-sectional studies [38, 40, 42–52]. The retrospective cohort [39] showed a higher incidence rate of PsA over time in patients with PsO and nail dystrophy [HR = 2.93; 95%CI 1.68–5.12] [39]. An increased risk of PsA in patients with nail PsO was observed in 12 of the 13 cross-sectional studies that evaluated this association [38, 40, 42–52] (OR = 2.92; 95%CI 2.34–3.64), although with a significant level of heterogeneity ($I^2 = 66\%$; $p = 0.0005$). The case–control study did not observe such a relationship (OR = 1.16; 95%CI 0.46–2.92) [53].

Eight small cross-sectional studies published between 1985 and 2010 specifically evaluated the link between nail PsO and DIP impairment [37, 49, 52, 54–57]. Of these, 5 showed a significant association between nail PsO and DIP involvement [37, 49, 52, 54, 55].

Recommendation

All patients with PsO should be evaluated for the presence of musculoskeletal manifestations. Those with involvement of the nails, intergluteal region, or scalp or extensive areas are at higher risk for musculoskeletal involvement. **Level of evidence: 2B; Strength of recommendation: B; Degree of agreement: 0.94.**

What are the comorbidities most associated with psoriatic arthritis?

Concomitant clinical conditions

The coexistence of clinical conditions associated with PsA, such as obesity, metabolic syndrome, cardiovascular disease (CVD), uveitis, inflammatory bowel disease, and mood disorders, has been reported. More than half of patients have at least 1 comorbidity that can negatively impact quality of life.

Obesity

The prevalence of obesity in patients with PsA is approximately 30–37% [58–60], and the incidence in these patients is 1.8–10.1% higher than that in control groups (NNH: 55–10) [60, 61]; when compared to patients with PsO without arthritis, there is a 3.5% increase ($p < 0.05$) in the incidence of obesity (NNH: 32) [58].

In addition, obesity seems to influence the therapeutic response in PsA. Obese individuals were less likely to achieve a therapeutic response based on the MDA criterion [obesity grade I with HR = 3.98; 95%CI 1.96–8.06, $p < 0.001$, and obesity grade II with HR = 5.4; 95%CI 3.09–9.43, $p < 0.001$] [62]. Intervention studies showed that weight loss increased the chance of achieving MDA [5–10% weight loss with OR = 3.75; 95%CI 1.36–10.36, $p = 0.011$ and ≥ 10% with OR = 6.67; 95%CI 2.41–18.41, $p < 0.001$] [63].

Metabolic syndrome

Approximately 40.6–44% of patients with PsA present metabolic syndrome* [64, 65], with an increased incidence of 5.24% ($p < 0.05$) compared to patients with other spondyloarthritis (NNH: 19) [66], 15.9% compared to patients with rheumatoid arthritis (NNH: 6) [66] and 22.9% ($p < 0.05$) compared to patients with PsO without arthritis (NNH: 4) [67]. A high prevalence of CVD risk factors was observed among metabolic syndrome components such as arterial hypertension, elevated waist circumference and triglycerides [64], as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) criteria.

Hypertension

Hypertension has a prevalence of 33.6–38.7% in patients with PsA [58, 60, 68]. In these patients, there was an increase of 2.3–11.8% ($p < 0.05$) compared to control patients (NNH: 14–8) [60, 68].

In addition, patients with PsA compared to those with PsO without arthritis have a 17.5% increased incidence ($p < 0.05$) of hypertension (NNH: 6) [58].

A longer disease duration may result in a higher risk of hypertension. Older patients with PsA for longer than 2 years have a higher risk of hypertension than patients in the early phase of the disease [increase of 22.9–49.3% ($p < 0.05$) (NNH: 4–2) vs. increase of 22.8–26.6% ($p < 0.05$) (NNH: 4)] [69].

Diabetes

The prevalence of diabetes in patients with PsA is 11.5–13.6% [58, 60, 69]. Compared to control patients, patients with PsA have increased rates, by 3.2–2.6–2.51% ($p < 0.05$), of diabetes (NNH: 31–38–40) [60, 61, 70].

Patients with PsA, when compared to patients with PsO without arthritis, have increased rates, by 5.3% ($p < 0.05$%) of type II diabetes (NNH: 19) [58]. Patients with a later age of onset of PsO symptoms and shorter time interval until diagnosis of PsA have a higher risk of diabetes [(2.4% increase ($p < 0.05$) (NNH: 42)] than do patients with PsA established for more than 2 years [69].

Hyperlipidemia

The prevalence of hyperlipidemia in patients with PsA is 17.5–20.7% [58, 60]. Such patients showed an increased risk, by 1.71–4.1–13.87% ($p < 0.05$), of hyperlipidemia when compared to controls (NNH: 58–24–7) [60, 61, 66].

Patients with PsA, compared to patients with PsO without arthritis, have an increased rate, by 6.2%, (– < 0.05%) of hyperlipidemia (NNH: 16) [58].

The LDL level, which is a risk factor for atherosclerosis, was significantly higher in patients with PsA than in patients without PsA (9.0 ± 10.7 vs. 2.9 ± 4.7 mg/dL; $p < 0.05$) [58].

Atherosclerosis/coronary artery disease

Systemic inflammation in PsA extends beyond the skin and joints. Recent studies highlight the increased risk of atherosclerotic disease and consequently major cardiovascular adverse events (combined outcome of myocardial infarction, stroke and cardiovascular death) in patients with PsA.

Patients with PsA have a 22.9–32% increased incidence of atherosclerosis ($p < 0.05$) compared to controls (NNH: 4–3) [71, 72]. Linear regression analysis comparing a cohort of patients with PsA with and without metabolic syndrome to non-PsO/PsA controls showed no correlation between atheromatous plaques and metabolic syndrome but rather a correlation with PsA alone [B = 0.865 (0.236–1.493), $p = 0.008$] [72].

Cardiovascular disease

Compared to control patients without PsA, patients with PsA showed a 3.2–7.5% increase ($p < 0.05$) in the prevalence of CVD risk (NNH: 31–13) [61, 73], and when compared to patients with PsO without arthritis, the risk of CVD increased by 4.9% ($p < 0.05$) (NNH: 20) [58].

Depression and/or anxiety

Compared to control patients matched for age, sex, geographic region and year of follow-up, patients with PsA had a 5.4% increased incidence ($p < 0.05$) for depression (NNH: 18) and 3.0% increased incidence ($p < 0.05$) for anxiety (NNH: 33) [61]. When compared to patients with PsO without arthritis, the incidence of depression and/or anxiety increased by 11.4% (p = 0.0001) (NNH: 9) [58].

Osteoporosis

Patients with PsA, compared to control patients matched for age, sex, geographic region and year of follow-up, had a 1% increased incidence ($p < 0.05$) of osteoporosis (OP) (NNH: 100) [61].

Compared to control patients, patients with PsA have a high probability of OP (OR = 4.04; 95%CI 3.80–4.29, $p < 0.0001$) and a consequent increased risk of fracture (OR = 3.41; 95%CI 2.94–3.96, $p < 0.0001$) [74].

