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Review

The Use of Biologic and Targeted Synthetic Disease-Modifying Drugs in the Treatment of Psoriatic Arthritis

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Abstract: Psoriatic arthritis (PsA) is a systemic inflammatory condition affecting the joints, spine, and entheses, as well as the skin and nails. It affects about 6–42% of patients with psoriasis (PsO), with a prevalence of 1–2 per 1000. PsA can precede skin disease in 7–14% of patients. Different clinical domains may be involved, including psoriatic skin disease, peripheral arthritis, axial involvement, dactylitis, enthesitis, and nail disease. Psoriatic arthritis is a complex, systemic inflammatory condition. While the exact mechanisms underlying PsA are not fully understood, it is believed that the disease arises from a combination of genetic predisposition and environmental triggers that lead to inflammatory processes in both the skin and joints. The treatment approach for PsA focuses on controlling inflammation, improving symptoms, and preventing joint damage. Early initiation of treatment is crucial for achieving better functional outcomes. Various therapeutic agents are available that target different inflammatory pathways. In this review article, various treatment options, focusing on biologic and targeted synthetic disease-modifying antirheumatic drugs, are discussed.

Keywords: Psoriatic arthritis; Psoriasis; inflammatory arthritis; pathogenesis; pharmacology; musculoskeletal disease; biologic therapy; targeted synthetic therapy; disease modifying rheumatic drugs

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1. Introduction

Psoriatic arthritis (PsA) is a systemic inflammatory condition affecting the joints, spine, and entheses, as well as the skin, nails, and eyes [1,2]. The first description differentiating PsA as a distinct disease entity was by Moll and Wright [3]. It affects about 6–42% of patients with psoriasis (PsO) [4] with a prevalence of 1–2 per 1000 [5]. PsA is more common in North America and Europe than in other parts of the world. Severe skin involvement, pustular PsO, psoriatic nail disease, scalp psoriasis, flexural involvement, Koebner phenomenon, and uveitis are risk factors for the development of PsA in patients with PsO [6,7]. Psoriatic arthritis can precede skin disease in 7–14% of patients [8].

Clinical features of PsA include psoriatic skin disease (Figure 1). Psoriatic arthritis has several patterns of joint involvement including asymmetric oligoarthritis, symmetric polyarthritis, distal interphalangeal joint predominant, destructive arthritis (mutilans), and spinal disease [3]. Spinal (axial) disease includes sacroiliitis, which is often asymmetric, and spondylitis, which is often discontinuous with non-marginal syndesmophytes [9–11]. Spinal disease may occur with other forms of peripheral PsA. Other features of PsA include enthesitis (inflammation of the insertion region of tendons and ligaments onto bone) [12], tenosynovitis, dactylitis [13] (Figure 2), and psoriatic nail disease including pitting and

onycholysis (Figure 3). Dactylitis is associated with more severe peripheral arthritis and spondylitis [14,15].

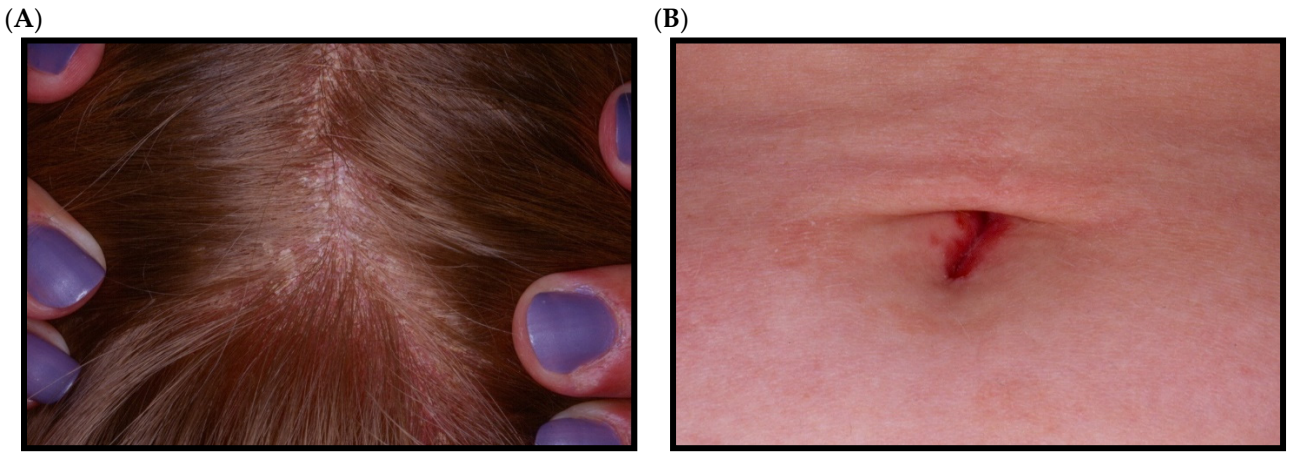

Figure 1. Psoriasis in the scalp (**A**) and umbilicus (**B**). There are well-defined, erythematous silvery-white plaques affecting the scalp and umbilicus. These lesions can be mild with slight scaling to severe with thick plaques.

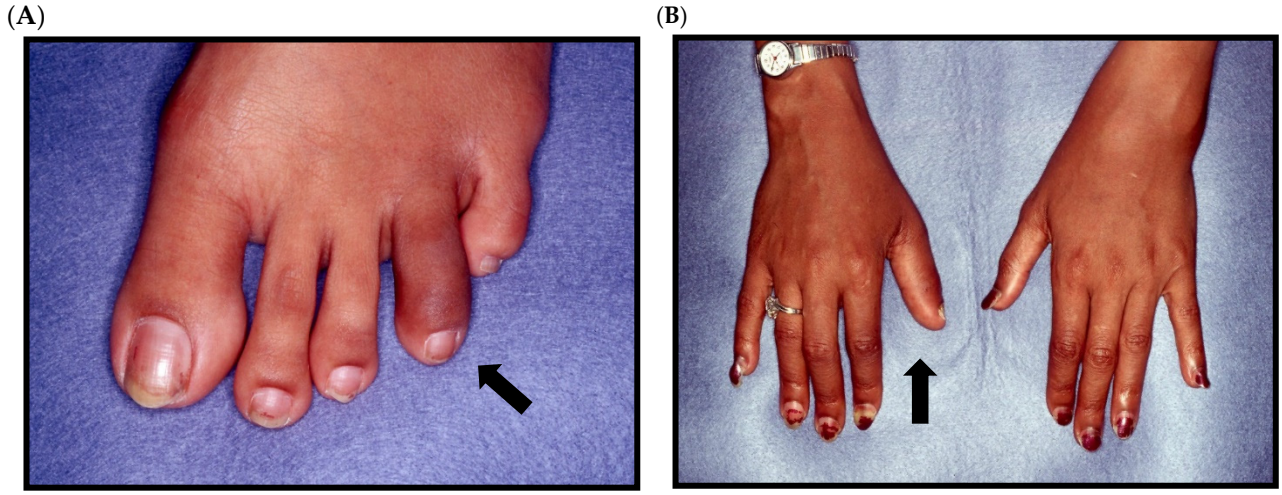

Figure 2. Dactylitis affecting the left 4th digit of the foot (**A**), and right thumb (**B**). Dactylitis is often referred to as a sausage digit and characterized by uniform swelling of a toe or finger.

