UNITED RHEUMATOLOGY

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CLINICAL PRACTICE GUIDELINE

Psoriatic Arthritis (PsA)

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Abbreviations

ACR	American College of Rheumatology
AS	Ankylosing spondylitis
axSpA	Axial spondyloarthritis
boDMARD	Biologic originator disease-modifying antirheumatic drug
bo/bs DMARD	Biologic originator/biosimilar disease-modifying antirheumatic drug
BSA	Body surface area
bsDMARD	Biosimilar disease-modifying antirheumatic drug
CASPAR	ClASsification criteria for Psoriatic ARthritis
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
DIP	Distal interphalangeal
DMARD	Disease-modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GI	Gastrointestinal
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire-Disability Index
HLA-B27	Human leukocyte antigen-B27
IBD	Inflammatory bowel disease
IBP	Inflammatory back pain
IL-12/23i	Interleukin-12/23 inhibitor
IL-17i	Interleukin-17 inhibitor
IL-23i	Interleukin-23 inhibitor
JAKi	Janus Kinase inhibitor
MDA	Minimal disease activity
MTX	Methotrexate
NPF	National Psoriasis Foundation
NSAID	Nonsteroidal anti-inflammatory drug
OSM	Oral small molecule—methotrexate, sulfasalazine, cyclosporine, leflunomide, apremilast
PASI	Psoriasis Area and Severity Index
PCV13	13-valent pneumococcal conjugate vaccine
PDE4i	Phosphodiesterase 4 inhibitor
PPSV23	23-valent pneumococcal polysaccharide vaccine
PsA	Psoriatic arthritis
QoL	Quality of life
RA	Rheumatoid arthritis

RF	Rheumatoid factor
SEAM-PsA	Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis
SI	Sacroiliac
TNFi	Tumor necrosis factor inhibitor
tsDMARD	Targeted synthetic disease-modifying antirheumatic drug
UC	Ulcerative colitis
US	United States
VAS	Visual analog scale
VLDA	Very low disease activity

Introduction

In the United States (US), approximately 3% of the general population (5 million adults) have been diagnosed with psoriasis. Between 0.4% and 2.28% of the population is reported to have undiagnosed disease.[1]

Psoriasis is a chronic inflammatory autoimmune disease of the skin, often presenting with scaly patches and epidermal hyperplasia. Patients complain of dryness, itching, redness, soreness, and even pain in the affected areas. The skin overlying the elbows, knees, scalp, lower back, face, palms, and soles of the feet are the most commonly affected areas. Skin disease is often marked by unpredictable remissions and flares. Epidermal hyperplasia is a response to the activation of the immune system mediated by $CD8^+$ and $CD4^+$ T lymphocytes.[2]

Psoriatic arthritis (PsA) is an autoimmune inflammatory arthritis that affects up to one third of the patients with psoriasis. It occurs equally in men and women between ages 30 to 50, and usually has a chronic progressive course. In addition to psoriasis, 80% to 87% of patients with PsA have concurrent psoriatic nail changes.[3, 4] The Toronto Psoriasis Cohort studied 464 patients with known psoriasis who had no evidence of PsA at the start of the study. During the course of the study (January 1, 2006 to September 5, 2014), 51 patients developed PsA and nine additional patients suspected of developing PsA were lost to follow up. The annual incidence of PsA in this study was 2.7 per 100 cases of psoriasis. The authors also found that there was an increased risk for developing PsA in patients with psoriatic nail lesions, severe psoriasis, a history of systemic retinoid use, and uveitis.[5] The majority of patients who develop PsA have a long history of psoriasis (up to 10 years prior to the development of PsA). In 15% of patients with PsA, psoriasis and PsA develop simultaneously; in an additional 15%, PsA appears before the skin disease. PsA is not commonly seen in African Americans or Asians.[6]

A study published in the *Annals of Rheumatic Disease* reported on 402 patients with a diagnosis of either PsA or ankylosing spondylitis (AS) (201 patients in each arm of the study) was designed to determine the incidence of overlapping disease.[7] Both groups were tested for human leukocyte antigen-B27 (HLA-B27) and C-reactive protein (CRP). The authors concluded that there was overlap of the two diseases, especially in patients with PsA who tested positive for HLA-B27. This suggests that PsA with axial disease may be considered as part of a spectrum of disease between AS and PsA (see *United Rheumatology Clinical Practice Guideline—Axial Spondyloarthritis (axSpA)*).

It is widely believed that both psoriasis and PsA are complex genetic, autoimmune/autoinflammatory disorders; however, the heritability of either disease is not completely understood.[8]

PsA can involve one or more of the following domains:[9-11]

- Peripheral arthritis (including measurement of tender and swollen joints)
- Axial disease
- Enthesitis
- Dactylitis
- Skin/psoriasis
- Psoriatic nail disease

- Sleep
- Fatigue
- Physical function
- Quality of life (QoL)
- Evidence of systemic inflammation (CRP/erythrocyte sedimentation rate [ESR])
- Depression and/or anxiety

It can be oligoarticular (≤4 joints) or polyarticular (≥5 joints) and may involve the distal interphalangeal (DIP) joints of the hands and feet only; or it may involve multiple joints, including the spine and sacroiliac (SI) joints. If the DIP joints are involved, nail changes are almost always present.[12]

PsA usually presents with joint pain and swelling, erythema, and warmth around the affected joint(s). Patients may also complain of joint stiffness or painful swelling and tenderness at the enthesis (bony insertion of ligaments, tendons, or joint capsules). Enthesitis (inflammation of the enthesis) most commonly occurs at the insertion of the plantar fascia, Achilles tendon, and around the elbow but can also be seen at the ligamentous attachments of the knees, ribs, spine, pelvis, and many other areas of the body. Dactylitis—a combination of enthesitis, tenosynovitis, and arthritis of all the joints of a single digit—is seen in up to 40% of patients with PsA. Clinically, when dactylitis is present, there is diffuse swelling of one or more digits.

PsA is often (but not always) asymmetric in distribution, especially early on in the course of the disease. This can help distinguish PsA from rheumatoid arthritis (RA), which is more commonly symmetric and less likely to involve the DIP joints than PsA. The distinction between PsA and RA is based on clinical and laboratory data. In addition to the small joints of the hands and feet, large joints of the lower extremities, spine, SI joints, and pelvis may be affected by PsA. Approximately 40% of patients with PsA will have spinal or SI joint involvement (spondyloarthropathy) causing back pain and progressive ankylosis similar to AS.[8] The majority of affected patients have peripheral PsA; only 5% have isolated axial PsA.

Sometimes, it is difficult to differentiate PsA from other rheumatic diseases, other types of arthritis, mechanical tendonitis, or fibromyalgia. Therefore, before treatment is started, it is essential that patients suspected of having PsA have a complete evaluation by a rheumatologist and, if there is significant skin involvement, a dermatologist as well. All PsA domains should be evaluated; including signs and symptoms of peripheral arthritis, skin psoriasis, enthesitis, dactylitis, axial joint disease (spondylitis or spondyloarthropathy, spine, and SI joints), and nail disease.

PsA can be very disabling and negatively impact the QoL of those affected. In a 2005 report in the *Journal of the American Academy of Dermatology*, 39% of the patients with PsA indicated that the disease was a significant or large problem in their everyday lives; 38% believed that it was a problem; and only 23% reported that it was a small problem or no problem in daily life.[13] Some patients with PsA are limited in their ability to perform activities of daily living, may be less productive at work, have increased absenteeism from work, and may be less likely to be employed than people without PsA. Patients may also suffer from decreased self-esteem and depression.

PsA can be associated with comorbidities, including but not limited to Type 2 diabetes, hyperlipidemia, obesity, hypertension, and cardiovascular diseases such as myocardial infarction, congestive heart failure,

cardiomyopathy, angina, and stroke.[14] These comorbidities are seen more frequently in patients with PsA than in those with only involvement of the skin. In addition, there may be an increased incidence of liver and gastrointestinal (GI) diseases, fibromyalgia, autoimmune eye disease, as well as depression.[15] In 2013, Husted et al. published a study of 631 patients with PsA and found that 42% had three or more comorbidities.[14]

Data on the economics of caring for patients with PsA is not widely available. Some reports combine patients with psoriasis only with patients having psoriasis and PsA. Brezinski et al.[12] published a systematic review of the overall costs of caring for patients with psoriasis and adjusted the base-year costs to 2013 dollars. They found that the direct costs were between $51.7 billion to $63.2 billion, with indirect costs ranging from $23.9 billion to $35.4 billion. Caring for comorbidities contributed another $36.4 billion in this study.