When the OP prevalence were compared among PsA and PsO patients, no differences were observed (3.5% vs. 2.9%; 95%CI 0.18–1.70, $p = 0.56$) (multivariate model adjusted for age, sex, education level, PsO duration, current smoking, Psoriasis Area and Severity Index (PASI) score, use of immunobiologics, methotrexate (MTX) and nonsteroidal antiinflammatory drugs (NSAIDs), CVD, hypertension, and gastrointestinal disease) [58].

Uveitis

Uveitis is a comorbidity that may be present in 7% of patients with PsA, unilaterally and bilaterally, with a similar distribution of anterior and posterior presentations and insidious onset in 19% of patients, occurring, on average, 9 years after the diagnosis of arthritis [75].

Patients with PsA, when compared to patients with PsO without arthritis, have an incidence of uveitis of 0.9–1.2% ($p < 0.05$) (NNH: 111–83) [61, 76].

Inflammatory bowel disease

Compared to controls, patients with PsA exhibited an increased risk for Cronh's disease (0.7–0.82%, $p < 0.05$; NNH: 142–117) and ulcerative colitis (0.38–0.6%, $p < 0.05$; NNH: 264–167) [61, 77].

Recommendation

The most frequent comorbidities in patients with PsA, such as metabolic syndrome, atherosclerosis, cardiovascular disease, mood disorders, inflammatory bowel disease, osteoporosis and uveitis, should be managed routinely in the clinical practice. **Level of evidence: 2B; Strength of recommendation: B; Degree of agreement: 0.96.**

Nonpharmacological treatment

Few studies have evaluated the benefit of exercise in patients with PsA [10, 78–80]. The results obtained for individuals with other inflammatory arthropathies [80] have been extrapolated for patients with PsA. Exercise can influence the inflammatory activity of PsA, as well as aerobic capacity and muscle strength, in addition to assisting in weight loss, which in turn was associated with a better response to treatment with immunobiologics [62, 81].

Is there evidence for benefits of physical exercise in the treatment of psoriatic arthritis?

Three studies [78–80, 82] with adequate scientific methodology provided specific evidence of exercise practice in PsA. The interventions studied were resistance exercises and high-intensity interval training (HIIT) [78, 80]. The outcomes analyzed were pain [78, 79], fatigue [78], strength [79], functional capacity [79], disease activity [78, 79], quality of life [79], maximum oxygen consumption (VO_2 max) [80], fat percentage [80] and body mass index [80].

Impact on aerobic capacity

Compared to a control group, patients subjected to HIIT training (3 times per week for 11 weeks) showed significant improvement in VO_2 max ($p < 0.001$); however, there was no significant difference in the following outcomes: fat percentage ($p = 0.14$) or body mass index ($p = 0.11$) [80].

Impact on disease activity

Compared to a control group, patients performing resistance exercises (twice a week for 12 weeks) showed significant improvement in their functional capacity [Health Assessment Questionnaire—Spondyloarthritis (HAQ-S), $p = 0.048$)], disease activity [BASDAI, $p = 0.038$], pain [Short-Form 36 (SF-36), $p = 0.017$] and general health (SF-36, $p = 0.002$) at the end of the protocol [79].

Compared to a control group, patients who performed HIIT training (3 times per week for 11 weeks) showed significant improvement in fatigue at a 12-week evaluation ($p = 0.005$), but there was no improvement regarding pain ($p = 0.47$) or disease activity using different metrics [Patient Global Assessment (PGA), $p = 0.85$; Disease Activity Score in 44 joints (DAS44), $p = 0.22$; ASDAS-CRP, $p = 0.42$; high sensitivity C-reactive protein (hs-CRP), $p = 0.67$)] [78]. When re-evaluated 6 months after the end of training, no benefit was observed for any of the analyzed outcomes.

Recommendation

Aerobic and resistance exercises should be individually prescribed to improve functional capacity, pain and quality of life**. Level of evidence: 1B; Strength of recommendation: A; Degree of agreement: 0.97.**

Drug treatment

NSAIDs, corticosteroids and conventional disease-modifying antirheumatic drugs (cDMARDs).

Corticosteroids (CSs) can be used as adjuvant treatment for disease [83]. Few randomized, double-blind, placebo-controlled clinical trials with NSAIDs have been conducted in PsA patients with peripheral involvement. As a therapeutic option for axial disease, NSAIDs have also not been specifically studied; therefore, measures and outcomes developed for ankylosing spondylitis (AS) have been accepted.

The drugs methotrexate (MTX), cyclosporine (CSP), leflunomide (LFN) and sulfasalazine (SSZ) are cDMARDs and have been used for several years to control the inflammatory process, modify disease progression, achieve remission and inhibit/reduce structural damage in PsA [84]. Most studies with these drugs evaluated their effects in patients with peripheral presentation and not with axial involvement.

What is the evidence for the use of corticosteroids in patients with psoriatic arthritis?

Local corticosteroid use

Intra-articular CSs injection (triamcinolone and methylprednisolone) at doses of 5–80 mg can be performed in inflamed joints, such as interphalangeal, knee and hip joints of patients with PsA. The probability of achieving an adequate clinical response in 3 months was 41.6%, but there may be recurrence in 25.5% of cases after 1 year [83].

Systemic CS use

The systemic use of CSs in patients with PsA has not been well studied. Nevertheless, these drugs have been prescribed, with caution, due to possible worsening of skin involvement, for PsA in 24.4–30% of cases [85]. In addition, specialists contraindicate the use of systemic CSs for the treatment of PsO, except in very special cases, and chronic use must be avoided [86].

Recommendation

The use of intra-articular CS injection is recommended for localized, mono- or oligoarticular disease, especially for patients who do not respond to systemic treatment. **Level of evidence: 2C; Strength of recommendation: B; Degree of agreement: 0.95.**

Due to the lack of quality data on the efficacy of the use of systemic CSs in PsA and the known adverse effects, their long-term use is not recommended. **Level of evidence: 5; Strength of recommendation: D; Degree of agreement: 0.94.**

What is the evidence for the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with psoriatic arthritis?

Peripheral arthritis

Short-term studies (2–4 weeks) show clinical scores improvement, including pain, joint swelling, morning stiffness and pain intensity [87, 88].

Small trials comparing different NSAIDs reported improvements regarding clinical parameters, pain and functional evaluations but were not able to demonstrate efficacy differences [89–91].

Axial disease

In patients with mild axial symptoms (inflammatory low back pain without functional loss or radiographic progression), the use of NSAIDs can reduce pain and improve stiffness [92]. Two prospective randomized studies, 1 with celecoxib (selective COX-2 inhibitor) [93] and 1 with diclofenac (nonselective NSAID) [94], evaluated radiographic inhibition in patients with AS, comparing the continuous and on-demand use of the drug over 2 years. In the study with celecoxib, less radiographic progression was observed in the continuous use group than in the on-demand group [93] ($p = 0.002$), and a post-hoc analysis showed that this reduction was greater in patients with evidence of inflammatory activity (erythrocyte sedimentation rate (ESR) and CRP) [95]. In the study with diclofenac, this difference was not observed [94] ($p = 0.39$). Thus, the decision to use NSAIDs continuously or not may vary depending on symptom severity, patient preferences and concomitant comorbidities, particularly gastrointestinal, renal and cardiovascular comorbidities.