Comorbid conditions prevalent in patients with PsA include uveitis, IBD, obesity, cardiovascular disease, diabetes mellitus, and monoclonal gammopathy [16–18]. PsA is associated with an increase in all-cause mortality of about 10% [19].

No specific laboratory test exists for diagnosing PsA. PsA was initially thought to be seronegative inflammatory arthritis [20]; however, studies have shown that a small subset of psoriatic arthritis patients have positive antinuclear antibodies, rheumatoid factor, and anti-cyclic citrullinated peptide antibodies (CCP). Acute-phase reactants can be elevated in about 30–40% of cases. HLA-B27 is a genetic marker linked to PsA, especially in cases with axial involvement [10,21,22].

Imaging findings of psoriatic arthritis include bony erosions and new bone production (Figure 4). Bone production usually occurs at the entheses and along the periosteum (Figures 4 and 5). PsA is one of the few forms of arthritis which can result in bone erosions and bone production in the same patient and even the same joint. Axial disease is more complicated. Patients who are HLA-B27 positive usually have symmetric sacroiliitis and ascending spondylitis with marginal syndesmophytes. Patients with other genetic

predispositions, such as HLA-B39, HLA-B08, and HLA-B38, more often have asymmetric sacroiliitis and discontinuous spondylitis with non-marginal syndesmophytes (Figure 6).

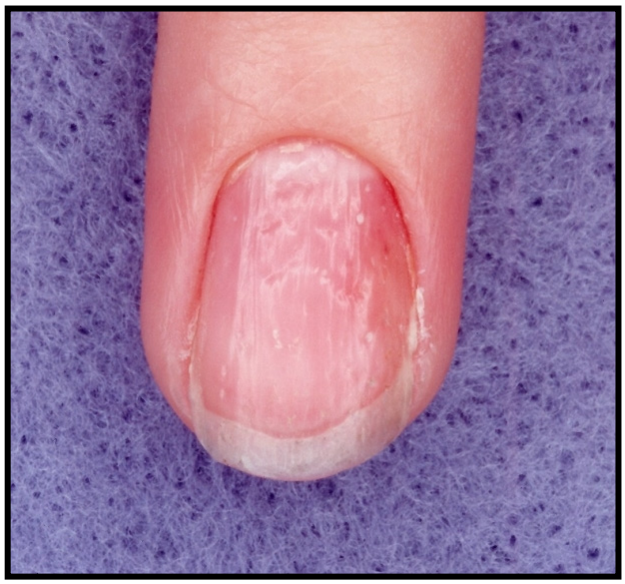

Figure 3. Psoriasis with nail pitting. Nail pitting may appear as small, shallow indentations on the surface of the nail.

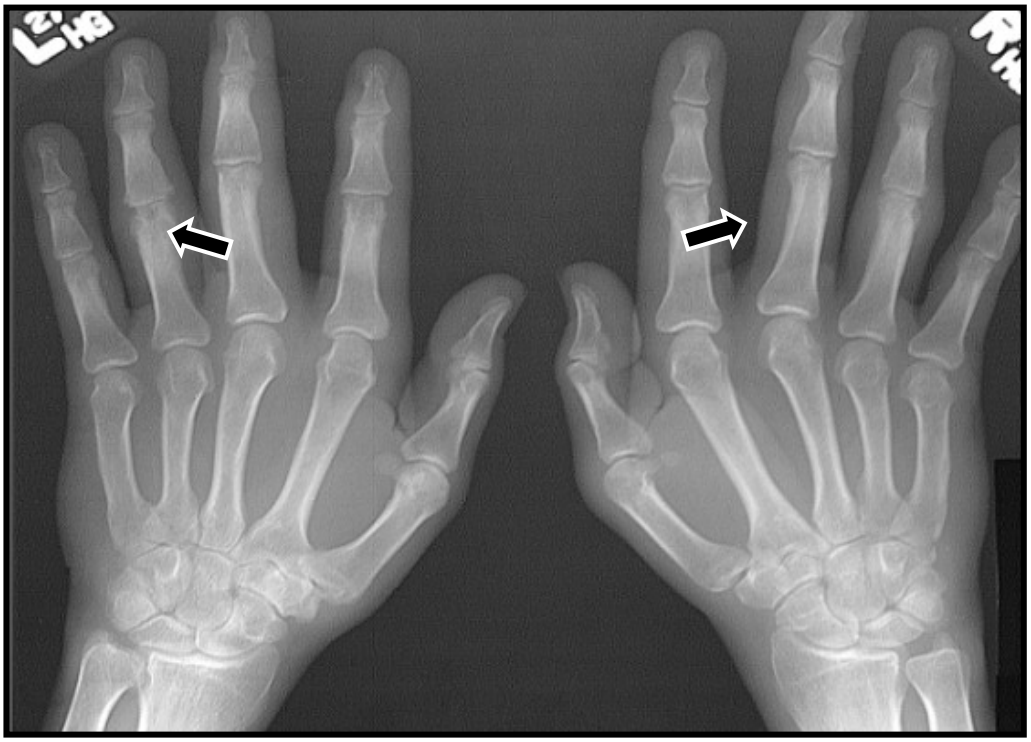

Figure 4. Psoriatic arthritis with bony destruction (erosions) and production at the 4th PIP joints. Left arrow highlights erosive change where the normal bone structure is eroded. This can appear as irregularities in the bone on imaging studies. The right arrow highlights soft tissue swelling.

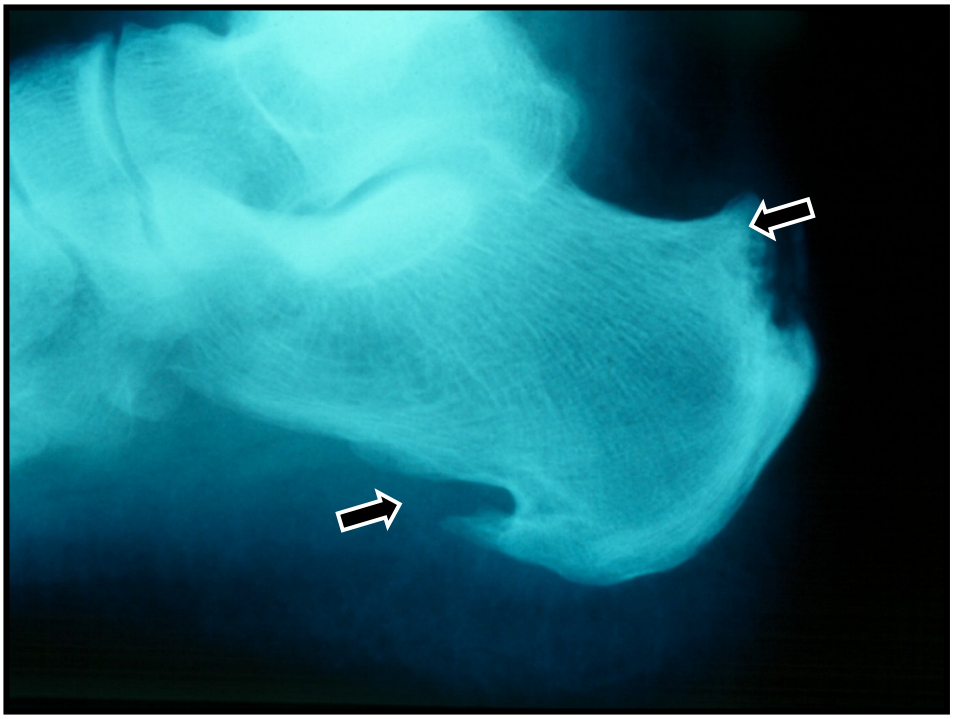

Figure 5. Psoriatic arthritis with entheseal involvement. Arrows show inflammation at sites where tendons or ligaments attach to the bone (entheses). Chronic enthesitis can lead to erosive changes or new bone formation.