Another study published in 2016 in the *Journal of Managed Care* compared 1230 patients with psoriasis and PsA to an equal number of patients with psoriasis without PsA (control group).[16] The authors found that patients in the PsA group had more comorbidities, hospital admissions, emergency room visits, and outpatient visits than those in the control group. The overall 5-year cost of care was $23,150 more per patient in the PsA group than in the control group; pharmacy costs were $17,696 more per patient in the PsA group; and medical costs were $5,077 greater per patient in this group. In general, the earlier the diagnosis of PsA is established and treatment initiated the better the outcome.[17, 18] Individuals who smoke, are older than 50, or have a history of a delay of 6 months or more since the onset of symptoms and diagnosis have a poorer outcome than young, non-smoking patients who have been diagnosed early.[18]

A 5-year follow-up study from the Swedish Early Psoriatic Arthritis Registry published in 2015 reported that men had a greater risk for bone erosions and structural damage than women.[19] Interestingly, the study also found that, although men improved clinically, they developed more joint damage than women, who demonstrated less clinical improvement than men but had less joint damage. The authors suggest that men and women may need different treatment planning. Women may need more attention to pain control and physical function, whereas men, especially those with dactylitis, may need more intense radiographic follow-up.

Diagnosis

Currently there is no single test to definitively diagnose PsA. The diagnosis is established clinically using physical examination, blood tests and at times imaging.

The CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria outlined below (Figure 1) are classification criteria used for entry into clinical trials. These criteria, published in 2006, are simple to use and have a sensitivity of 91.4% and specificity of 98.7%.[20] Although they were initially designed for clinical trials and are not validated for use in a clinical setting, they are commonly used as diagnostic criteria in rheumatology practices.

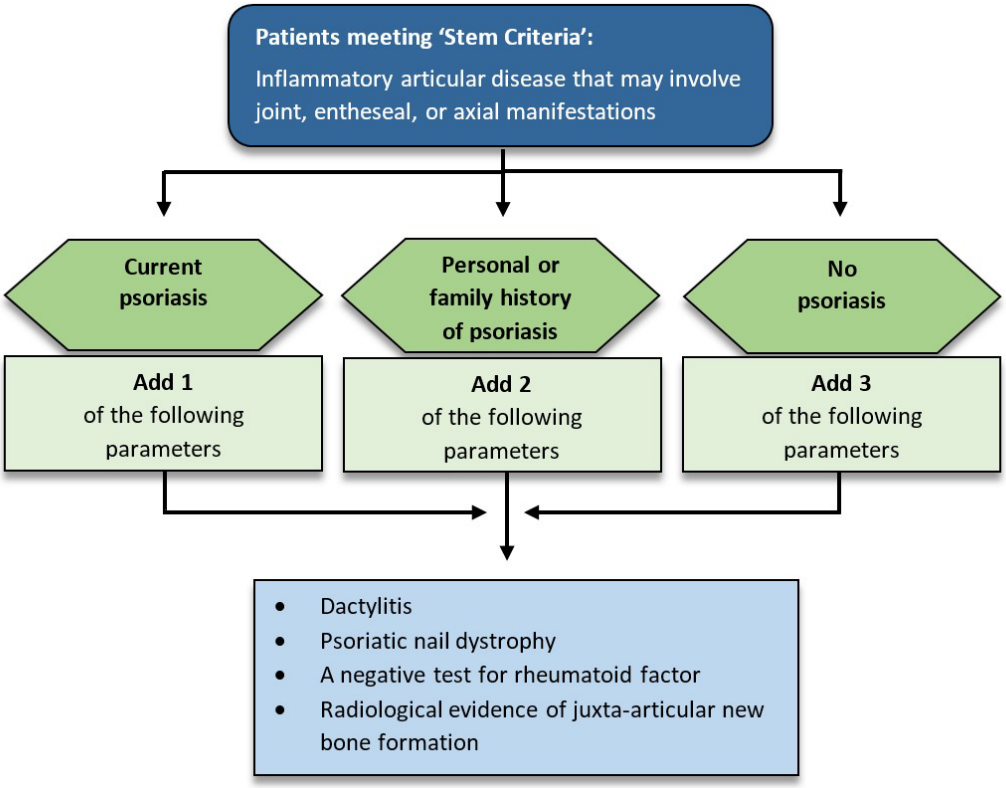

Figure 1. CASPAR classification criteria for the diagnosis of PsA

CASPAR, ClASsification criteria for Psoriatic ARthritis; PsA, psoriatic arthritis Adapted from Taylor WJ, et al.[20]

Patient Assessment

As with other rheumatologic diseases, it is important to establish the diagnosis and initiate treatment as soon as possible.

Initial evaluation of a patient who meets the CASPAR classification criteria for PsA should include the following (other tests may be appropriate in certain clinical settings):

- Detailed medical history, including a detailed vaccination history and information concerning possible uveitis, Crohn's disease, or ulcerative colitis (UC) and depression
- Laboratory tests ○ Complete blood count (CBC)
  - ○ CRP (elevated levels are seen in 40% of patients with PsA)[8] ○ ESR (elevated levels are seen in 40% of patients with PsA)[8] ○ HLA-B27 (positive in 25% of patients with PsA).[8] If positive, there is an increased risk of axial disease and more aggressive course of disease.
  - ○ Comprehensive metabolic panel ○ Screening for hepatitis B and hepatitis C ○ Rheumatoid factor (RF) (negative in 95% of patients with PsA)[8] ○ Anti-cyclic citrullinated protein antibodies (negative in 95% of patients with PsA)[8]

- Baseline radiographs of areas of clinical involvement. Radiographic changes include the following:[6]
  - Peripheral joints—bone loss with joint space narrowing and eccentric erosions, periostitis, ankylosis, enthesophytes
  - Axial skeleton—sacroiliitis and vertical syndesmophytes
    - Bilateral sacroiliitis ≥Grade 2 (minimal changes, no narrowing of the joint space but with small erosions or sclerosis)
    - Unilateral sacroiliitis ≥Grade 3 (definitely abnormal with erosions and sclerosis on both sides of the joint; and widening, narrowing, or fusion of the joint)
- Patient Global Assessment (PGA)
- Patient pain visual analog scale (VAS)
- HAQ-DI Health Assessment Questionnaire-Disability Index
- Physician Global Assessment
- Number of tender joints
- Number of swollen joints
- If there is skin psoriasis, Psoriasis Area and Severity Index (PASI; see Glossary) or body surface area (BSA) assessment

At this time, there is no confirmatory laboratory test to establish the diagnosis of PsA,[21] but many patients test negative for RF (performed by any method other than latex fixation) and antinuclear antibodies, and some test positive for HLA-B27.

Active disease is diagnosed in patients (who have met the CASPAR classification criteria above) with any of the following:[22]

- ≥1 tender and inflamed joint(s)
- ≥1 tender enthesis point(s)
- ≥1 dactylitic digit(s)
- Inflammatory back pain (IBP, see Glossary)

Patients are considered to have a **poor prognosis** if they have at least 1 of the following:[23]

- ≥5 actively inflamed joints
- Elevated acute-phase reactants (CRP, ESR)
- Imaging evidence of disease progression
- Poor response to nonsteroidal anti-inflammatory drug (NSAID) therapy or prior use of steroids
- Loss of function or diminished QoL

According to the 2018 American College of Rheumatology/National Psoriasis Foundation (ACR/NPF) Guideline for the Treatment of Psoriatic Arthritis,[24] a patient with one or more of the following has **severe PsA:**

- Bone erosions
- Elevated acute-phase reactants (CRP, ESR)
- Joint deformities that interfere with function
- Impairment of QoL
- Active PsA at multiple sites, which may include enthesitis and/or dactylitis
- Rapidly progressive disease
- Function-limiting PsA at a number of sites

In addition, the ACR/NPF Guideline states that severe psoriatic skin disease is defined as one or more of the following:[24]

- PASI of ≥12
- BSA of ≥5% to 10%
- Involvement of face, nails, scalp, feet, and hands
- Physical or mental impairment

Management of Patients with PsA

The management of patients with PsA should be based on a treat-to-target paradigm, with therapy aimed at achieving remission or minimal disease activity (MDA, see below) or the lowest level of disease, as quickly as possible.[25] Some authors have proposed the more stringent criteria for (VLDA), which are closer to remission.[26]

As Ritchlin et al.[6] recommended in their 2017 article, “The domain with the highest level of activity drives the treatment choices” (Page 966). If there is psoriatic skin disease, coordination of treatment with a dermatologist is strongly encouraged. In addition, patients with comorbidities should be referred to the appropriate medical specialist(s). Regular close monitoring and re-evaluation of therapy are essential to maintain improvement or stability of this disease, avoid medication toxicity, and identify new comorbid conditions early.