Enthesitis

There are no adequately designed clinical studies that evaluate the effect of NSAIDs on enthesitis [96], but based on clinical experience and expert opinion, NSAIDs may be the first-line treatment in these cases [9].

Dactylitis

There are no clinical studies evaluating the use of NSAIDs in cases of dactylitis, but in daily practice, NSAIDs are the most commonly prescribed medications [97].

The evidence that the use of NSAIDs can trigger or exacerbate PsO is weak and based on case reports [98–100]. A single case–control study found a greater chance of exacerbation of skin lesions in patients who recently used NSAIDs (OR = 3.7; 95%CI 1.6–7.1) [101]. The

possibility should be considered that skin lesion exacerbation occurs simultaneously with arthritis, and thus, there is a potential bias in the observed associations [98–101]. The NSAIDs already described as potential triggers of PsO skin lesions are indomethacin [98], phenylbutazone [99], ibuprofen [100], diclofenac and naproxen [101].

Recommendation The use of NSAIDs is recommended as a symptomatic treatment in cases of peripheral arthritis **Level of evidence: 1B; Strength of recommendation: A; Degree of agreement: 0.95**, enthesitis **Level of evidence: 5**; **Strength of recommendation: D; Degree of agreement: 0.96**, dactylitis **Level of evidence: 5 Strength of recommendation: D; Degree of agreement: 0.96**, and axial manifestations **Level of evidence: 5; Strength of recommendation: D; Degree of agreement: 0.96.**

There is no evidence of a difference in efficacy among NSAIDs. **Level of evidence: 1B**, **Strength of recommendation: B; Degree of agreement: 0.96**.

The choice of the drug should be based on the physician's familiarity with the drug and the patient's individual preference, respecting the concomitant clinical conditions **Level of evidence: 5; Strength of recommendation: B; Degree of agreement: 0.96.**

What is the evidence for the use of conventional DMARDs in the treatment of psoriatic arthritis?

Methotrexate (MTX)

MTX is one of the most widely used cDMARDs worldwide for the treatment of PsA, [102, 103] despite few clinical trials evaluating its effectiveness [104] and controversial clinical evidence.

A study in which patients were administered MTX at a dose of 2.5–5.0 mg every 12 h for 3 consecutive days for 12 weeks showed, compared to patients who did not use it, no benefit in relation to swelling, morning stiffness, pain, or joint involvement, but there was a reduction in the physician-rated evaluated severity score [105].

In another open-label, prospective, randomized study with 35 patients with recent-onset oligoarticular PsA, the use of intramuscular MTX 10 mg/week combined with NSAIDs was compared with the use of NSAIDs for 3 months. Significant improvement ($p<0.05$) was observed regarding the number of painful and swollen joints, ESR, visual analog scale (VAS) for pain and physician global assessment in both groups. A comparison between groups showed significant superiority in terms of number of painful and swollen joints in those on MTX. After this period, the placebo group received MTX, for a duration of 6 months, and comparisons between the groups at the end of 6 months showed no significant differences [106].

The Methotrexate In Psoriatic Arthritis (MIPA) study showed that after 6 months, oral MTX at a dose of 15 mg/week was not superior to NSAIDs for reducing painful and swollen joints, as evaluated by the Psoriatic Arthritis Response Criteria (PsARC) (OR = 1.77; 95%CI 0.97–3.23), DAS-28 (OR = 1.70; 95%CI 0.90–3.17) and American College of Rheumatology 20% improvement criteria (ACR20) (OR = 2.00; 95%CI 0.65–6.22), although there were significant improvements in the following outcomes: patient ($p=0.03$) and physician ($p<0.001$) global assessment and skin scores ($p=0.02$) [107].

The TIght COntrol of inflammation in early Psoriatic Arthritis (TICOPA) study, an open-label, randomized controlled, parallel group trial with 206 patients evaluated, for 48 weeks, the target-based model for the treatment of patients with early PsA. The evaluations were performed every 4 weeks, with MTX dose escalation (15, 20, 25 mg/week) and subsequent combination with other cDMARDs as needed to achieve the MDA response. Patients undergoing target-based treatment showed better results than patients receiving standard therapy, with a greater probability of achieving ACR20 (OR = 1.91; 95%CI 1.03–3.55, $p=0.039$), ACR50 (OR = 2.36; 95%CI 1.25–4.47, $p=0.008$), ACR70 (OR = 2.64; 95%CI 1.32–5.26, $p=0.006$) and ≥ 75% PASI improvement (PASI75) (OR = 2.92; 95% CI 1.51–5.65, $p=0.001$) [108].

In a double-blind study, 851 patients with PsA were randomly allocated at a 1:1:1 ratio into 3 treatment arms: subcutaneous (sc) MTX 20 mg/week monotherapy, etanercept (ETN) 50 mg/week monotherapy, and MTX 20 mg/week + ETN 50 mg/week combination therapy; an evaluation at week 24 found that the ACR20 (50.7% vs. 60.9% vs. 65.0%, respectively) and MDA (22.9% vs. 35.9% vs. 35.7%, respectively) responses were significantly higher in patients who received ETN monotherapy vs. MTX monotherapy (ACR20, $p=0.029$ and MDA $p=0.005$) and in patients who received combination therapy vs. MTX monotherapy (ACR20, $p=0.005$ and MDA $p=0.005$). Patients in the 2 ETN groups showed less radiographic progression at week 48 than did patients who received MTX monotherapy [109]. Thus, although the results for MTX monotherapy had been inferior to those observed for ETN, ACR20 was achieved by 50% and MDA by 23% of patients who received MTX monotherapy, and thus, it could be an initial approach for patients with peripheral disease.

Cyclosporine (CSP)

A multicenter, randomized, open, controlled trial evaluated 99 patients with PsA (1:1:1) treated with CSP (3–5 mg/kg/day) or SSZ (2 g/day) for 6 months, both combined with symptomatic therapy (NSAIDs, analgesics and/or prednisone ≤ 5 mg/d), or treated with

symptomatic therapy alone. There was a significant difference regarding pain reduction (VAS) in the CSP versus SSZ and symptomatic therapy groups ($p < 0.05$). There was also a greater reduction of swollen joints number ($p = 0.05$), painful joints ($p = 0.01$), joint pain/sensitivity score ($p = 0.002$), spondylitis functional index ($p = 0.002$), and patient and physician global assessments, in favor of CSP versus symptomatic therapy. In the comparison between SSZ and symptomatic therapy, there was a reduction only in the spondylitis functional index in the SSZ group ($p = 0.03$) [110].

A small, open-label, controlled and randomized prospective study evaluated 35 patients with PsA treated with CSP (3–5 mg/kg/day) or MTX (7.5–15 mg/week) and found that after 12 months, the medications had similar benefits regarding improvements in joint pain/swelling, morning stiffness, grip strength, CRP and inflammatory disease activity based on patient and physician global assessments [111].