(**A**) Asymmetric sacroiliitis.

(**B**) Psoriatic spondylitis with non-marginal syndesmophytes.

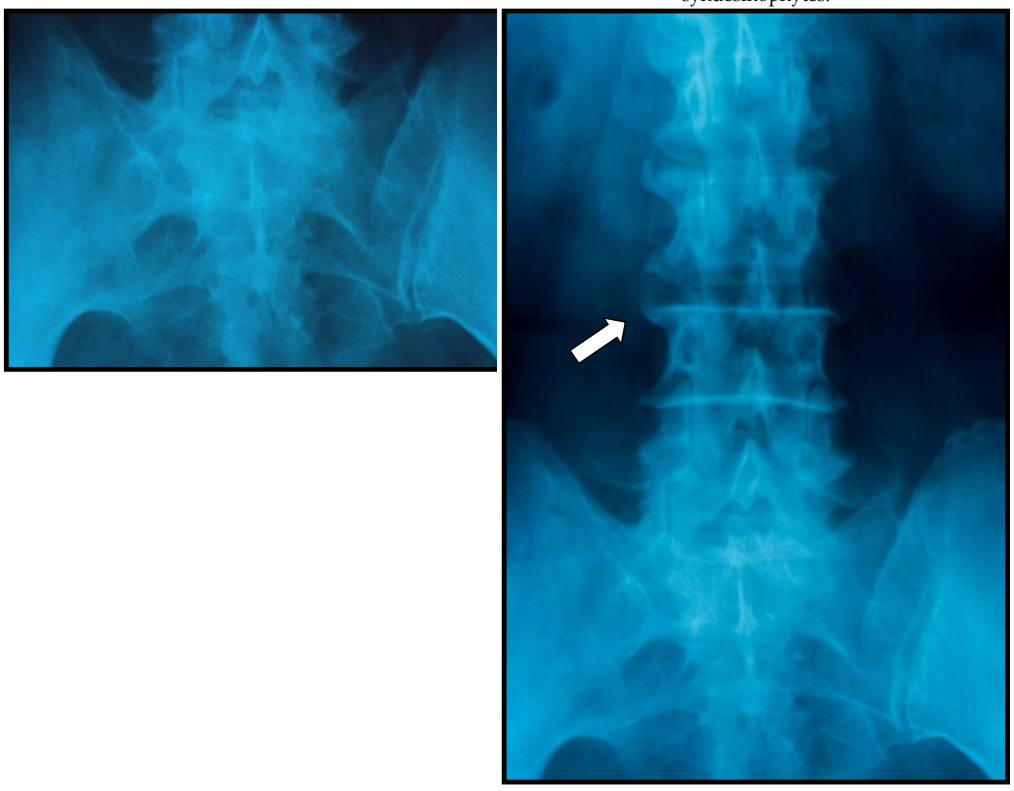

Figure 6. Psoriatic arthritis with axial involvement. Inflammation and associated symptoms are more pronounced on one side of the sacroiliac joint than compared to the other in asymmetric sacroiliitis (**A**). Syndesmophytes are bony growths that form in the spine due to chronic inflammation. In psoriatic arthritis (**B**) these syndesmophytes may bridge adjacent vertebrae.

Diagnosis is based on clinical features, including an inflammatory arthritis, presence of PsO, and negative rheumatoid factor and anti-cyclic citrullinated antibodies. Various classification criteria have been proposed, including the most recent, the CASPAR criteria [23]. Early diagnosis and treatment are crucial to prevent joint damage progression and manage skin disease effectively [24].

2. Pathogenesis

Psoriatic arthritis is a complex, systemic inflammatory condition that has similarities with both psoriasis and other inflammatory joint diseases, such as rheumatoid arthritis and spondyloarthritis. Although the precise mechanisms of PsA are not known, it is thought to result from a combination of genetic predisposition and environmental triggers that lead to inflammatory processes within both the skin and joints [25–27] (Figure 7). Despite these shared pathways, the specific immune mechanisms and clinical manifestations can vary significantly between the skin and joint disease.

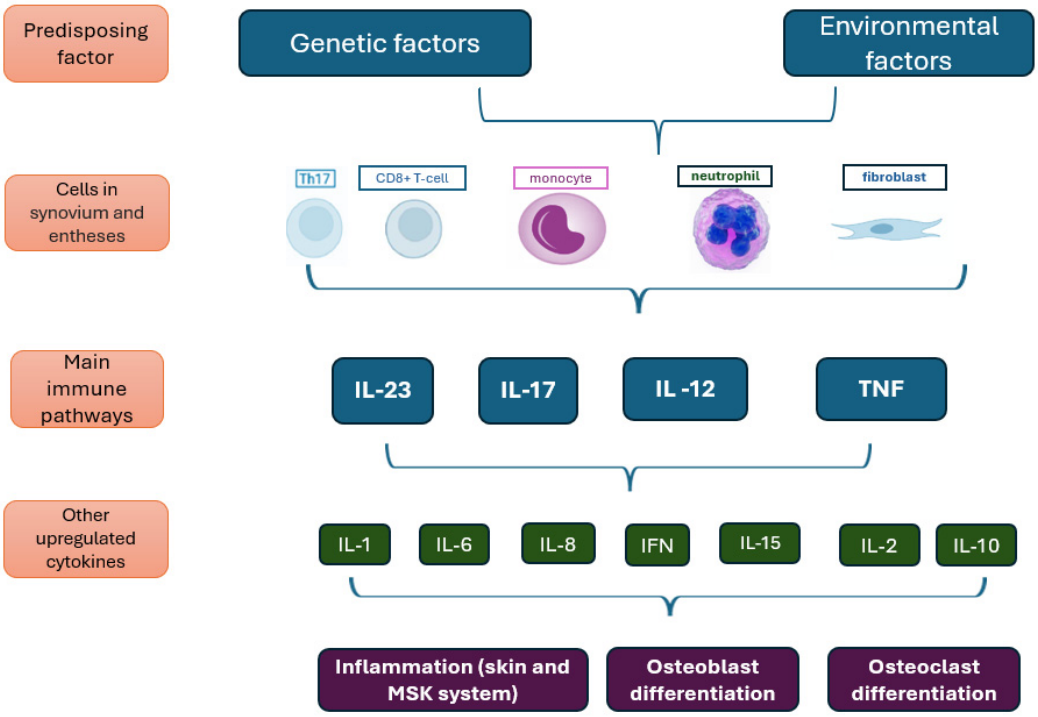

Figure 7. The etiopathogenesis of psoriatic arthritis begins with genetic and environmental factors that activate various immune and inflammatory systemic cells leading to the production of proinflammatory cytokines.