Remission is often defined as no evidence of active disease (see Patient Assessment, above). To achieve MDA, the patient must meet five of the following seven conditions; to achieve VLDA, the patient must meet all seven:[27]

1. Tender joints ≤1
2. Swollen joints ≤1
3. Pain VAS ≤15
4. Patient Global Assessment ≤20
5. HAQ-DI ≤0.5
6. PASI <1 or BSA ≤3
7. Tender entheseal points ≤1

In the study by van Mens et al.,[26] VLDA was reached by fewer patients than MDA. The authors felt that VLDA was closer to remission than MDA. However, they cautioned that VLDA may be too stringent and achievement of this very low level of disease may be difficult for many patients. It has yet to be determined if the course of the disease is better for those at VLDA compared to those at MDA. It is also unknown at this time whether achieving VLDA results in overtreatment of patients and increased adverse reactions to medications.

Radiographic progression can be defined as an increase in Sharp/van der Heijde scores of the hands and feet of >0.[27] Comorbidities must be considered as well when developing a treatment plan. These include but are not limited to:[8, 28]

- Uveitis
- Inflammatory bowel disease (IBD)
- Cardiovascular disease
- Obesity, metabolic syndrome
- Diabetes
- Depression and anxiety
- Chronic hepatitis
- Non-alcoholic fatty liver disease, infections
- Hypertension
- Chronic alcohol abuse
- Renal disease
- Malignancies, including skin cancer
- Osteoporosis
- Central sensitization syndrome (fibromyalgia)
- Interstitial lung disease
- Recurrent or increased susceptibility to cirrhosis

Patients with comorbidities should be referred to the appropriate medical specialist for management.

Due to dysregulated immune function and exposure to immunomodulating medications, patients with PsA have an increased risk of infection. Prior to starting therapy, it is important to obtain a detailed vaccination history. Providers should assess the need for a variety of vaccinations according to the Centers for Disease Control and Prevention (CDC) schedule which include the following:[29]

- Annual flu vaccine
- PCV13 (13-valent pneumococcal conjugate vaccine)—one dose if not previously administered followed by one dose of PPSV23 (23-valent pneumococcal polysaccharide vaccine) at least 1 year after the PCV13 vaccination
- Recombinant zoster vaccine for adults 50 years of age and older—2 doses
- Human papillomavirus vaccine—2 or 3 doses for patients up to age 26
- Hepatitis A vaccine—2 to 3 doses if antibody negative
- Hepatitis B vaccine—3 doses if antibody negative
- Tetanus, diphtheria, and pertussis vaccine—1 dose followed by a booster every 10 years

The 2018 ACR Guideline indicates that biologics should not be delayed if killed vaccines are used. However, if live attenuated vaccines are used then biologics should be delayed.[24]

Patients older than 50 should receive a herpes zoster vaccination, if not previously done**.** Currently, there are two herpes zoster vaccines available: **Zostavax®**, which contains live virus and is considered to be contraindicated by the CDC for this population, and **Shingrix®**, which contains a non-live subunit of the virus. Shingrix is reported to be 97% effective against shingles when compared to Zostavax, which is 51% effective against herpes zoster. If patients have active PsA requiring treatment, Shingrix is the vaccine of choice because not only is it more effective but also avoids delaying the start of treatment.

According to the CDC, mumps, measles and rubella vaccine and varicella vaccine are contraindicated in immunocompromised patients.

The date and result of the most recent tuberculosis evaluation should be documented and the patient rescreened annually. A travel history to areas where certain fungal diseases are prevalent is also important.

Management should always be directed by a rheumatologist or under the supervision of a rheumatologist. PsA is a very heterogenous disease and one or more domains (including but not limited to peripheral arthritis, axial arthritis, dactylitis, enthesitis, skin psoriasis, or psoriatic nail dystrophy) may be involved at the same time. The provider should choose a treatment plan that takes into account as many of the involved domains as possible.[9-11] Treatment should also be adjusted if the established target is not reached within the expected timeframe.

Nonpharmacologic Treatment

Nonpharmacologic treatments should be part of every patient's treatment plan, if possible. These include low-impact exercise such as swimming, yoga, and Tai Chi; physical and/or occupational therapy; massage therapy; and acupuncture. Some patients may prefer high-impact exercises.[24] In addition, patients should be strongly encouraged to stop smoking and lose weight.

Pharmacologic Management

PsA is a heterogeneous disease, and different drugs are preferred for the management of different domains. Patients commonly have more than one domain involved. When developing a pharmacologic treatment plan, it is important to ***consider <u>all</u> of the involved domains***,[9-11] the severity of the disease, the presence of poor prognostic factors, comorbidities, and the patients' preferences. Treatment should be planned based on the most dominant domain but should cover as many involved domains as possible.

Rheumatology providers should coordinate care with the patient's dermatologist and primary care provider, in addition to other medical specialists when appropriate. All patients should have an annual total body skin screening for non-melanoma skin cancers by a dermatologist.

Continuous monitoring of a patient's response to treatment is important as it may reveal inadequate disease control indicating a need for modification or change in drug management.

Pharmacologic treatment should be started as soon as possible after the diagnosis is confirmed. The goal of treatment should be either a complete remission or minimal disease activity (MDA).

Table 1 lists drugs used for the pharmacologic management of patients with PsA.

Table 1. Drugs used for the pharmacologic management of PsA

Drug	Route of Administration	Contraindications
NSAIDs	Oral	GI bleeding, history of gastric ulcers, congestive heart failure, cirrhosis, renal disease[30]
Glucocorticoids	Oral, IA, or rarely IV	
csDMARDs/OSM*		
MTX (Rheumatrex® or generic)	Oral	Alcoholism, alcoholic liver disease, other chronic liver disease; pre-existing blood dyscrasias, known allergy to MTX, planning for pregnancy[31]
MTX (Otrexup™ or Rasuvo® or generic)	SQ	Alcoholism, alcoholic liver disease, other chronic liver disease; pre-existing blood dyscrasias, known allergy to MTX, planning for pregnancy[30]
Leflunomide (Arava®)	Oral	Alcoholism, alcoholic liver disease, other chronic liver disease, pre-existing blood dyscrasias, severe skin psoriasis
Sulfasalazine (Azulfidine®)	Oral	Allergy to sulfa, leucopenia

Drug	Route of Administration	Contraindications

bDMARDs (includes both boDMARDS and bsDMARDS		
boDMARDs		
TNFi	IV	At doses >5 mg/kg Remicade is contraindicated in patients with moderate to severe heart failure
Infliximab-qbtx (Remicade®)	SQ	Enbrel is contraindicated in patients with sepsis and IBD
Etanercept (Enbrel®)	SQ and IV	None
Adalimumab (Humira®)	SQ	None
Golimumab (Simponi®)	IV	None
Golimumab (Simponi® Aria)	IV or SQ	None
Certolizumab pegol (Cimzia®)		
IL-12/23i	SQ	May exacerbate inflammatory bowel disease
Ustekinumab (Stelara®)		
IL-17i	SQ	None
Secukinumab (Cosentyx®)	SQ	
Ixekizumab (Taltz®)		
IL-23i	SQ	Allergy to Tremfya
Guselkumab (Tremfya)		
T cell costimulation inhibitor	IV or SQ	None
Abatacept (Orencia®)		
bsDMARDs	SQ	Same as for boDMARDs reference drugs
Erelzi (etanercept-szzs) biosimilar to Enbrel	SQ	
Amjevita** (adalimumab-atto) biosimilar to Humira	IV	
Inflectra (infliximab-dyyb) biosimilar to Remicade	IV	
Renflexis (nfliximab-abda) biosimilar to Remicade	IV	
Ixifi (infliximab-qbtx) biosimilar to Remicade	SQ	
Cyltezo (adalimumab-adbm) biosimilar to Humira	SQ	
Hyrimoz (adalimumab-adaz) biosimilar to Humira	SQ	
Hulio (adalimumab-fkjp) biosimilar to Humira		
tsDMARD	Oral	Not recommended in combination with boDMARDs
Tofacitinib (Xeljanz®) (JAKi) can be used in patients who also have ulcerative colitis		Active serious infection Thrombosis, DVT, arterial thrombosis Do not administer live vaccines while on Xeljanz