An open, non-randomized, prospective 12-month study compared patients who received CSP (2.5–3.75 mg/kg/day), adalimumab (ADA) (40 mg 14/14 days) or a combination of both; a PsARC response was observed in 65%, 85% and 95% of patients, and an ACR50 response was observed in 36%, 69% and 87% of patients on the 3 different therapeutic regimens, respectively [112], demonstrating the benefit of CSP, the superiority of the immunobiologic ADA relative to CSP, and synergism, with better response when CSP is used in combination with the immunobiologic ADA [113].

Leflunomide (LFN)

A double-blind, randomized, placebo-controlled study evaluated the use of LFN (100 mg/day for 3 days followed by 20 mg/day) in 190 patients with PsA and observed a 29.2% increase in PsARC response (NNT: 3), 16.3% increase in ACR20 response (NNT: 6) and improvement in HAQ functional capacity, with a reduction of 0.19 [113]. In the same study, clinical improvements in skin lesions, as assessed by the PASI75, were significantly higher in the LFN group (17.4% vs. 7.8%, $p = 0.048$). The main adverse events observed were diarrhea and increased transaminases in the LFN group [113].

An observational cohort study was conducted to evaluate the efficacy and safety of LFN alone or in combination with MTX in patients with PsA. Of 85 patients, 43 (50.6%) used LFN alone, and 42 (49.4%) received combined LFN and MTX therapy. Thirty patients (16 LFN and 14 LFN + MTX) discontinued treatment due to toxicity. Of the 55 patients who continued using the drugs, there was a $\geq 40\%$ reduction in the count of actively inflamed joints in 38%, 48% and 56% at 3, 6 and 12 months, respectively. PASI75 was reached by 19% of patients at 3 and 6 months and by 32% at 12 months. Those who received MTX were more likely to achieve a PASI50 response [114].

Sulfasalazine (SSZ)

A multicenter, prospective, double-blind, randomized, placebo-controlled study compared the efficacy and tolerability of SSZ in patients with PsA and, after 24 weeks, showed only a reduction in pain, as measured by VAS, without differences in other outcomes, including morning stiffness, affected joints number or the Ritchie joint index [115].

Two other studies, with short-term follow-up and a reduced number of patients, demonstrated a minimal effect of SSZ when compared to placebo in relation to pain, morning stiffness and global disease activity assessment [116, 117].

Recommendation The use of methotrexate (MTX) is recommended as the first choice among cDMARDs for the treatment of skin and peripheral joint involvement in PsA **Level of evidence: 1B**, preferably at doses higher than 15 mg/week and subcutaneously. **Level of evidence: 5 Strength of recommendation: B; Degree of agreement: 0.93.**

If MTX is not available or cannot be used regarding safety issues, CSP, LFN or SSZ could be used in cases of peripheral arthritis **Level of evidence: 2B; Strength of recommendation: B; Degree of agreement: 0.93.**

There is NO scientific evidence for using cDMARDs in patients with axial involvement, as well as there is limited evidence for enthesitis. **Level of evidence: 5; Strength of recommendation: D; Degree of agreement: 0.89.**

Treatment of PsA with immunobiologics and targeted synthetic drugs In addition to the drugs commercially available in Brazil at the time of the systematic literature review (December 2019), guselkumab (approved in 2020 for PsA) [118, 119] and direct comparison studies also published in 2020 [120, 121] were included.

1. Biologic DMARDs (bDMARDs)

   - Tumor necrosis factor inhibitors (TNFi): monoclonal antibodies (infliximab, adalimumab, golimumab, certolizumab pegol) and soluble receptor (etanercept)
   - Interleukin-17 inhibitors (IL17i)/anti-IL17 (secukinumab and ixekizumab)
   - Interleukin-12/23 inhibitors (IL12/23i)/anti-IL2/23 (ustekinumab)
   - Interleukin 23 inhibitors/anti-IL23 (guselkumab)
   - T-lymphocyte costimulation inhibitor (abatacept)

2. Targeted synthetic or small-molecule DMARDs (tsDMARDs)
   - Janus kinase 1 and 3 inhibitor (JAKi) (tofacitinib)

Phase 3 clinical studies with different bDMARDs (abatacept [122], adalimumab [123], certolizumab [124], etanercept [125, 126], golimumab [127], infliximab [128], ixekizumab [129], secukinumab [130, 131], ustekinumab [132], guselkumab [118, 119], and tsDMARDs (tofacitinib [133]) and a meta-analysis demonstrated the superiority of these drugs relative to control groups (patients using NSAIDs and/or cDMARDs) for skin (PASI) and joint outcomes [Health Assessment Questionnaire-Disability Index (HAQ-DI) and ACR20, ACR50 and ACR70 efficacy criteria)].

When are biologic DMARDs or targeted synthetic DMARDs indicated for the treatment of PsA?

bDMARDs should be initiated in patients with PsA and peripheral arthritis who present with active disease despite the use of at least one cDMARD (preferably MTX) for a minimum period of 3 months. Active disease can be defined by the presence of any of the following conditions: peripheral arthritis, spinal inflammation, enthesitis, dactylitis or skin or nail lesion due to PsO and/or extra-articular manifestations such as uveitis or inflammatory bowel disease. Active disease can also be defined using measures that evaluate peripheral joint involvement, such as the DAPSA or MDA (Tables 1 and 2), and axial involvement, such as the BASDAI or ASDAS-CRP (Tables 3 and 4).

Although evidence regarding the efficacy of MTX in PsA is controversial and is based on studies with low methodological quality and using low doses of the drug [109, 133, 134], a course of MTX $\geq$ 15 mg/week for at least 3 months should be attempted before switching treatment to a bDMARD. The tsDMARD tofacitinib can be used in patients with peripheral arthritis in cases of failure of at least 1 bDMARD for a minimum of 3–6 months or when a bDMARD cannot be used.

For PsA with axial involvement, a bDMARD should be started after failure with at least 2 NSAIDs, preferably from different classes, used for a minimum period of 30 days each. This recommendation is based on studies conducted in patients with axial spondyloarthritis because there is still no consensus regarding axial PsA, and the first study that recruited patients with these characteristics did not include in their inclusion criteria imaging tests that confirmed this diagnosis [8, 135].

Recommendation

A bDMARD should be initiated in patients with PsA and peripheral arthritis who remain with active disease despite the use of cDMARD, preferably MTX, for at least 3 months. **Level of evidence: 1B; Strength of recommendation: A. Degree of agreement: 0.95.**

In the case of failure or inability to use a bDMARD, a tsDMARD can be used. **Level of evidence: 1B; Strength of recommendation: B. Degree of agreement: 0.95.**

The use of a bDMARD is recommended in patients with PsA and axial manifestations who remain with active disease despite the use of 2 classes of NSAIDs, in full dose, for at least 30 days each. **Level of evidence: 1B; Strength of recommendation: B; Degree of agreement: 0.92.**

Is there a difference in the efficacy of biologic DMARDs and targeted synthetic DMARDs in the treatment of PsA?