Psoriatic arthritis is highly heritable, with multiple genetic factors contributing to its development [28]. Different genes are associated with different clinical phenotypes. *HLA-B*0801* and *HLA-C*0701* are linked to peripheral synovitis, *HLA-B*2705* is associated with axial and entheseal involvement, and *HLA-B*5701* and *HLA-C*0602* are associated with skin involvement [25]. Focusing specifically on axial disease, *HLA-B27* is associated with symmetric sacroiliitis and ascending spondylitis with marginal syndesmophytes, while *HLA-B39*, *HLA-B08*, and *HLA-B38* are associated with asymmetric sacroiliitis and discontinuous spondylitis with non-marginal syndesmophytes (termed psoriatic spondylitis) [29,30]. There are genetic differences between PsA and PsO; *HLA-C*0602* is more strongly associated with PsO than PsA, while *HLA-B*2705*, *HLA-B*3901*, and *HLA-B*0801* are associated with PsA and not with PsO [25]. Other genetic risk factors include polymorphisms of genes involved in immune regulation, such as TNF-α (*TNFAIP3*) and IL-23 signaling pathways

(*IL-23R*), which play significant roles in the inflammatory process characteristic of PsA and PsO [31].

Environmental factors also play a role in the development of PsA, especially in individuals with psoriasis. Potential triggers include infections like streptococcal infection, as well as trauma and obesity. [32,33]. Furthermore, changes in the gut and skin microbiomes might contribute to disease pathogenesis [34,35], although it is not clear whether these changes are causal or correlative. Dysbiosis in the gut may trigger IL-23 production [36]. IL-23 is produced by resident CD14+ myeloid cells in the enthesis [37], which activates resident CD4-, CD8-, and IL-23R+ T cells [38]. The relationship between environmental factors and genetic predisposition underscores the multifactorial nature of PsA.

The immune responses in PsA are driven by a dysregulation of both innate and adaptive immunity [39]. Key players include T cells, particularly CD8+ T cells, and monocytes, which contribute to inflammation in the skin and joints [40,41]. Cytokine pathways, especially those involving TNF-α, IL-23/IL-17, and IL-22 [36,42], play crucial roles in the pathogenesis of PsA, as these cytokines are found at elevated levels in affected tissues. The overlap of immune pathways in PsA and psoriasis supports the idea of shared pathogenetic origins, although the distinct clinical manifestations in skin and joint disease indicate unique underlying mechanisms in each [36,43,44].

3. Treatment Approach

The treatment approach for psoriatic arthritis (PsA) focuses on controlling inflammation, improving symptoms, and preventing joint damage. Early initiation of treatment is crucial for achieving better functional outcomes [45]. Different therapeutic agents are available that target various inflammatory pathways (see Table 1, Figure 8). Recommendations and treatment pathways may vary between different guidelines (e.g. American College of Rheumatology [ACR] and European Alliance of Associations for Rheumatology [EULAR]) and some recommendations from the guidelines for treatment are based on low or very low evidence. Treatment considerations should also include medical comorbidities, cost, and availability of medication in particular regions. The use of systemic glucocorticoids should generally be avoided because they can trigger psoriatic flares on withdrawal and lead to associated toxicities.

Table 1. Therapeutic choice in the treatment of PsA.

Class of Medication	Medications	Comments
Conventional DMARDs		
Oral small molecules	Methotrexate Sulfasalazine Cyclosporine Leflunomide	
Biologic DMARDs (bDMARDs)		
TNFi Monoclonal antibody Receptor fusion protein Pegylated Fab’	Adaimumab, Infliximab, Golimumab Etanercept Certolizumab pegol	FDA approved for PsA, PsO

Table 1. *Cont.*

Class of Medication	Medications	Comments
IL-17i IL-17Ai IL-17A/Fi	Secukinumab, Ixekizumab, Bimekizumab	FDA approved for PsA, PsO FDA approved for PsO and PsA
IL-12/23i	Ustekinumab	FDA approved for PsA, PsO
IL-23i Monoclonal antibody to p19 subunit of IL23	Guselkumab Risankizumab	FDA approved for PsA, PsO
CTLA-4i	Abatacept	FDA approved for PsA
	Targeted Synthetic DMARDs (tsDMARDs)	
PDE4i	Apremilast	FDA approved for PsA, PsO
JAKi	Tofacitinib, Upadacitinib	FDA approved for PsA

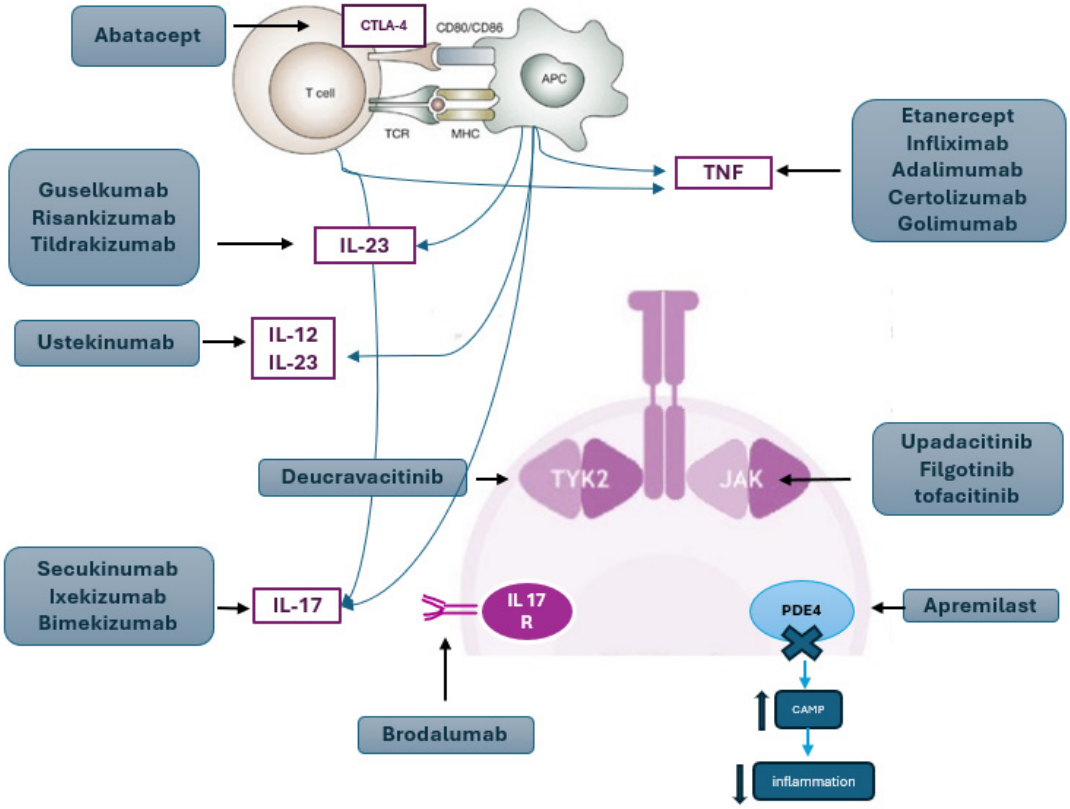

Figure 8. Summary of pathogenic pathways and the mechanisms of action of biologic and targeted synthetic DMARDs. Arrows show the targets of various biologics and targeted synthetic DMARDs. Eg. Apremilast inhibits phosphodiesterase-4 (PDE4) resulting in increases in cyclic adenosine monophosphate (cAMP) levels resulting in decreased inflammation.

4. Disease Manifestation and Treatment Selection

Treatment is tailored to specific disease manifestations, such as peripheral arthritis, axial arthritis, dactylitis, enthesitis, skin and nail changes, and ocular disease. In cases with multiple domain involvement, therapies that address all domains are preferred. For example, a tumor necrosis factor inhibitor (TNFi), interleukin 17 inhibitor (IL-17i), or Janus kinase inhibitor (JAKi) should be selected for patients with axial disease. For patients with concomitant uveitis or inflammatory bowel disease, a monoclonal antibody TNFi is

preferred. IL-23i or JAKi could also be considered but the data regarding their efficacy for uveitis is limited.