Drug	Route of Administration	Contraindications
PDE4i/OSM Apremilast (Otezla®)	Oral	Allergy to Otezla
Cyclosporin Immunosuppressive drug used for skin psoriasis	Oral	• Not to be used for more than 1 year • Do not use if: ○ Compromised immune system ○ Severe gout ○ Abnormal renal function ○ Hypertension ○ History of cancer other than basal cell or squamous cell of the skin

*There is no role for csDMARDs in the management of patients whose only complaint is axial PsA or enthesitis[22] boDMARDs, biologic originator disease-modifying antirheumatic drugs; bsDMARDs, biosimilar disease modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DVT, deep venous thrombosis; GI, gastrointestinal; IA, intra-articular; JAKi, Janus Kinase inhibitor; IBD, inflammatory bowel disease, IL-17Ai, interleukin-17A inhibitor; IL-12/23i, interleukin-12/23 inhibitor; IL-23i, interleukin-23 inhibitor; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; OSM, oral small molecule; PDE4i, phosphodiesterase 4 inhibitor; PsA, psoriatic arthritis; SQ, subcutaneous; TNFi, tumor necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug

Tumor necrosis factor inhibitors (TNFi) are frequently used for the management of patients with severe skin disease, severe PsA, axial PsA, enthesitis, dactylitis, and concomitant IBD. These drugs are divided into three categories: monoclonal antibodies, soluble fusion molecules, or neither. The drugs are classified below:[24, 32-35]

- Monoclonal antibodies ○ Infliximab-qbtx (Remicade®) ○ Adalimumab (Humira®) ○ Golimumab (Simponi®) ○ Golimumab (Simponi® Aria)
- Monoclonal antibody fragment ○ Certolizumab pegol (Cimzia®)
- Soluble fusion molecule ○ Etanercept (Enbrel®)

Not all TNFi drugs can be used for the same indications. For example, soluble fusion molecules should not be used in patients with IBD.

Patients with PsA often have multiple comorbidities which must be considered when deciding if a particular TNFi medication should be used. The contraindications for the use of these drugs include but are not limited to:[24, 36]

- Current infection
- History of recurrent or chronic infections
- Untreated tuberculosis (active or latent)
- Moderate to severe congestive heart failure
- Multiple sclerosis or other demyelinating diseases

- Optic neuritis

Peripheral Arthritis

Guidelines from national and international rheumatology specialty organizations are inconsistent with one another regarding the use of MTX for patients with PsA that involves peripheral joints only. The data supporting the use of MTX as an initial treatment for PsA is limited. The Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects with Psoriatic Arthritis (SEAM-PsA) evaluated treatment-naïve PsA patients using either MTX monotherapy, etanercept monotherapy, or a combination of MTX and etanercept. The study demonstrated that patients did respond to MTX monotherapy but without placebo control.[37] There was greater improvement with a TNFi drug in this population. The European League Against Rheumatism (EULAR) recommends MTX as the initial drug for the treatment of patients with peripheral PsA especially if there is skin disease. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) rates the csDMARDs (MTX, leflunomide, sulfasalazine) or oral small molecules (OSMs, which include the csDMARDs and apremilast), and TNFi drugs as strongly recommended for the management of peripheral arthritis for this same population. However, GRAPPA also indicates that csDMARDs (the ones listed above) should be used first. The new ACR Guideline indicates that MTX is an option for this population, but that TNFi drugs are their first choice, unless contraindicated.[22, 24, 38]

For disease-modifying antirheumatic drug (DMARD)-naïve patients with **peripheral joint involvement only (no evidence of axial disease, entheseal involvement, dactylitis, severe skin disease, or previously defined severe PsA) and no evidence of poor prognostic factors**, United Rheumatology recommends a trial of an OSM for 3 months (Figure 2) and, if the patient fails to achieve MDA, switching to the appropriate biologic which is usually a TNFi drug. If the patient has skin involvement an interleukin-17 inhibitor (IL-17i), interleukin-23 inhibitor (IL-23i) or interleukin-12/23 inhibitor (IL-12/23i) drug are preferred to a TNFi drug.[39]

If MTX is chosen as the initial OSM it should be started at 10 mg to 15 mg per week orally and the dose escalated up to a maximum of 25 mg per week depending on the patient's response. At doses of 15 mg per week or more, split dosing should strongly be considered (the total dose is divided into two separate doses taken 8 hours apart). At 20 mg per week, some providers switch to subcutaneous MTX.[40] At this dose, there is better absorption of the drug subcutaneously than orally. If either MTX or leflunomide are contraindicated, a phosphodiesterase 4 inhibitor (PDE4i, apremilast) can be tried, taking into consideration any history of depression. Apremilast or sulfasalazine should also be used if the patient has a history of uncontrolled diabetes. Leflunomide or sulfasalazine should not be chosen if there is more than mild skin involvement. At the end of 12 weeks, if the patient is in remission or has reached MDA with an OSM, then treatment should be continued with the same drug at the same dose and the patient monitored carefully to ensure that there is no change in disease activity. If at the end of 3 months, the patient has not reached remission or MDA with an OSM, then a biologic should be tried. Monotherapy with a TNFi drug or with an IL-17i or an IL-23i is preferred, but a targeted synthetic (tsDMARD) or a T cell costimulation inhibitor can be considered when skin involvement is mild. Interleukin-12/23i drugs should

be considered if the patient has IBD or prefers less frequent administration of medications. Targeted synthetic DMARDs or ustekinumab (IL-12/23i) should be considered if the patient has UC or Candida infections, using tsDMARDs if the patient prefers an oral medication. A T cell costimulation inhibitor can be considered, if the patient has recurrent or serious infections, or a demyelinating disease such as but not limited to multiple sclerosis (Figure 2).[24]

Patients with poor prognostic factors and/or severe skin disease and/or severe PsA with no axial disease and/or no entheseal disease and/or no dactylitis should be started on a biologic originator/biosimilar disease-modifying antirheumatic drugs (bo/bs DMARD) initially (Figure 3). Drug selection should be based on all domains involved and all comorbidities. If there is significant skin involvement, abatacept or a Janus Kinase inhibitor (JAKi) drug **should not be the first or second choice**. For more significant arthritis, a TNFi or IL-17i or IL-23i should be the first choice. If there is active spondylitis only, a TNFi or IL-17i should be chosen initially. Use of a monoclonal type TNFi or an IL-12/23i drug should be considered; if the patient has IBD or a drug that is given less often is preferred. A JAKi drug can be considered, if the patient has a history of UC or recurrent Candida infections, or prefers an oral medication. A T cell costimulation inhibitor such as abatacept can be considered, if there is a history of recurrent or serious infections and/or demyelinating disease, or stable IBD.[24]

If the patient achieves remission or MDA after 3 months on the initial therapy, then the current treatment should be continued. If neither remission or MDA is reached, then a different bo/bs or tsDMARD should be started (Figure 3).[24]