Abatacept (ABA)

In a clinical study, patients with PsA and previous failure of cDMARDs and/or anti-TNFs were randomly assigned to receive placebo, ABA 3 mg/kg, ABA 10 mg/kg or ABA at 2 doses, 30 mg/kg followed by 10 mg/kg. When the general population was analyzed (with and without previous use of anti-TNF) at 6 months of follow-up, there was an increase in the proportion of patients who achieved an ACR20 response with intravenous ABA treatment (NNT: 5) at the 30/10 mg/kg dose (23%) and (NNT: 4) at the of 10 mg/kg dose (29%). The was no difference in the ACR20 response between the 3 mg/kg dose and placebo. The ACR50/70 responses at 6 months were studied only as an exploratory analysis, and the authors described that the proportions of patients who achieved ACR50 and ACR70 were numerically higher among those receiving ABA compared to placebo: the difference was greater in the group receiving 10 mg/kg, with 25% of these achieving ACR50 and 13% achieving ACR70 [122].

Another randomized clinical trial compared sc ABA 125 mg weekly with placebo, evaluating the proportion of patients who achieved ACR20 at week 24: 39.4%, ABA versus 22.3%, placebo ($p < 0.001$); this efficacy was maintained at the 52nd week [136]. There was no significant difference in the proportion of patients in the ABA and placebo groups who achieved ACR50 and ACR70. The proportion of patients who achieved clinically significant improvements in the HAQ-DI at week 24 (decrease of at least 0.35 points compared to baseline) was evaluated: although numerically more patients achieved this outcome in the ABA group, there was no significant difference between the ABA and placebo groups (31.0% versus 23.7%, $p = 0.097$) [136].

Adalimumab (ADA)

In adult patients with moderate to severe active PsA, treatment with sc ADA 40 mg every 14 days increased the proportion of patients who achieved ACR20 (NNT: 2) by week 24 by 42% [123]. After 48 weeks, 56%, 44%

and 30% of patients who received ADA achieved ACR20, ACR50 and ACR70 responses, respectively [137].

When compared to placebo at week 24 in the ADEPT study, ADA had the following effects:

- increased the proportion of patients who achieved a clinically significant decrease in the HAQ-DI (decrease at least 0.3 points) by 23.6% (NNT: 4) at week 24 [138]; and
- increased the proportion of patients with complete resolution of HAQ-DI (HAQ-DI = zero) by 20.9% (NNT: 5) [138].

At 2 years of follow-up, in the same study, the percentages of patients who achieved ACR20, ACR50, and ACR70 responses were 57.3%, 42.7% and 29.9%, respectively. A full functional response (HAQ-DI = zero) was achieved by 38.5% of patients, and the proportion of patients who reached the clinically significant decrease for the HAQ-DI was 47.6% [138].

In another study, treatment with 40 mg ADA in alternating weeks for 24 weeks resulted in 65%, 43% and 27% of patients achieving ACR 20/50/70 responses, respectively [139].

Certolizumab (CTZ)

In 1 study, patients with PsA were randomly assigned to 1 of 3 groups: placebo, 200 mg of CTZ every 2 weeks or 400 mg of CTZ every 4 weeks [124]. Patients with previous anti-TNF therapy were not excluded. CTZ therapy resulted in the following:

- 27.6% increase (NNT: 4) in the proportion of patients who achieved ACR20 in week 12 (with the dose of 400 mg every 4 weeks) [124];
- 33.7% increase (NNT: 3) in the proportion of patients who achieved ACR20 in week 12 (with the dose of 200 mg every 2 weeks) [124].

Etanercept (ETN)

Compared to placebo, the treatment of patients with active PsA with ETN 25 mg twice a week for 12 weeks increased the ACR20 response by 60% (NNT: 2) and increased the functional response by 29% (NNT: 3) [125].

In another study, patients with PsA and an inadequate response to NSAIDs were treated with ETN 25 mg twice a week, with the following results compared to placebo:

- at week 12, the ACR20 response increased by 44% (NNT: 2) [125]; and
- at week 24, functional improvement (HAQ) increased by 48% (NNT: 2) [125].

These results were maintained long term: the ACR20 response in patients using ETN was 64% at 12 months [140].

Another study evaluated outcomes reported by patients and found that in patients with PsA treated with ETN 25 mg twice a week, 47.2% exhibited improvements in the HAQ-DI at 24 weeks, with 41.2% of patients showing a full response (HAQ-DI = zero) at 48 weeks [141].

Golimumab (GOL)

In the GO-REVEAL study, among patients diagnosed with PsA and with inadequate response to cDMARDs and NSAIDs treated with GOL 50 mg or 100 mg every 4 weeks, 42% and 36% achieved an ACR20 response at 14 and 20 weeks, respectively, regardless of combined treatment with MTX [127]. At week 24, patients treated with GOL 50 and 100 mg had better physical function scores than did patients who received placebo [142].

With GOL, a sustained clinical response was maintained at 2 years; at week 104, 63%, 46% and 29% of patients receiving GOL 50 mg every 4 weeks achieved ACR20, ACR50 and ACR70 responses, respectively [143]. A sustained clinical response was also maintained at 5 years (62.8% with an ACR20 response, 43.4% with an ACR50 response and 30.8% with an ACR70 response with a dose of 50 mg every 4 weeks) [144].

Patients with PsA diagnosed at least 6 months prior and who were naive to biologic treatment received intravenous GOL at a dose of 2 mg/kg at weeks 0 and 4 and thereafter every 8 weeks. At week 24, compared to placebo, GOL treatment resulted in the following:

- 52.5% increase in the ACR20 response (NNT: 2) [145];
- 47.2% increase in the ACR50 response (NNT: 2) [145]; and
- a greater decrease in HAQ compared to baseline (−0.63 vs. − 0.14; $p<0.05$) [145].

Guselkumab (GUS)

GUS was superior to placebo in a phase 2 clinical trial, with 58% of patients with PsA receiving 100 mg GUS on weeks 0 and 4 and every 8 weeks thereafter, achieving ACR20 on week 24; in comparison, 18% of patients receiving placebo achieved the same outcome (NNT = 3) [146].

A randomized, double-blind, phase 3 clinical trial that studied the efficacy of guselkumab in patients with PsA with previous failure of cDMARDs used the proportion of patients who achieved ACR20 at week 24 as an outcome. This study showed that GUS was superior to placebo: 33% of patients in the placebo group

achieved ACR20 at week 24, and 64% of patients who received GUS every 4 weeks (NNT = 3) and 64% of those who received GUS at weeks 0 and 4 and every 8 weeks thereafter (NNT = 3) achieved ACR20 at week 24 [119]. At week 24, patients using GUS also showed a greater decrease in the HAQ-DI compared to baseline than did patients receiving placebo [119].

Infliximab (IFX)

The results of the IMPACT 1 study showed that among patients with a diagnosis of PsA established for more than 6 months, with cDMARD treatment failure, and with peripheral polyarthritis treated with IFX 5 mg/kg on weeks 0, 2, 6 and 14, 55% achieved an ACR20 response in week 16 (NNT: 2), 46% achieved an ACR50 response (NNT: 2), and 29% achieved an ACR70 response (NNT: 3) [128].