- Treat-to-Target Approach

The goal is to achieve remission or low disease activity [46]. Treating to target, where the treatment is guided by measuring disease activity and adjusted in patients with active disease compared to standard care in the TICOPA trial, showed that treating to target resulted in better outcomes for the patients [47].

- Multispecialty Coordination

A coordinated approach involving rheumatologists, primary care clinicians, and relevant specialists (e.g., dermatologists) is crucial for comprehensive care, especially for managing comorbid conditions.

- Comorbidities
    - Common comorbidities include cardiovascular disease, obesity, and mental health disorders (anxiety, depression), which may influence treatment choices.
    - Cardiovascular risk should be assessed for all patients, and JAKi should be used cautiously in those with cardiovascular risk factors [48].
    - Weight loss is advised for obese patients, as it improves PsA outcomes [49].
    - Special attention is needed for patients with anxiety and depression, as these conditions can impact medication choice. Some drugs, like apremilast and brodalumab (for PsO), should be avoided in those with severe anxiety or depression due to potential suicide risks [50].
- Other considerations

Combination therapy (e.g. ustekinumab and etanercept) is possible to treat severe refractory PsA [51]. Other combinations have been used to treat PsA, but there is no clinical trial data to support their use at this time.

- Adjunctive therapies

Additional therapies include NSAIDs, methotrexate, sulfasalazine, cyclosporine, leflunomide, systemic glucocorticoids, and intra-articular glucocorticoids. Glucocorticoids are generally avoided unless used for psoriatic arthritis flares [52].

- Different clinical domains of psoriatic arthritis respond variably to bDMARDs and tsDMARDs [53].

European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of PsA with pharmacological therapies, 2023 (Figure 9) are as follows [54]:

1. Treatment should be aimed at reaching remission or low disease activity.
2. NSAIDs may be used to relieve musculoskeletal signs and symptoms; local injections of glucocorticoids may be considered as adjunctive therapy.
3. In patients with polyarthritis, or those with monoarthritis/oligoarthritis and poor prognostic factors (structural damage, elevated acute-phase reactants, dactylitis, or nail involvement), a csDMARD should be initiated rapidly, with methotrexate preferred in those with clinically relevant skin involvement.
4. In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD should be commenced.
5. In patients with peripheral arthritis and an inadequate response to at least one bDMARD, or when a bDMARD is not appropriate, a JAKi may be considered, taking safety considerations into account.
6. In patients with mild disease and an inadequate response to at least one csDMARD, in whom neither a bDMARD nor a JAKi is appropriate, a PDE4i may be considered.

7. In patients with unequivocal enthesitis and an insufficient response to NSAIDs or local glucocorticoid injections, therapy with a bDMARD should be considered.
8. In patients with clinically relevant axial disease with an insufficient response to NSAIDs, therapy with a TNFi, IL-17i, or JAKi should be considered.
9. Treatment choice may be dictated by extra-articular manifestations: relevant skin involvement—IL-17i, IL-23i, IL-12/23i; uveitis—monoclonal antibody TNFi; IBD—monoclonal antibody TNFi, IL12/23i, IL-23i, JAKi.
10. In patients with an inadequate response or intolerance to a bDMARD or JAKi, switching to another bDMARD or JAKi should be considered, including one switch within a class.
11. In patients with sustained remission, tapering of DMARDs may be considered.

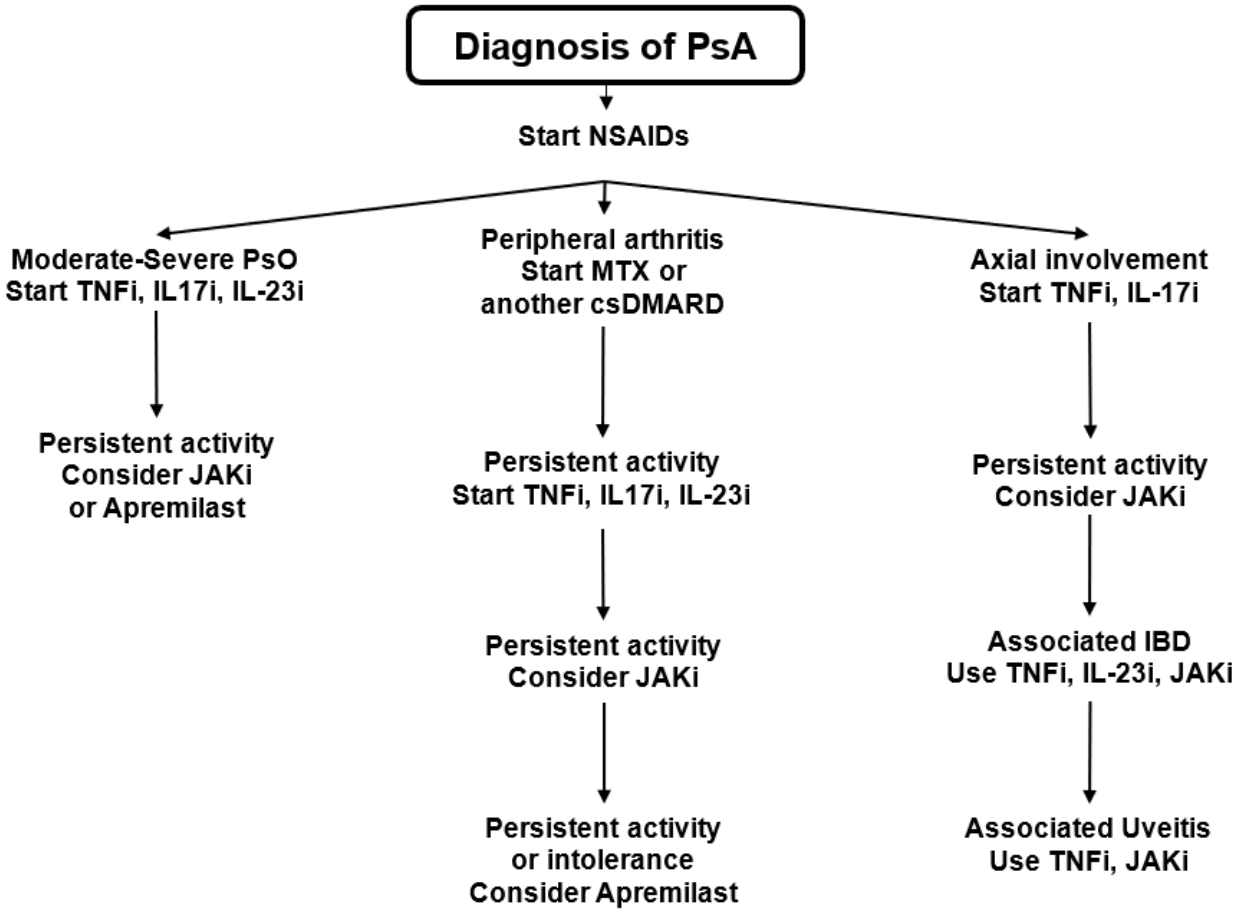

Figure 9. Treatment paradigm for PsA.