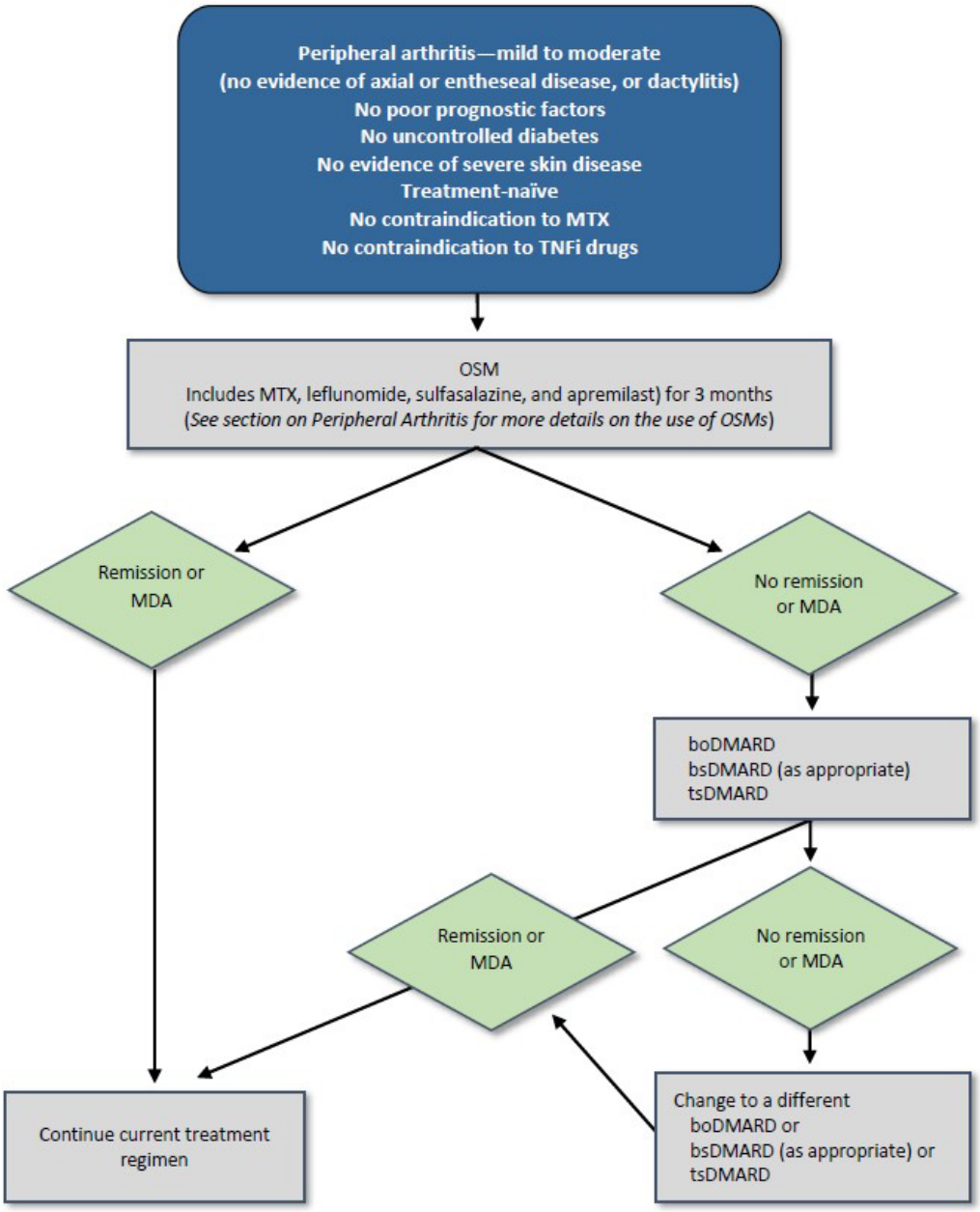

Figure 2. Initial treatment of patient with peripheral PsA and no evidence of axial disease, enthesitis or dactylitis

Note: Please see text for additional information about the drug classifications and contraindications

boDMARD, biologic disease-modifying antirheumatic drug; bsDMARD, biosimilar disease-modifying antirheumatic drug; MDA, minimal disease activity; MTX, methotrexate; OSM, oral small molecule; PsA, psoriatic arthritis; TNFi, tumor necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug

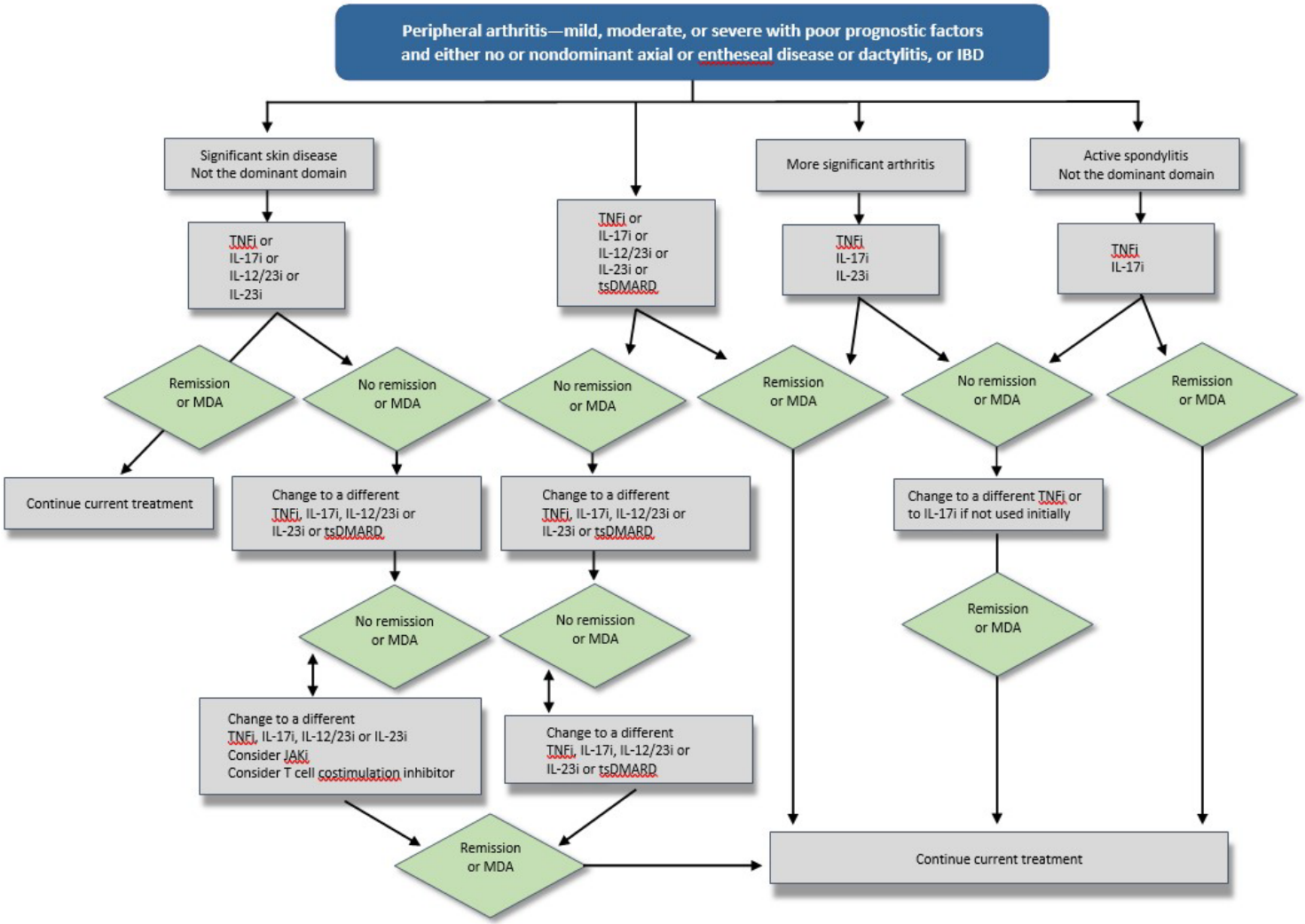

Figure 3. Management of PsA with no evidence of axial disease, enthesitis or dactylitis and presence of either poor prognostic factors, and/or severe PsA and/or severe skin disease

Note: Please see text for additional information about the drug classifications and contraindications

IL-17i, interleukin-17 inhibitor; IL-12/23, interleukin-12/23 inhibitor; JAKi, Janus Kinase inhibitor; MDA, minimal disease activity; PsA, psoriatic arthritis; TNFi, tumor necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug

Axial PsA (Spondylitis or Spondyloarthropathy and Sacroiliitis)

Axial disease rarely occurs alone; it frequently occurs in combination with peripheral PsA. Clinical findings of IBP or imaging findings of sacroiliitis establish the diagnosis of axial disease. Initial treatment for mild or stable disease should begin with NSAIDs given on a continuous schedule and not on an as-needed basis. Prescribing a proton pump inhibitor along with oral NSAIDs may help diminish GI adverse events.

Physical therapy should also be initiated. Systemic treatment with glucocorticoids should be avoided.[41] SI joint injections of steroids can be considered in appropriate situations. At this time, **conventional synthetic DMARDs, IL-12/23 inhibitors, IL-23inhibitors and PDE4i inhibitors are not indicated for the treatment of patients with axial PsA or for those with a combination of peripheral joint arthritis and axial disease.** For patients failing to respond to NSAIDs, a TNFi or IL-17i drug should be used as the initial biologic originator disease-modifying antirheumatic drug (boDMARD). If the patient fails to respond to the initial boDMARD (TNFi or IL-17i), a different TNFi or IL-17i should be tried until the clinical target is reached.