In the IMPACT 2 study, which evaluated patients with the same profile described above, the following results were reported for the infliximab 5 mg/kg group compared to the placebo group at week 24:

- higher ACR20 (38%; NNT: 2), ACR50 (37%; NNT: 3), ACR70 (25%; NNT: 4) response rates [147]; and
- 32% increase (NNT: 3) in the proportion of patients who achieved a clinical response (HAQ) [147].

After 2 years of follow-up, the ACR20, ACR50 and ACR70 response rates in the IFX group were 45%, 45% and 35%, respectively [148].

Ixekizumab (IXE)

Patients with PsA who never received biologic therapy were randomly assigned to 1 of 4 groups administered the following subcutaneous injections: placebo (N = 106), IXE 80 mg every 2 weeks (N = 103), IXE 80 mg every 4 weeks (N = 107) or ADA (active control) 40 mg once every 2 weeks (N = 101). Both IXE regimens included an initial dose of 160 mg. The primary objective was to compare the proportion of patients in the placebo and IXE groups who achieved ACR20 at week 24. The study had no objective nor the power to compare ADA and IXE. At week 24, IXE, compared to placebo, increased the proportion of patients who achieved ACR20 by 31.9% (NNT: 3) at the dose given every 2 weeks and by 27.7% (NNT: 4) at the dose given every 4 weeks [129]. At weeks 12 and 24, functional disability improved significantly with both IXE dosages compared to placebo [129].

Secukinumab (SEC)

In a phase 3 study to evaluate the efficacy and safety of SEC (75, 150 and 300 mg) in patients with PsA, the ACR20 response after 24 weeks was 54% with 300 mg SEC, 51% with 150 mg SEC, 29% with 75 mg SEC and 15% with placebo [131].

In a randomized, double-blind clinical trial, SEC (75 and 150 mg) was compared to placebo in patients with active PsA previously treated with cDMARDs or anti-TNFs. The following ACR20 response rates were observed at week 24: 50% and 50.5% in the SEC 150 and 75 mg groups and 17.3% in the placebo group. Improvements were maintained until week 54 [131].

Patients with active PsA were treated with SEC 300 mg, 150 mg, 75 mg or placebo at weeks 0, 1, 2, 3, and 4 and every 4 weeks thereafter [149]. At week 24 in the general study population (with or without previous use of anti-TNFs), the following were observed:

- compared to placebo, SEC 300 mg increased the proportion of patients who achieved ACR20 by 38.7% (NNT: 3) [149]; and
- compared to placebo, SEC 150 mg increased the proportion of patients who achieved ACR20 by 35.7% (NNT: 3) [149].

Among the patients who previously used anti-TNFs, only those who received SEC 300 mg had outcomes that were significantly different from those for patients in the placebo group, with SEC 300 mg increasing the proportion of patients who achieved ACR20 (31.2% increase, NNT: 4), ACR 50 (18.7% increase, NNT: 6) and ACR70 (15.2% increase, NNT: 7) [149].

Regarding functional improvement at week 24 (measured by the decrease in HAQ-DI score from baseline), both SEC 150 and 300 mg were more effective than placebo in patients who had not previously used anti-TNFs, and the 300 mg dose was more effective than placebo in patients who previously used anti-TNFs [149].

Tofacitinib (TOF)

One study evaluated the efficacy of oral TOF 5 mg twice daily and 10 mg twice daily versus placebo in patients with prior cDMARDs failure, using sc ADA 40 mg every 2 weeks as an active comparator. At 3 months, in the group that received TOF 10 mg twice daily, 28% (NNT: 4) of patients achieved an ACR20 response and 30% (NNT: 3) achieved an ACR50 response, and patients who received TOF had better functional outcomes than those who received placebo (decrease in HAQ-DI of − 0.4 with TOF vs. − 0.18 with placebo; $p < 0.05$) [133].

Ustekinumab (UST)

In patients with active PsA, treatment with UST increased the ACR20, ACR50 and ACR70 response rates by 28% (NNT: 4), 18% (NNT: 6) and 11% (NNT: 9), respectively, at the 12th week of follow-up [132].

At week 12, in the UST group, there was a 25% increase (NNT: 4) in the proportion of patients who achieved clinically significant improvement on the HAQ (decrease of at least 0.3 points) [132].

Another study showed that UST increased the proportion of patients who achieved an ACR20 response by 23.6% at week 24 (NNT: 4) [150]. In a subgroup of patients previously treated with anti-TNFs, efficacy was also observed; at week 24, the following results were obtained (UST versus placebo): ACR20, 35.6% vs 14.5% and mean change in HAQ-DI compared to baseline, − 0.13 versus 0.0 [150].

At week 52, UST efficacy was maintained, with 38.9% of patients achieving ACR20 and with a mean change of − 0.13, compared to baseline, on the HAQ-DI [150].

Direct comparison studies involving anti-IL17 and anti-TNF immunobiologics A randomized, multicenter, nonblind clinical trial compared IXE versus ADA in patients with PsA and previous cDMARD failure; the evaluator of the primary outcome was blinded, but patients and investigators were not blinded. The primary outcome in this study was a composite outcome: proportion of patients who simultaneously achieved ACR50 and PASI100. Regarding the simultaneous outcome ACR50 + PASI100, IXE was superior to ADA (36% IXE vs. 28%; $p = 0.036$). When only the articular outcome was evaluated (ACR50), there was no significant difference between the 2 drugs (51% IXE vs. 47% ADA). When only the cutaneous outcome (PASI100) was analyzed, IXE generated a better response than ADA (60% IXE vs. 47% ADA) [120].

A randomized double-blind clinical trial compared SEC with ADA and used the proportion of patients who achieved ACR20 at week 52 as the primary outcome. This study did not demonstrate the superiority of SEC over ADA for the primary outcome (67% SEC vs. 62% ADA), but treatment with SEC was associated with a higher drug retention rate [121].

There are no direct comparison studies among the TNFa inhibitors, but an indirect evaluation showed no clinically relevant efficacy difference [151, 152].

A direct comparison of anti-TNF and anti-IL-17 drugs showed no difference between the classes regarding their efficacy in musculoskeletal symptoms, but anti-IL-17 drugs were superior for the treatment of skin manifestations of PsO [120, 121].

No direct comparison studies involving drugs with other mechanisms of action, such as ABA (T-lymphocyte co-stimulation inhibitor) and GUS (anti-IL-23), were available at the time these recommendations were performed.

During the implementation of these recommendations, the results of the first direct comparison of a Janus kinase 1 inhibitor (upadacitinib, UPA) and ADA were presented [153]; the results indicated the superiority of upadacitinib 30 mg compared to ADA in achieving ACR20 at week 12. In addition, MDA was more achieved by PsA patients with prior inadequate response or intolerance to at least one b-DMARD taking UPA 15 mg/ day than placebo at week 24 (28.9% vs. 2.8%, $p < 0.001$). However, the study (SELECT PSA1) had not yet been published at the time of publication of these recommendations and the drug upadacitinib was not commercially available for the treatment of PsA in Brazil.