5. Conventional Synthetic DMARDs (csDMARDs)

5.1. Methotrexate

Methotrexate has been widely used for treating PsA, although relatively few studies have specifically examined its efficacy in this condition. There was no significant difference between methotrexate and placebo in the Methotrexate in Psoriatic Arthritis (MIPA) trial, but design flaws and dosing issues affected the results [55].

The study by Lindström et al. compared methotrexate treatment outcomes in early psoriatic arthritis (PsA) and rheumatoid arthritis (RA). The results indicated that while disease activity improved during methotrexate monotherapy for both conditions, the improvement was notably greater in RA compared to PsA. This suggests that methotrexate

may be less effective in managing disease activity in PsA than in RA, highlighting the need for careful treatment consideration based on individual patient response [56].

Methotrexate remains an important treatment option, especially in resource-limited settings, and can reduce immunogenicity when used concomitantly with certain biologic therapies. Regular laboratory monitoring with methotrexate is required, and it can be associated with adverse reactions including oral ulcers, nausea, and fatigue. Methotrexate should be avoided during pregnancy due to its potential teratogenic effects.

Methotrexate can be used as first-line treatment for PsA, as its use is sometimes mandated by health systems before other therapies are considered. If methotrexate is ineffective or poorly tolerated, alternatives include other csDMARDs such as leflunomide, sulfasalazine, and cyclosporine, or transitioning to a TNFi [57]. The CONTROL study indicated that adding a TNFi is more effective than increasing the methotrexate dosage in patients with residual disease [58].

5.2. Sulfasalazine

Sulfasalazine is one of the oral treatment options for PsA, with a prior study showing effectiveness compared to placebo [59]. It is not effective for axial disease or skin disease. It has potential gastrointestinal side-effects and requires laboratory monitoring.

5.3. Leflunomide

Leflunomide is another oral medication with reported efficacy in PsA [60]. It has potential hematological and hepatotoxic effects and requires monitoring. It is teratogenic and should be avoided in pregnancy. It has a very long half-life so it should be used with caution in women of childbearing potential. It is not very effective for psoriatic skin disease.

5.4. Cyclosporine

A prior study showed that cyclosporine therapy could be efficacious in treating psoriatic arthritis and psoriasis [61]. It also requires toxicity monitoring. It is rarely used to treat PsA as there are more effective and safer therapies.

6. Biologic DMARDs (bDMARDs)

6.1. TNF Inhibitors

6.1.1. TNFis Are Generally the Preferred First bDMARD Therapy for Moderate to Severe Disease

This approach is supported by the 2015 and 2021 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations, while the 2023 European Alliance of Associations for Rheumatology (EULAR) recommendations do not specify one specific bDMARD over another [53,57]. There are five TNFi options available for treating PsA, including adalimumab, infliximab, golimumab, etanercept, and certolizumab pegol. There is insufficient data to suggest that one is superior to the others, so the choice of medication is based on patient preferences regarding the route of administration (subcutaneous versus intravenous), frequency of administration, cost, and insurance coverage.

TNFis are effective for peripheral arthritis, axial involvement, and can also be effective for treating enthesitis, dactylitis, psoriasis skin and nail disease, IBD, and uveitis [54]. Monoclonal antibody TNFis should be used in patients with uveitis or IBD as comorbidities. However, their use should be avoided in patients with congestive heart failure, demyelinating diseases such as multiple sclerosis and optic neuritis, untreated mycobacterial or other chronic infections, or a history of serious infections. It is important to screen for latent tuberculosis and hepatitis prior to beginning therapy. TNFis are often used in combination with methotrexate and can be used in combination with apremilast [62]. In patients with

PsA, TNFi use has demonstrated the ability to slow the progression of radiographic joint damage [63]. TNFis were effective in treating PsA in phase 3 clinical trials both with or without methotrexate. However, a large observational study found that patients treated with a combination of TNFis and methotrexate had higher remission rates compared to those treated with TNFis alone [64].

6.1.2. Etanercept

Etanercept is a dimeric p75 TNF-α receptor-IgG Fc fragment fusion protein that binds to TNF and is administered via subcutaneous injection. The FDA approved etanercept as the first bDMARD and TNFi for the management of PsA [65,66]. Etanercept is effective as monotherapy for both PsA and PsO [66,67]. In a 48-week randomized placebo-controlled study, patients receiving etanercept achieved an ACR20 response rate of 59% compared to versus 15% with placebo, and a PASI75 response rate of 23% versus 3% with placebo at week 12 ($p < 0.0001$), with these results remaining consistent at 24 and 48 weeks. Etanercept also reduced radiographic progression [66]. Some studies have shown no significant improvement in response when etanercept is combined with csDMARDs [68–70].

6.1.3. Adalimumab

Adalimumab is a human anti-TNF-α monoclonal antibody administered via subcutaneous injection. Adalimumab can decrease disability and slow the development of joint damage in PsA and PsO [71–73]. In the 24-week randomized, double-blind, placebo-controlled study, Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT), adalimumab was effective in reducing disease activity of PsA with an ACR20 response in 57% (compared to 14% in placebo), an PASI75 response in 59% (compared to 1% in placebo), and a reduction in radiographic progression [71]. The response rates were maintained over 2 years [72].

6.1.4. Infliximab

Infliximab is a chimeric monoclonal antibody derived from both human and mouse components targeting TNF-α and is administered as an intravenous infusion. It has been proven to have short-term and sustained benefits for patients with PsA showing improvement in skin and joint symptoms [74,75]. In the infliximab IMPACT 2 trial, 58% of patients receiving infliximab achieved an ACR20 response, compared to only 11% of those on placebo at week 14. Improvement in dactylitis, enthesopathy, and arthritis were maintained through 24 weeks [76].

6.1.5. Golimumab

Golimumab is a human monoclonal antibody targeting TNF-α, which can be administered as a subcutaneous injection or an intravenous infusion. It is effective in treating psoriatic arthritis as well as psoriasis affecting the skin and nails [77–80].

6.1.6. Certolizumab Pegol

Certolizumab is a pegylated Fab fragment of a humanized anti-TNF-α monoclonal antibody administered as a subcutaneous injection. It effectively improves the signs and symptoms of PsA, such as those affecting the joints, enthesitis, dactylitis, skin, and nails [81]. Since this molecule lacks an Fc portion, it does not cross the placenta into the fetal circulation so it may be a preferred treatment in women who are pregnant or of reproductive age.

6.2. IL-17 Inhibitors

IL-17A and IL-17F are thought to play a role in the inflammatory process of PsA. IL-17 is primarily produced by a certain population of CD4+ T helper cells, Th17 cells. These

agents are effective in treating peripheral arthritis, axial involvement, and skin disease, but do not appear to be effective for uveitis or IBD. The primary adverse event associated with these medications is an increased infection risk, particularly mucocutaneous candida infections. Screening for hepatitis and tuberculosis is important, and patients should be monitored throughout treatment. IL-17is can be used in patients who do not respond to TNFis, experience an adverse reaction, or in whom they are contraindicated. IL-17is may be considered for treatment before TNFi use in patients with more severe psoriasis.

6.2.1. Secukinumab

Secukinumab is a human monoclonal antibody targeting anti-IL-17A, which has been shown to be effective in treating PsA, including peripheral arthritis, axial disease, enthesitis, dactylitis, skin and nail disease. This medication may be administered as a subcutaneous injection but is also available as an intravenous infusion. It inhibits radiographic progression [82–84]. The FUTURE 1 trial, a 24-week study involving secukinumab at doses of 150 mg and 75 mg, resulted in an ACR20 response in 50% (compared to 17.3% in placebo) and a PASI75 response in 61.1% (compared to 8.3% in placebo) [82]. There was no significant difference in response between patients with or without concomitant methotrexate or prior TNFi use. The results in the FUTURE 2 study using secukinumab 300 mg and 150 mg showed very similar results. Secukinumab has disease-modifying effects and has been shown to inhibit radiographic progression [85,86]. It is also effective in patients with psoriatic spondylitis [87].