If there is a contraindication to TNFi drugs or the patient has severe skin disease in addition to axial PsA (with or without peripheral PsA), an IL-17i drug should be used (Figure 4).[24, 28, 42] If there is concomitant inflammatory bowel disease, TNFi should be used preferentially over IL-17i.[24]

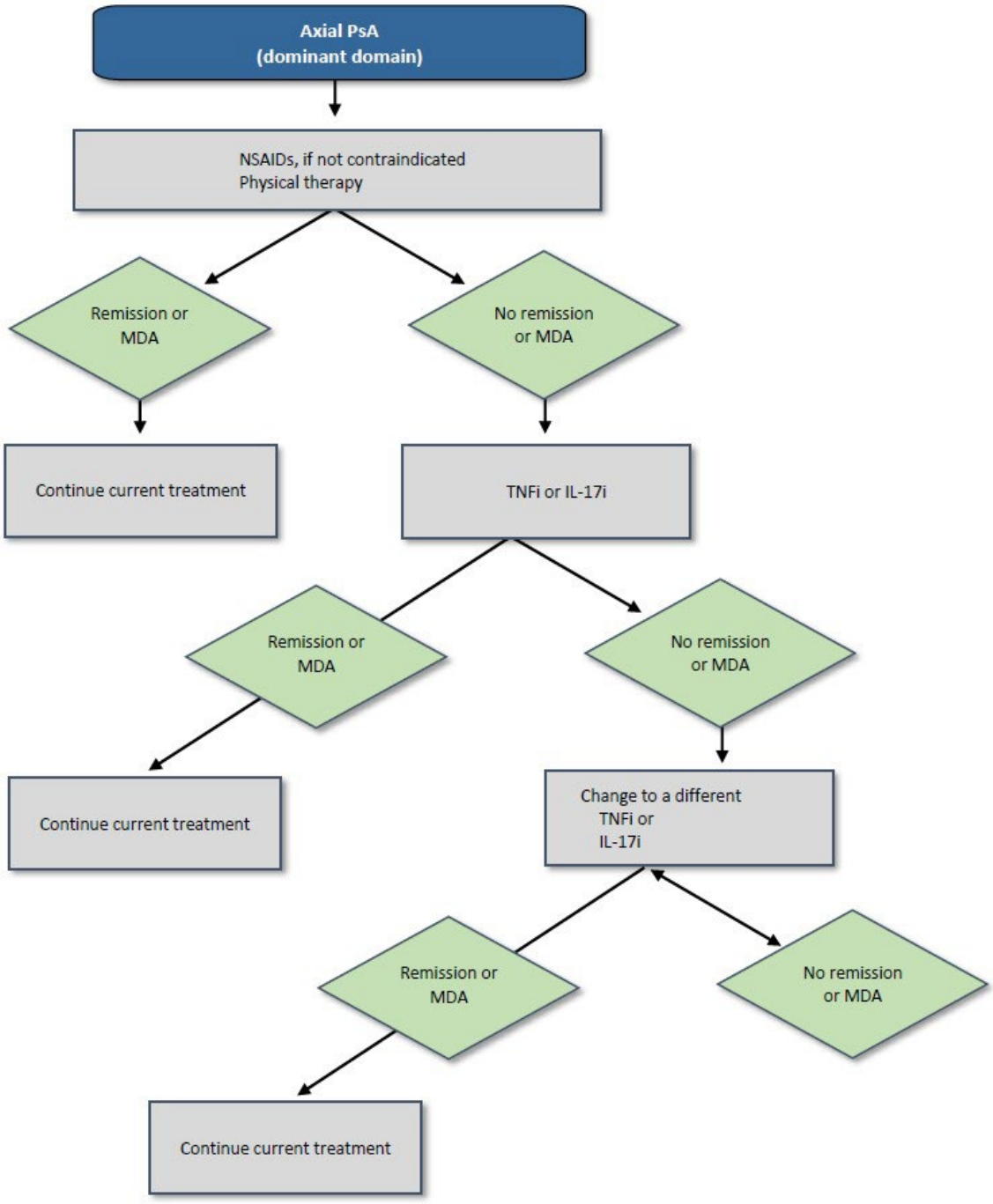

Figure 4. Axial PsA (dominant domain)

Note: Please see text (*Axial PsA*) for additional information. All medication decisions must take into account the patient's complete medical history, including but not limited to adverse events related to drugs, skin disease, inflammatory bowel disease, and other comorbidities

IL-17i, interleukin-17 inhibitor; MDA, minimal disease activity; NSAIDs, nonsteroidal anti-inflammatory drugs; PsA, psoriatic arthritis; TNFi, tumor necrosis factor inhibitor

Enthesitis

An enthesis is the area where a tendon or ligament inserts into a bone. Inflammation at the enthesis is quite common in PsA, affecting up to half of the patients. This often occurs at the insertion of tendons or ligaments such as the Achilles' tendon, the plantar fascia, and ligaments and tendon insertions at the lateral epicondyles. It may also be seen in the vertebrae of patients with axial PsA. In fact, enthesitis and/or dactylitis may be the initial presenting complaint(s) or symptom(s).[43] Ultrasound has been found to be a good imaging test for enthesitis.

Physical therapy should be started. Local steroid injections should be used with extreme caution, because data suggest potential structural damage and rupture of the enthesis.[44] The patella and Achilles tendons should not be injected. **Conventional synthetic DMARDs are not recommended for patients whose main domain of involvement is enthesitis.[22, 44]** The patient should be started on NSAIDs initially. If there is an inadequate response to NSAIDs, the patient should be started on either a TNFi, IL-17i, IL-12/23i, IL-23i or a tsDMARD. If the patient fails to respond to the first DMARD, then she/he can be switched to another TNFi or, if not already tried, to an IL1-7i, IL12/23i, IL-23i or a tsDMARD until remission or MDA is reached. If the second DMARD fails to achieve remission or MDA, then a different drug from the other groups mentioned above should be tried until remission or MDA is achieved.

For patients with contraindications to bo/bs DMARDs or NSAIDs and a history of recurrent infections or for those who prefer an oral medication, a PDE4i drug (apremilast) can be used.[24, 44] For patients for whom NSAIDs are contraindicated *and* who do not have either severe skin disease and/or severe PsA, a PDE4i drug such as apremilast may be used initially. In this group, if there is no remission or MDA with apremilast, then a bo/bs DMARD or tsDMARD should be tried. If the patient has a contraindication to a TNFi or severe skin disease, then an IL-17i or IL-12/23i or IL-23i drug should be tried. If the patient has a history of IBD, then an IL-12/23i drug can be used (see Figure 5).