Recommendation For the treatment of peripheral arthritis, dactylitis and enthesitis, the use of any of the following drugs is recommended: anti-TNFs (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), anti-IL-17 (ixekizumab and secukinumab), anti-IL-12/23 (ustekinumab) and anti-IL-23 (guselkumab). **Level of evidence: 1B; Strength of recommendation: A; Degree of agreement: 0.98.**

The choice of drug and mechanism of action should take into account patient preference (in regard to the route of administration and frequency of use, for example), concomitant clinical conditions, medical history (e.g., history of tuberculosis, fungal infections, and herpes zoster), cost, availability in the health system and presence of extra-articular manifestations of PsA. **Level of evidence: 5; Strength of recommendation: D; Degree of agreement: 0.99.**

In patients with axial manifestations, the use of anti-TNF and anti-IL-17 drugs is preferentially recommended. **Level of evidence: 1B; Strength of recommendation: B; Degree of agreement: 0.98.**

In patients with PsA and severe PsO, anti-IL-23, anti-IL-17, and anti-IL-12/23 drugs are preferentially recommended over anti-TNFs. **Level of evidence: 1B; Strength of recommendation: A; Degree of agreement: 0.95.**

In patients with recurrent uveitis, the use of anti-TNF monoclonal antibodies is recommended. **Level of evidence: 1B; Strength of recommendation: B; Degree of agreement: 0.99.**

In patients with concomitant active Crohn's disease, the use of IFX, ADA, CTZ, and UST is preferentially recommended. **Level of evidence: 1B; Strength of recommendation: B; Degree of agreement: 0.98.**

In patients with concomitant active ulcerative colitis, the use of IFX, ADA, GOL, UST or TOF is preferentially recommended. **Level of evidence: 1B; Strength of recommendation: B; Degree of agreement: 0.98.**

Is there a difference in the safety of biologic DMARDs in the treatment of PsA?

Tuberculosis

TNF is part of the type I immune response and plays an important role in the host defense against intracellular pathogens, such as mycobacteria, and it is essential for granuloma formation. TNF inhibitor treatment was associated with several reported cases of TB [154–158].

In contrast, to date, there has been no report of latent tuberculosis infection (LTBI) reactivation in patients using anti-IL17, and in UST phase III trials, of the 167 patients with LTBI before treatment, only 1 patient who did not receive treatment with isoniazid experienced LTBI reactivation [159]. There are still not enough data on GUS to draw conclusions.

There is clearly a lower risk of LTBI activation in patients using non-TNF biologics. However, there is no contraindication to the use of anti-TNFs in patients with LTBI, but treatment with these agents should preferably be started 30 days after the start of treatment for LBTI.

Candidiasis

Interleukin-17 is part of the type 17 immune response and plays a role in the defense against fungal infections. The number of *Candida* infectious events was higher in patients treated with anti-IL17 than in those treated with placebo [120, 121].

In direct comparison studies of anti-IL-17 versus anti-TNF, as expected, a higher rate of *Candida* infections was identified in patients using anti-IL-17 (SPIRIT H2H: 2.5% IXE vs. 0.7% ADA; EXCEED: 4% SEC vs. 2% ADA) [120, 121].

In general, when a patient develops oral and/or esophageal candidiasis, this event usually occurs during the induction period; the use of the biologic should be continued, and concomitant treatment with oral systemic antifungals should be administered. Notably, disseminated candidiasis has not been observed to date.

Demyelinating disease

Although there is a lack of evidence supporting a causal relationship between TNF blockade and the onset of demyelinating diseases, a 0.02–0.2% incidence rate for demyelinating disorders has been described in patients undergoing treatment with these agents [160–167].

The use of anti-TNF therapy should be avoided in patients with a family history or occurrence of multiple sclerosis or other demyelinating diseases [168, 169].

To date, there are no reports of worsening or onset of demyelinating diseases in patients treated using IL-17 and IL-12/23 inhibitors, suggesting that their use is safe in these patients (23, 24) [170, 171]. Regarding the use of anti-IL-23, there are not sufficient data to provide recommendations.

Herpes zoster

A higher incidence of herpes zoster was observed among patients with PsA who used TOF than among those who received placebo [172] and among those who used ADA [133].

General serious adverse events and discontinuation due to adverse events

Regarding serious adverse events and the treatment discontinuation rate due to adverse events, there is no apparent difference among biologic classes in pivotal studies or in indirect comparison studies [129–131, 149, 173–175].

Studies comparing IXE and ADA reported that adverse events were more frequent in patients who received IXE (69.6% IXE vs. 61.1% ADA). However, ADA was associated with more serious adverse events (3.5% IXE vs. 8.5% ADA). In addition, there was no significant difference in the drug discontinuation rate due to serious or nonserious adverse events [120].

Another randomized double-blind study that compared SEC to ADA did not find a difference in the proportion of patients presenting general adverse events (77% SEC vs. 79% ADA) or serious adverse events (8% SEC vs. 7% ADA). Patients using ADA had more hypersensitivity reactions (9% SEC vs. 14% ADA), and the discontinuation rate due to adverse events was higher in the ADA group: 3.5% (SEC) vs. 7% (ADA) [121].

Recommendation

Screening and treatment of LTBI or active disease is recommended before using any immunobiologics and JAK inhibitors. **Level of evidence: 2B; Strength of recommendation: B; Degree of agreement: 0.98.**

In general, the biologics used for the treatment of PsA have similar safety profiles, and the particularities inherent to the cytokine to be inhibited should be considered. **Level of evidence: 5; Strength of recommendation: B; Degree of agreement:**

Degree of agreement: 0.96

The use of anti-TNFs in patients with demyelinating disease or class III or IV heart failure is not recommended. **Level of evidence: 4; Strength of recommendation: C; Degree of agreement: 0.99.**

The use of JAK inhibitors in patients with history of disseminated or recurrent herpes zoster is not recommended. **Level of evidence: 1B; Strength of recommendation: A; Degree of agreement: 0.99.**

The use of IL-17 inhibitors in patients with a history of severe or recurrent fungal infections is not recommended. **Level of evidence: 1B; Strength of recommendation: A; Degree of agreement: 0.98.**

Is there evidence for the use of conventional DMARDs combined with biologic DMARDs or target synthetic DMARDs?

To date, there was no difference in efficacy between monotherapy with bDMARDs and combined therapy with bDMARDs and MTX. Pivotal studies on anti-TNF agents for the treatment of PsA allowed patients receiving MTX at the beginning of the study to continue or stop using MTX, and similar clinical responses were observed between patients who received combined therapy with MTX and those who received anti-TNF monotherapy [123, 124, 126, 127, 176]. The SEAM-PsA study (Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis), comparing MTX monotherapy vs. ETN monotherapy vs. MTX combined with ETN, evaluated patients with early PsA and observed that combined therapy was not superior to anti-TNF therapy alone but that both were superior to MTX monotherapy [177]. Observational studies found higher percentages of patients with PsA receiving MTX combined with anti-TNFs than receiving anti-TNF monotherapy. Similar to clinical trials, data obtained from registers such as SSTA (South Swedish Arthritis Treatment Group Register) and NOR-DMARD (NORwegian DMARD Register) showed that combined therapy with MTX did not influence the therapeutic response [178, 179]. A small benefit of the concomitant use of MTX and anti-TNFs was observed in the ACR20 response rate in patients in the DANBIO (DANish BIOlogics Registry) [180] and in the ACR20/50/70 outcomes in the ADA arm of the SPIRIT H2H study [120].