6.2.2. Ixekizumab

Ixekizumab is a humanized IL-17A monoclonal antibody effective in treating PsA, including peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail disease, and is administered via subcutaneous injection [88–90]. In the 24-week SPIRIT-P1 trial, ixekizumab was compared to adalimumab and placebo in a randomized, placebo-controlled, double-blind trial; ixekizumab was as effective as adalimumab for joint disease with an ACR20 response in 57.9% vs. 57.4%, respectively (30.2% in placebo), but superior for skin disease with a PASI75 response in 71% vs. 54.4%, respectively (10.4% in placebo) [91]. This study was extended to 52 weeks with the same results [92]. In the 52-week open-label SPIRIT H2H trial comparing ixekizumab and adalimumab, ixekizumab showed superiority due to better outcomes for skin disease [93]. Ixekizumab was compared to guselkumab for the treatment of PsO and found to have similar responses for skin disease but superior responses for nail disease in a non-inferiority study [94].

6.2.3. Bimekizumab

Bimekizumab is a humanized monoclonal antibody directed against both IL-17A and IL-17F, administered as a subcutaneous injection. It was initially approved by the FDA for PsO and was found to be superior to secukinumab at the 300 mg dose [95]. Bimekizumab was studied in PsA patient who were bDMARD naïve in the 52-week BE OPTIMAL trial. The ACR20 response rate with bimekizumab was 71.2% (compared to 23.8% in placebo) and the PASI75 response rate was 81.6% (compared to 12.9% in placebo) [96]. Bimekizumab is now approved for the management of PsA. Patients receiving bimekizumab showed an increased risk of infection, especially mucocutaneous candidiasis [96,97]. The BE COMPLETE trial included patients with active PsA and previous inadequate response of intolerance to TNF inhibitors. The ACR20 response was 67% in the active treatment group (compared to 15.8% in placebo) and the PASI75 response was 82.4% (compared to 10.2% in placebo) [97]. Bimekizumab demonstrated a very robust skin response and the improvements in both skin disease and joint symptoms in PsA patients were maintained through 3 years without any new safety signals [98].

6.2.4. Brodalumab

Brodalumab is a human monoclonal antibody targeting the IL-17 receptor administered as a subcutaneous injection. Brodalumab has shown excellent efficacy for the treatment of PsO, and is FDA approved for this indication [99]. It has also been studied in PsA and has good efficacy [100,101]. Due to a black box warning for depression and suicide, brodalumab is not used in the treatment of PsA.

6.3. IL-12/23 and IL-23 Inhibitors

IL-12/23is and IL-23is are designed to target key pathways in the inflammatory process associated with PsO and PsA. IL-23, a cytokine critical for the differentiation and survival of Th17 cells, plays a pivotal role in driving inflammation in both skin and joints. By inhibiting IL-23, these agents lead to significant improvements in the symptoms of PsA and PsO, particularly in the skin and peripheral joints, by decreasing activation of inflammatory cells. IL-12/23is and IL-23is are not effective for axial disease in comparison to TNFis and IL-17is, making them suitable for patients primarily experiencing peripheral arthritis or those with concomitant conditions such as inflammatory bowel disease (IBD). Several post hoc analyses provide some evidence that ustekinumab [102,103] and guselkumab [104] may have efficacy in psoriatic spondylitis.

IL-12/23is and IL-23is may be used in patients who have failed prior therapies or in those for whom axial involvement is not a concern. In cases where other treatments have been insufficient, IL-23is provide a targeted approach that can address both skin and joint symptoms with an excellent safety profile, making them an increasingly popular option in the management of PsA and PsO. IL-23is are effective for skin disease with efficacy comparable to IL-17is, making them a good option for patients with more severe skin disease.

Ustekinumab is a monoclonal antibody directed against the p40 subunit shared by both IL-12 and IL-23 and inhibiting the activity of these cytokines. Guselkumab, risankizumab, and tildrakizumab are monoclonal antibodies directed against the p19 subunit of IL-23 inhibiting its activity and reducing the amount of T cells that differentiate into Th17 cells. Guselkumab and risankizumab are FDA approved for the treatment of PsA and PsO while tildrakizumab is only approved for PsO.

6.3.1. Ustekinumab

Ustekinumab is a human monoclonal antibody that targets the shared p40 subunit of IL-12 and IL-23, interfering with its binding to receptors on inflammatory cells [105,106]. It is given as a subcutaneous injection. In phase 3 trials, ustekinumab demonstrated effectiveness in treating both PsA and PsO. In the 1-year PSUMMIT 1 trail, ustekinumab was effective in reducing the signs and symptoms of PsA; the ACR20 response was 46.0% (compared to 22.8 in placebo) and the PASI75 response was 59.9% (compared to 11.0% in placebo) [107]. Ustekinumab was effective in patients who had previously been treated with a TNFi, but the effect was less pronounced [106]. Ustekinumab does inhibit radiographic progression in patients with PsA. Ustekinumab is used less frequently since the arrival of IL-23is as these tend to be more effective, especially for skin disease, and have a better safety profile. Ustekinumab is effective and FDA approved for ulcerative colitis so it may be considered in patients with this comorbidity.

6.3.2. Guselkumab

Guselkumab is a human anti-IL-23-specific monoclonal antibody that targets the p19 subunit of IL-23 and is administered as a subcutaneous injection. It is effective for the treatment of PsA and PsO [108–110]. The DISCOVER-1 trial was a 24-week phase 3 study of

patients with PsA including some patients previously treated with a TNFi. In the patients who received guselkumab, the ACR20 response was 52% (compared to 22% in placebo) and the PASI75 response was 76% (compared to 14% in placebo). The PASI100 (100% clear) response was 26% (compared to 6% in placebo) [109]. In the DISCOVER-2 trial where all the PsA patients were bDMARD naïve [110] and the COSMOS trial which only included only patients who were inadequate responders to TNFis [111], the joint and skin responses were similar. The risk of infection for patients receiving guselkumab was comparable to that of those on placebo, demonstrating a good safety profile [109,110]. Long-term efficacy and safety of guselkumab has been documented for up to 2 years [112]. Guselkumab is also FDA approved for the management of ulcerative colitis and has efficacy in Crohn's disease which should be considered when treating patients with these comorbidities.

6.3.3. Risankizumab

Risankizumab is a humanized anti-IL-23 antibody that targets the p19-protein subunit of IL-23 and is administered as a subcutaneous injection. It is effective for the treatment of PsA and PsO, both in biologically naïve patients and in patients with inadequate response to biologic therapies [113–115]. In the 24-week KEEPsAKE 1 trial in which the PsA patient were naïve to bDMARDs, the ACR20 response was 57.3% (compared to 33.5% in placebo) and the PASI90 response was 52.3% (compared to 9.9% in placebo) [113]. The ACR and PASI90 responses were similar in the KEEPsAKE 2 trial which included patients with PsA who had previously been treated with up to two bDMARDs [115]. Risankizumab is FDA approved for ulcerative colitis and Crohn's disease, which is important to consider for patients with these comorbid conditions.