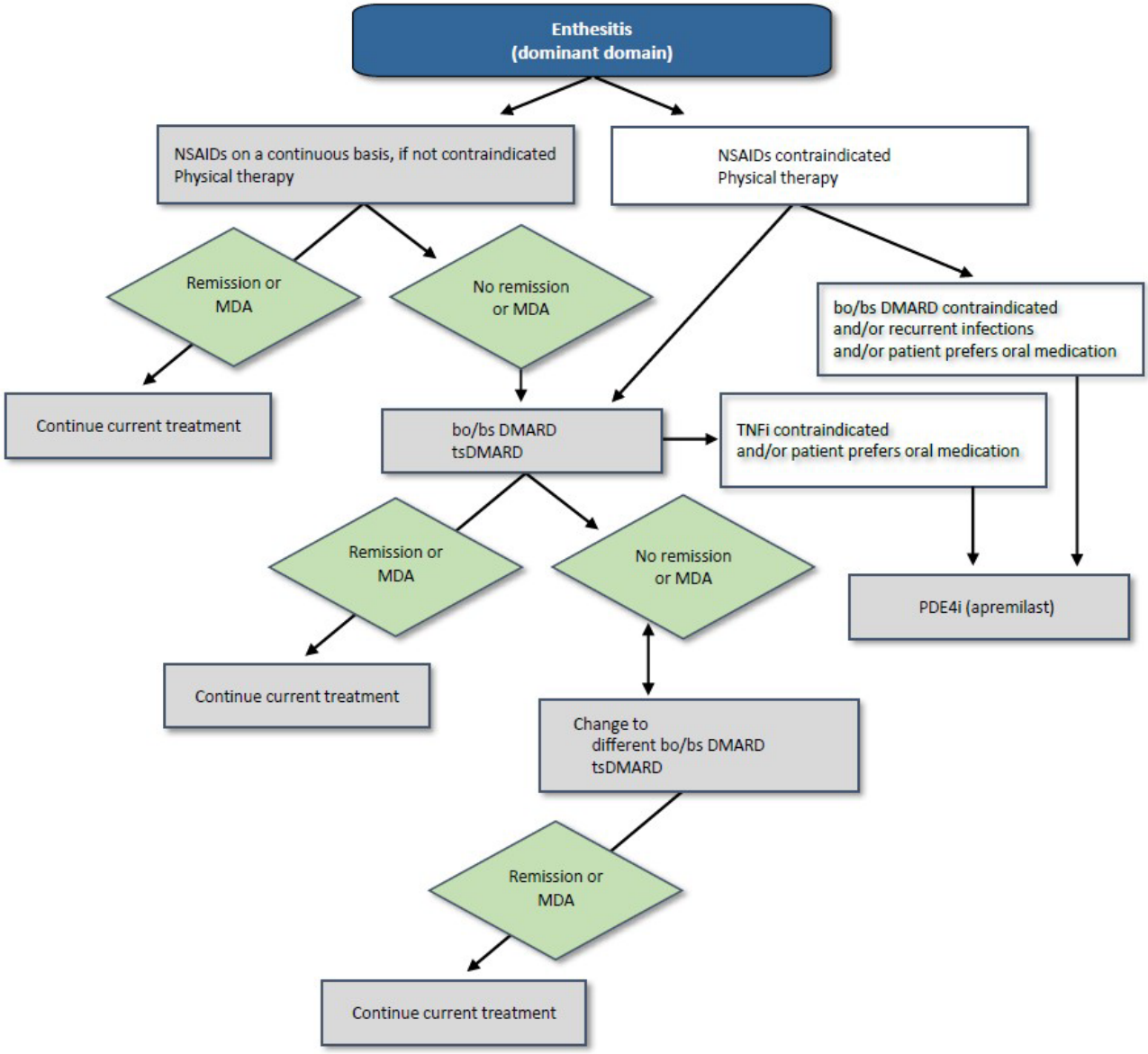

Figure 5. Enthesitis (dominant domain)

Note: Please see text (*Enthesitis*) for additional information. All medication decisions must take into account the patient's complete medical history, including but not limited to adverse events related to drugs, skin disease, IBD, and other comorbidities as well as the patient's preferences

bo/bs DMARD, biologic originator/biosimilar disease-modifying antirheumatic drug; IBD, inflammatory bowel disease; MDA, minimal disease activity; NSAIDs, nonsteroidal anti-inflammatory drugs; PDE4i, phosphodiesterase 4 inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug

Dactylitis

Dactylitis, commonly called 'sausage digit', describes inflammation of an entire digit with diffuse swelling, pain, and tenderness of the digit. It is frequently associated with progressive disease. Unfortunately, there is only weak evidence supporting the use of a specific drug for this domain.

Patients with dactylitis should receive a trial of a boDMARD of the TNFi or IL-17i class, IL-12/23i, IL-23i, tsDMARD (tofacitinib), or PDE4i (apremilast). If the patient has severe skin disease, the IL-17i or IL-23i class should be chosen first. If there are recurrent infections, PDE4i (apremilast) should be utilized (Figure 6).

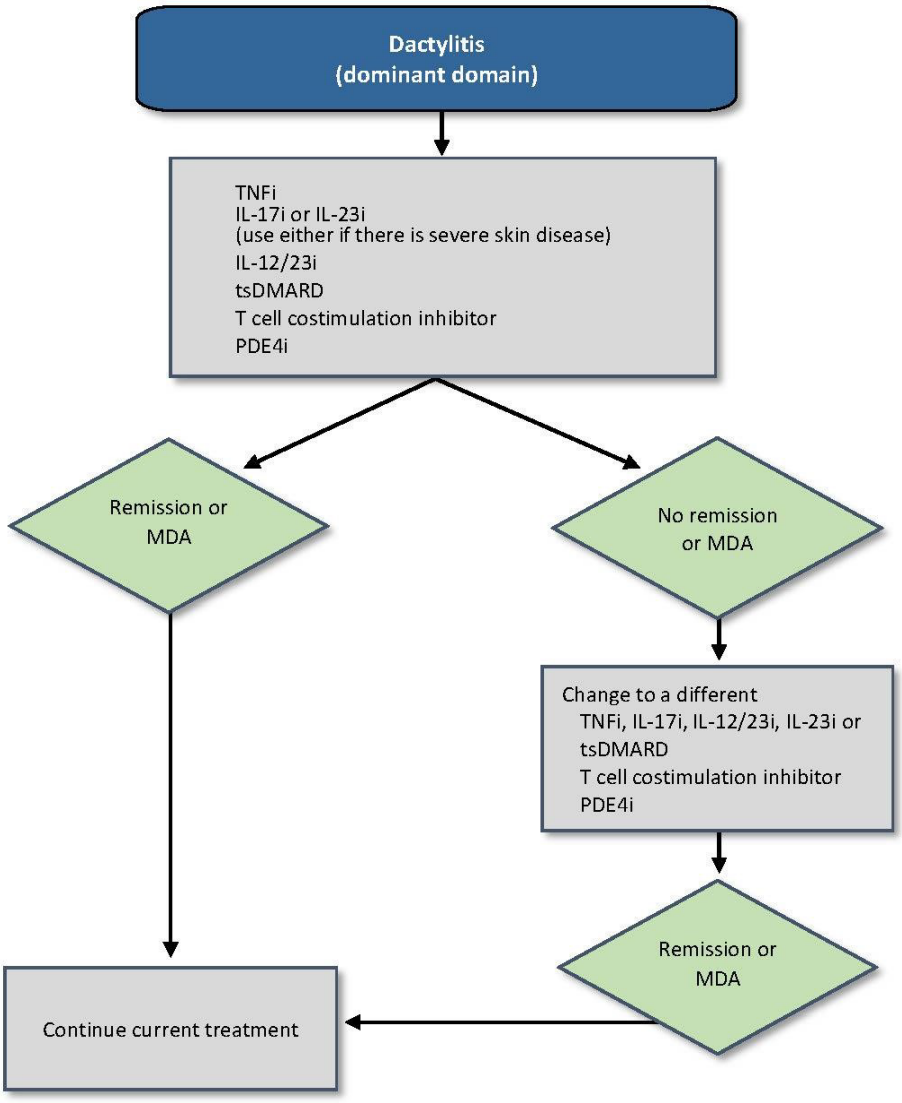

Figure 6. Dactylitis (dominant domain)

Note: Please see text (*Dactylitis*) for additional information. All medication decisions must take into account the patient's complete medical history, including but not limited to adverse events related to drugs, skin disease, IBD, and other comorbidities as well as the patient's preferences

IBD, inflammatory bowel disease; IL-17i, interleukin-17 inhibitor; IL-12/23i, interleukin-12/23 inhibitor (such as ustekinumab); IL-23i, interleukin-23 inhibitor (such as guselkumab); MDA, minimal disease activity; PDE4i, phosphodiesterase 4 inhibitor; TNFi, tumor necrosis factor inhibitor (such as abatacept); tsDMARD, targeted synthetic disease-modifying antirheumatic drug (such as tofacitinib)

Active PsA and Concomitant Inflammatory Bowel Disease

For patients with active PsA and IBD who are treatment-naïve, the initial drug of choice should be a monoclonal antibody TNFi drug (infliximab, adalimumab, or golimumab). Etanercept is a fusion molecule and **should not be used for these patients**.[24, 35] In addition, IL-17i drugs should be avoided in patients with

IBD. If the patient does not achieve remission or MDA and has Crohn's disease then an IL-12/23i (ustekinumab) or an alternative monoclonal antibody can be tried until the desired result is achieved. If the patient has ulcerative colitis and fails to reach the desired target using a TNFi monoclonal antibody, a different monoclonal antibody, or ustekinumab (an IL-12/23i drug), or tofacitinib, a JAKi drug, should be tried. See Figure 7.