Regarding the drug retention rate, studies results are divergent. In the SSTA registry, there was better retention of bDMARDs with concomitant use of MTX due to the lower occurrence of adverse events [6], and in the NOR-DMARD registry and British Society for Rheumatology Biologics Register (BSRBR), higher retention was observed for patients treated with IFX and ADA who received MTX concomitantly, which was not observed for patients treated with ETN [179, 181]. The Analyses of the COnsortium of Rheumatology Researchers of North America (CORRONA) registry showed no difference in anti-TNF persistence between patients on combined therapy and monotherapy (32.4 vs. 30.8 months, $p=0.73$); however, when anti-TNF agents (ADA, ETN, IFX) were analyzed separately, the concomitant use of MTX increased IFX persistence [180, 182]. Thus, outcomes may depend on the anti-TNF agent evaluated and possible anti-drug antibody formation. Immunogenicity in response to anti-TNF therapy may result in lower serum drug concentrations, loss of therapeutic response and shorter drug survival [22, 23]. The concomitant use of MTX may reduce the formation of anti-drug antibodies [147, 180, 182].

Studies of UST, SEC and IXE [129, 183] showed no differences between patients who received MTX and those who did not [130, 131, 150, 184]. No data were reported in the studies on TOF [133, 172] and GUS [118, 119, 180].

Recommendation

Regarding monoclonal anti-TNF biologics, the concomitant use of MTX is recommended to increase drug survival, **Level of evidence: 2B; Strength of recommendation: B,** although there is no evidence of increased efficacy **Level of evidence: 1B; Strength of recommendation: A. Degree of agreement: 0.88.**

Regarding tsDMARDs or biologics other than anti-TNF, there is no evidence of increased efficacy or drug survival with concomitant use of cDMARDs. **Level of evidence: 1B; Strength of recommendation: A**. **Degree of agreement: 0.97.**

Is there evidence for switching biologic and small-molecule DMARDs in patients with psoriatic arthritis?

Treatment switch in patients with PsA occurs due to therapeutic failure, which may be due to inefficacy, adverse events, difficulties in accessing the drug or inability to administer it [131, 133, 149, 150, 183, 185–188].

Approximately 30 to 50% of patients with PsA discontinue anti-TNFs during the first year of treatment due to adverse events or inefficacy. Throughout follow-up, it has been found that treatment effectiveness decreases [11, 189].

The literature does not present evidence for all possible switches, but with more use experience, data accumulate that support the eventual need for replacements.

When the reason for switching from an anti-TNF drug to a second anti-TNF drug was the occurrence of adverse events, an adequate response was observed in 60% of patients, while in patients in whom the switch was due to primary failure, the response rates varied between 20 and 80%, and lower rates were related to a third anti-TNF drug [185–191].

The drug retention rate tends to decrease with time of use: it is lower with the second agent and even lower with a third agent [192, 193].

Recommendation

In patients with PsA and failure to bDMARD, switching to any other immunobiologic agent or to JAK inhibitors is recommended, with no differences between

drugs **Level of evidence: 1B**, and the most relevant manifestations of the disease and concomitant clinical conditions should be considered **Level of evidence: 5; Strength of recommendation: B**. **Degree of agreement: 0.96.**

When the therapeutic failure of an anti-TNF agent is attributed to skin inflammatory activity, switching to drugs with another mechanism of action, such as anti-IL23, anti-IL17 or anti-IL-12/23 agents, can be evaluated. **Level of evidence: 1B; Strength of recommendation: B. Degree of agreement: 0.95.**

When the therapeutic failure of any anti-TNF agent is attributed to serious adverse events, especially infections, switching to drugs with another mechanism of action, such as anti-IL-17, anti-IL-12/23, and anti-IL23 agents or selective costimulation modulator, can be considered. **Level of evidence: 2B; Strength of recommendation: B; Degree of agreement: 0.98.**

If there is a preference for oral medication or contraindications to injectable medications, the use of tofacitinib may be considered. **Level of evidence: 5; Strength of recommendation: D; Degree of agreement: 0.96.**

Conclusions

The recommendations presented here bring together the current scientific evidence for doctors and other health professionals involved in the care of patients with psoriatic disease.

These guidelines considered the current criteria, therapeutic efficacy, safety and critical evaluation and experience of a panel of experts in the standardization of the clinical management of PsA.

However, the autonomy of professionals to choose the best approach among the different therapeutic options is respected and ensured. But it is necessary to take into account some factors that must be remembered when monitoring the treatment, such as:

1. Some DMARDs used in PsA treatment can impact untreated HBV and HCV. Patients should be screened for HBV and HCV prior to therapy initiation. Seek gastroenterology/hepatology input regarding the use of antivirals when initiating patients with active or past HBV on therapy. [194]
2. Biological therapy, especially TNFi, increased the risk of developing TB. Screening and treatment of LTBI or active disease is recommended before using any immunobiologics and JAK inhibitors. [195]
3. Many csDMARDs as well as bDMARDs and JAKi are associated with an increased risk for nonmelanoma skin cancer. Patients should be counseled to undergo full skin assessment annually [196].

Although the objective of this guideline has not included the questioning on therapeutic management after clinical remission in PsA patients, the most recent evidence has supported the tapering approach of cDMARDs and bDMARDs, according to the opinion of the physician and based on the validated instruments for measuring the disease activity.

Abbreviations

ACR: American College of Rheumatology; ASAS: Assessment of Spondyloarthritis International Society; ASDAS-PCR: Ankylosing Spondylitis Disease Activity Score with C Reactive Protein level; BASDAI: Bath Ankylosing Spondylitis Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BSA: Body surface área; CASPAR: Classification criteria for psoriatic arthritis; CORRONA: Consortium of Rheumatology Researchers of North America Registry; CRP: C reactive protein; CVD: Cardiovascular disease; DAPSA: Disease activity in psoriatic arthritis; DAS 28: Disease activity score in 28; DAS44: Disease activity score in 44 joints; bDMARD: Biologic disease-modifying antirheumatic drugs; cDMARD: Conventional disease-modifying antirheumatic drugs; tsDMARD: Targeted synthetic disease-modifying antirheumatic drugs; EARP: Early psoriatic arthritis screening questionnaire; ESR: Erithrocyte sedimentation rate; HAQ: Health assessment questionnaire; HAQ-S: HAQ modified for the Spondyloarthropathies; HIIT: High intensity interval training; MDA: Minimal disease activity; NSAIDs: Nonsteroidal anti-inflammatory drugs; NNH: Number need to harm; NNT: Number need to treat; PASE: Psoriatic arthritis screening evaluation; PASI: Psoriasis Area and severity index; hs-CRP: High sensitivity C reactive protein; PGA: Patient's global assessment; PGA: Physician global assessment; PEST: Psoriasis epidemiology screening tool; PsA: Psoriatic arthritis; PsARC : Psoriatic arthritis response criteria; PsO: Psoriasis; TOPAS-II: Toronto psoriatic arthritis screen-2nd version; VAS: Visual analogue scale; VLDA: Very low disease activity.

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