6.3.4. Tildrakizumab

Tildrakizumab is a humanized monoclonal antibody directed against the p19 subunit of IL-23 administered as a subcutaneous injection. It is FDA approved for PsO [116]. Tildrakizumab has shown efficacy in PsA but has not been FDA approved at this time [117].

6.4. Abatacept

Abatacept is a CTLA4-IgG Fc fragment fusion protein, a selective T-cell costimulation modulator. Abatacept is not effective for the treatment of skin psoriasis but is an option for the management of peripheral arthritis in PsA [118]. The efficacy for joint disease is modest (ACR20 response of 39.4% compared to 22.3% in placebo). For this reason, abatacept is not commonly used in patients with PsA.

6.5. Targeted Synthetic DMARDs (tsDMARDs)

6.5.1. Apremilast

Apremilast is an oral phosphodiesterase 4 inhibitor (PDE4i) that has demonstrated benefits for peripheral psoriatic arthritis, with some additional effects on skin disease, enthesitis, and dactylitis [119–123]. The results were very similar across these phase 3 trials. Cutolo M. et al. conducted a phase 3, randomized, controlled trial of apremilast in patients with psoriatic arthritis, showing positive results in the PALACE 2 trial [121]. At 16 weeks, the ACR20 response was 32.1% in the active treatment arm (compared to 18% in placebo), and the PASI50 response was 41% (compared to 18.9% in placebo). The ACR20 response was 52.6% and the PASI50 response was 58.9% in the open-label extension to week 52. Apremilast has no proven benefit for axial involvement in psoriatic arthritis. The efficacy of apremilast appears to be similar to other agents but is associated with additional adverse events including gastrointestinal intolerance and depression [124]. It does have the advantage as it is an oral agent and it is not associated with an increased risk of infection or laboratory abnormalities [125].

6.5.2. Janus Kinase Inhibitors (JAKis)

Tofacitinib and upadacitinib are oral JAKis which are FDA approved for the treatment of PsA and are also effective for axial spondyloarthritis. Baseline laboratory tests should include a lipid panel, screening for latent tuberculosis, hepatitis, and assessment of cardiovascular and malignancy risk factors. There is an increased risk for infection with this class of medication, particularly herpes zoster. Other potential toxicities include elevated liver function tests, elevated cholesterol, and neutropenia. JAKis have a black box warning for malignancy, major adverse cardiovascular events (MACE), and thrombosis. In patients with rheumatoid arthritis, tofacitinib treated patients had a higher risk for cardiovascular events and malignancy than patients treated with TNFis [48,126].

6.5.3. Tofacitinib

Tofacitinib is an oral JAKi that specifically targets JAK1 and JAK3. Tofacitinib is FDA approved for use in patients with PsA who have not responded to at least one TNFi. Additionally, it can be used for patients with active PsA who have contraindications to the use of a TNFi [127,128]. In a three-month phase 3 study, tofacitinib was evaluated against adalimumab and a placebo. The ACR20 response for patients receiving tofacitinib 5 mg bid was 50%, while it was 52% in patients on adalimumab, compared to 33% for the placebo group [127]. At 12 months, the ACR20 response was 68% and 60%, respectively. The results in a trial of PsA patients with an inadequate response to TNFis were similar [128].

6.5.4. Upadacitinib

Upadacitinib is an oral JAKi with specific activity on JAK1. It has been demonstrated in randomized trials to be effective for active PsA [129,130]. Upadacitinib 15 mg daily was compared to adalimumab and placebo in the 12-week phase 3 SELECT-PsA 1 trial. The ACR20 response was 70.6% with upadacitinib and 65.0% for adalimumab (compared to 36.2% for placebo) [129]. The results of a study of PsA patients refractory to bDMARDs showed similar results [130].

6.6. Potential Treatments

6.6.1. Deucravacitinib

Deucravacitinib is an oral selective tyrosine kinase 2 inhibitor (TYK2i) that has shown promise in the treatment of psoriatic arthritis (PsA). By targeting TYK2, it inhibits key inflammatory pathways involved in disease pathogenesis. The medication is currently FDA approved for the management of moderate to severe plaque psoriasis [131]. Furthermore, it has been shown to be effective in reducing joint inflammation in clinical trials, though it has not yet received FDA approval for treatment of PsA [132]. Deucravacitinib presents a potential treatment option for PsA, with research ongoing to evaluate its long-term safety and efficacy.

6.6.2. Filgotinib

Filgotinib is an oral JAKi that selectively targets JAK1. It has been studied for the treatment of PsA and has shown potential in improving symptoms such as joint inflammation and enthesitis. However, filgotinib is not currently FDA approved for PsA. While clinical trials have indicated efficacy in PsA and other inflammatory conditions, concerns about safety, particularly related to infections and thrombosis, remain important considerations in its use. At present, further studies are not being pursued.

6.6.3. Brepocitinib

Brepocitinib selectively inhibits the activation of JAK1 and TYK2. It is currently being studied for PsA treatment.

7. Discussion

The choice of treatment for psoriatic arthritis should consider the clinical domains involved in each patient (e.g., peripheral arthritis, axial arthritis, dactylitis, enthesitis, skin, and nails) and comorbidities such as uveitis and IBD. Treatment should be tailored based on the severity of symptoms and the specific domains affected. Recommendations and treatment pathways may vary between guidelines, but one approach to management of patients with PsA is outlined in Figure 9. Patients who have moderate to severe psoriasis would benefit from starting with TNFi, IL17i, or IL-23i use. If there is persistent activity, either apremilast or a JAKi could be considered. Patients who have predominantly peripheral arthritis would benefit from the initiation of methotrexate or another csDMARD. TNFi, IL17i, and IL23i use should be considered in patients who have persistent peripheral arthritis despite csDMARDs. If the patient primarily exhibits axial involvement, TNFi and IL17i use should be considered early in the treatment process. If these options are unsuccessful, a JAKi could then be considered.

Shared decision-making is crucial, and patient preferences must be considered including route of administration, i.e., oral, subcutaneous, intravenous. Coordination between rheumatology, dermatology, and primary care physicians is essential, especially when considering comorbid conditions such as uveitis, IBD, cardiovascular disease, obesity, and depression.

For axial disease, NSAIDs, TNFis, IL-17is, and JAKis have proven efficacy. In cases of enthesitis and dactylitis, bDMARDs and JAKis have shown effectiveness. Systemic glucocorticoid use should generally be avoided due to the risk of psoriatic flares and associated toxicities. Regular monitoring of psoriatic arthritis patients is recommended at intervals of 3–6 months to assess disease activity and monitor medication toxicity.

Despite significant advancements in understanding the pathogenesis of PsA and the development of targeted therapies, achieving remission or minimal disease activity remains challenging. PsA may impact a patient's quality of life and may require a more holistic view of disease management. PsA has a multifactorial pathogenesis which also necessitates a multifaceted treatment approach. This approach may include lifestyle modifications, such as adopting a healthier diet and engaging in physical activity, in addition to pharmacologic intervention [133]. Cost of therapy, particularly for biologic and targeted synthetic DMARDs, can be a barrier to treatment and should be considered when managing patients with PsA.

In cases of inadequate response to biologic therapy, it is important to reevaluate the diagnosis, assess treatment adherence, consider comorbid conditions such as depression that may contribute to symptoms, and determine if concomitant fibromyalgia is playing a role in persistent symptoms.

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