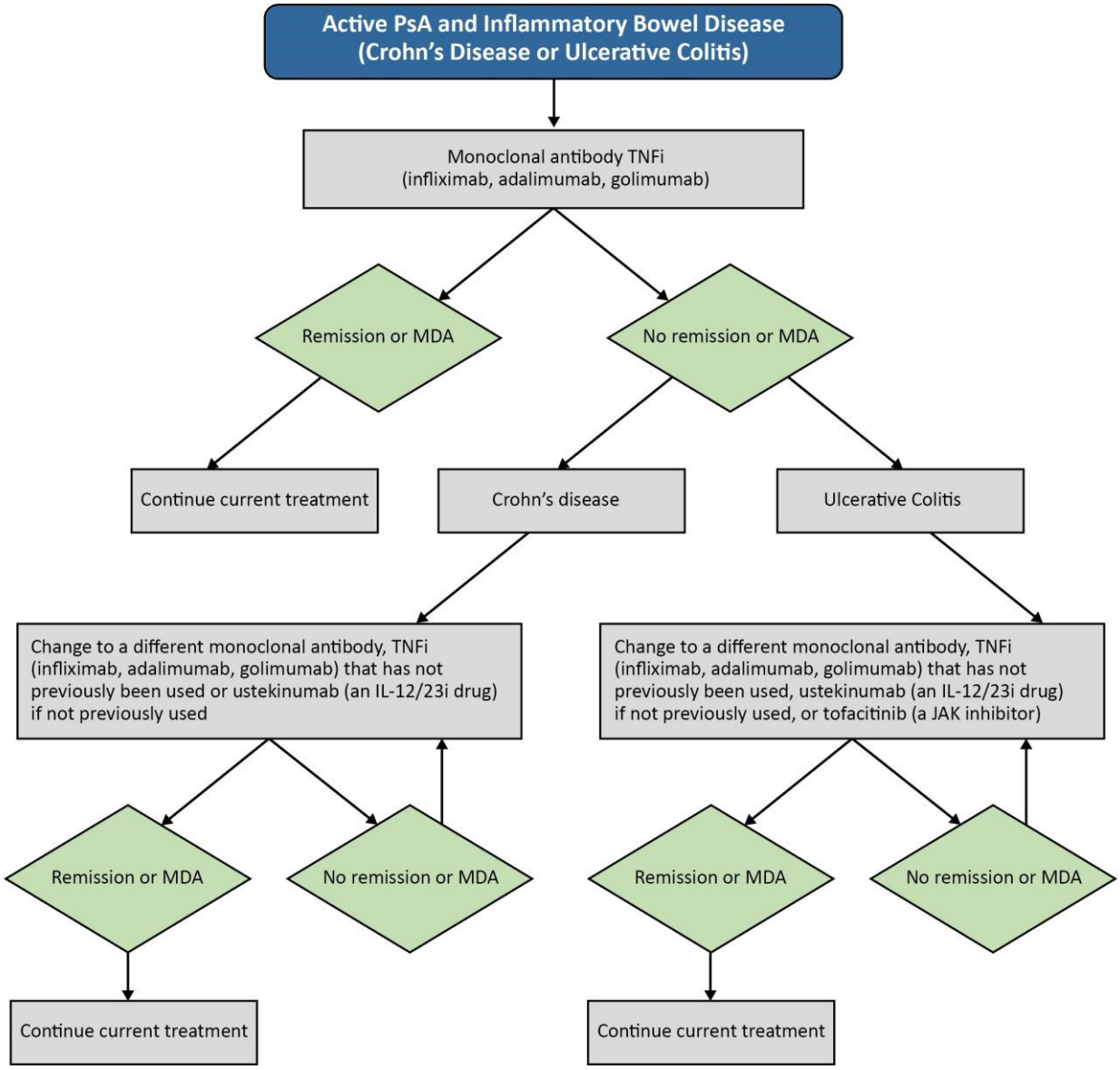

Figure 7. Active PsA and inflammatory bowel disease

Note: Please see text (*Active PsA and concomitant Inflammatory Bowel Disease*) for additional information. All medication decisions must take into account the patient's complete medical history, including but not limited to adverse events related to drugs, skin disease, inflammatory bowel disease, and other comorbidities. Etanercept is a fusion molecule TNFi agent that should not be used in patients with inflammatory bowel disease; IL-17i drugs should also be avoided in patients with IBD

IBD, inflammatory bowel disease; IL-12/23i, interleukin-12/23 inhibitor; IL-17i, interleukin-17 inhibitor; IL-23i, Interleukin-23 inhibitor; MDA, minimal disease activity; PsA, psoriatic arthritis; TNFi, tumor necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug

Monitoring

When caring for a patient with PsA, clinicians must have a treatment target—either remission or MDA— in mind. In clinical practice, fewer patients achieve and maintain remission than MDA.

Once patients have started therapy, they should be seen at 4- to 6-week intervals until the disease is stable and as close to target as possible. At that point, they should be seen as appropriate. An MDA score should be measured at every visit, and medications should be adjusted as appropriate. Once patients have achieved MDA, they can be seen every 6 months, with disease measurements obtained at each visit. Any patient experiencing a change in symptoms or functional ability should be seen as soon as possible. Monitoring of blood tests should be performed at regular intervals, as clinically appropriate. It is suggested that X-rays should also be repeated as clinically appropriate. Tuberculosis testing should be done annually. Patients should also have annual screening for skin cancer.

Patients who are taking MTX should have repeat liver function tests at least once during the first 3 months of treatment. Those who continue on the drug should have liver function tests along with renal function tests every 6 months. All blood tests should be drawn at least 5 days after the last dose of MTX.[45]

For patients on TNFi drugs, blood tests should be done prior to starting treatment and should include a CBC, liver and renal function tests, and electrolytes. Four weeks after starting therapy, the CBC, liver and renal function tests, and electrolytes should be repeated. At 3 months, the blood tests should be repeated. If the results are stable, the tests should be repeated every 3 to 6 months.[45] If a patient does achieve a sustained, true remission (complete remission for 6 consecutive months or more) then "cautious tapering of DMARDs may be considered" according to EULAR.[39] This option is used infrequently but it is possible that, by decreasing the dose of medication, side effects may be minimized and the cost of treatment reduced. If a provider thinks tapering may be appropriate, it should be discussed in depth with the patient and the final decision should be made jointly by the physician and patient, especially since tapering carries a risk of relapse. EULAR is very clear that tapering in this population does not mean stopping treatment but rather establishing the lowest effective dose of drug(s).[39]

Glossary

Health Assessment Questionnaire Disability Index (HAQ-DI)	The HAQ-DI is a practical self-reported tool that patients can complete in the waiting either on paper or a tablet or online or over the phone. It consists of 10 items 8 of which must be answered. The HAQ-DI is easy for patients to fill out. The questionnaire can be scored by a trained office assistant. The score is calculated by adding all the scores and then dividing by the number of questions answered. More detailed information can be found at at https://www.niehs.nih.gov/research/resources/assets/docs/haq_instructions_508.pdf , accessed 12/3/2021, or https://www.andersonmg.com/images/pdf/HAQ-DI_0.pdf , accessed 12/3/2021.
Inflammatory back pain (IBP)	Chronic back pain for at least 3 months and four of the following five parameters:[28] 1. Age of onset <40 years 2. Insidious onset 3. Improvement with exercise 4. Lack of improvement with rest 5. Nocturnal pain that improves upon arising
Minimal disease activity (MDA)	Very low disease activity is a measure of PsA activity when the patient meets **five** of the following: 1. Tender joints ≤1 2. Swollen joints ≤1 3. Pain VAS ≤15 4. Patient Global Assessment ≤20 5. HAQ-DI <0.5 6. PASI <1 or BSA ≤3 7. Tender entheseal points ≤1
Oral small molecule (OSM) drugs	This group of drugs consists of MTX, sulfasalazine, cyclosporin, leflunomide, and apremilast.

Psoriasis Area and Severity Index (PASI)	Severity of psoriasis of the skin, based on the body surface area involved. The affected body surface area is the percent of skin on the head, trunk, arms, and legs with erythema, induration, and scaling of the skin; with 1% body surface area equivalent to the surface area of the patient's palm (including the fingers). A free PASI online calculator can be found at http://pasi.corti.li/.
Very low disease activity (VDLA)	Very low disease activity is a measure of PsA activity when the patient meets **all** of the following: 1. Tender joints ≤1 2. Swollen joints ≤1 3. Pain VAS ≤15 4. Patient Global Assessment ≤20 5. HAQ-DI <0.5 6. PASI <1 or BSA ≤3 7. Tender entheseal points ≤1

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1.1.2023	2023 update	Feb 2023