Overview of the Drug Therapy of Psoriatic Arthritis

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ABSTRACT

Psoriatic arthritis is an inflammatory disease associated with psoriasis, with an estimated prevalence of psoriatic arthritis among patients with psoriasis ranging from 4% and 30% in global population. Clinical manifestations include joint involvement, nail changes, enthesitis and dactylitis. The choice of pharmacological therapy depends upon clinical presentation. For patients with mild musculoskeletal symptoms, NSAIDs can be used. Disease-modifying anti-rheumatic drugs (DMARDs) should be employed for polyarthritis and more severe cases. Conventional DMARDs and biologic DMARDs are both proven efficacious in psoriatic arthritis. Recently, numerous DMARDs have been developed with promising results. The choice of drug therapy is discussed in this article.

Keywords: *Psoriatic arthritis, Disease-modifying anti-rheumatic drug, Tumor necrosis factor inhibitor, Interleukin inhibitor, Biologic DMARD*

INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory disease associated with psoriasis. It comprises both musculoskeletal and non-musculoskeletal manifestations, where the latter includes skin and nails, and potentially guts and eyes. PsA affects men and women equally.[1] Active chronic PsA is also associated with cardiovascular, psychological and metabolic comorbidities, which together with the musculoskeletal symptoms, impose a significant patient burden with impact on quality of life and accelerated mortality.[1] Estimates of the prevalence of PsA among patients with psoriasis have ranged from 4 to 30%.[1] Early identification of PsA and early initiation of therapy are important for improving long-term outcomes. This article provides an overview of the disease and summarizes the drug treatments for PsA.

PATHOPHYSIOLOGY

The pathophysiology of PsA involves a complex interaction between genetic, immunologic, and environmental factors. Five percent of first-degree relatives of patients with PsA will develop an inflammatory arthritis.[2] Although the exact genetic mechanisms are not known, human leukocyte antigen alleles within the major histocompatibility complex have been strongly implicated. Psoriatic arthritis shares similar disruptions to the immune system as other immune-mediated inflammatory diseases (e.g., rheumatoid arthritis, Crohn's disease). These diseases involve immune-pathologic features, including neutrophil infiltration, CD4+ lymphocytes, CD8+ T-cells and multiple inflammatory cytokines (e.g., interleukin (IL)-6, IL-12, IL-17, IL-23), and tumor necrosis factor (TNF) in the synovial tissue and synovial fluid.[3] Some environmental factors are suspected to be associated with PsA, including skin trauma and infections.[4]

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Psoriatic arthritis is an inflammatory seronegative spondyloarthropathy. It is estimated that patients have cutaneous manifestations for an average of 12 years before onset of PsA.[5] Given a heterogeneous disease, clinical manifestations include peripheral joint and axial skeleton involvement, nail changes, enthesitis, tenosynovitis, and dactylitis. Patients may present with one or more of these symptoms and arthritis may be monoarticular (involving a single joint), oligoarticular (involving 1 to 4 joints), or polyarticular (involving many joints).

Diagnosis of PsA involves physical examination of affected joints, nail and skin changes, imaging like X-ray to show joint damage and blood tests to assess ESR, rheumatoid factors and anti-CCP antibodies. Various classification systems are developed to help identify PsA. Two commonly used classification systems for diagnosis of PsA are Classification of Psoriatic Arthritis (CASPAR) criteria and Moll and Wright criteria. CASPAR criteria are a set of diagnostic rules that could be used to classify PsA patient. To meet the criteria, a patient must have inflammatory articular disease, and score at least 3 points from the following list of features: current psoriasis (assigned a score of 2; all other features were assigned a

score of 1), a history of psoriasis (unless current psoriasis was present), a family history of psoriasis (unless current psoriasis was present or there was a history of psoriasis), dactylitis, juxtaarticular new bone formation, negative rheumatoid factor, and nail dystrophy.[6] Moll and Wright criteria are the original criteria used and is still commonly used. The diagnosis of psoriatic arthritis requires negative serology for rheumatoid factor plus 1 of the following 5 subtypes: Polyarticular symmetric arthritis, Oligoarticular (< 5 joints) asymmetric arthritis, Distal interphalangeal joint predominant arthritis, Spondylitis predominant arthritis and Arthritis mutilans.[7] A comparative study demonstrates that the sensitivity of CASPAR criteria and Moll and Wright criteria is 91.7% and 85.8% respectively.[8]

TREATMENT GOALS AND COMMON ENDPOINT

The primary goal of treating patients with PsA is to maximize health-related quality of life, through (1) control of symptoms; (2) prevention of structural damage; and (3) normalization of function and social participation. Abrogation of inflammation is an important component to achieve these goals.[9]

Therapeutic decisions are needed to be individualized and made jointly by doctor and patient. Treatment choices may be affected by various factors, including disease activity, previous therapies, prognostic factors such as structural damage, comorbid conditions and patient factors such as cost and convenience.[10]

A general approach to managing patients with PsA is summarized in European League Against Rheumatism (EULAR) guideline 2019 **(Figure 1)**.[9] In EULAR guideline 2019, it is recommended that patients with polyarticular disease should receive a csDMARD (methotrexate, leflunomide, sulfasalazine) either as first-line drug or only after a short course of NSAIDs. Polyarticular disease is defined as 5 or more swollen joints.

In patients with peripheral arthritis and an inadequate response to at least one csDMARD, a biological DMARD (bDMARD) should be considered. bDMARDs are biologic agents that aim at different cytokines such as TNF, IL-17, IL-12/IL-23, IL-23 as well as targeted synthetic DMARD (tsDMARD) that inhibit phosphodiesterase-4 (PDE-4) or Janus kinases (JAKs).[9] Currently, for the RCTs reviewed for PDE4i, TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors, IL-23 inhibitors and JAK inhibitors, there were no differences in efficacy for these treatment options in subgroups of patients with or without csDMARDs.[10]

Multiple outcome measures may be used to evaluate effectiveness of treatments in PsA. Examples include arthritis response, skin severity, patient function and quality of life.[11] The PsA arthritis response is commonly assessed with the American College of Rheumatology (ACR) response criteria. The ACR response criteria are a set of measures that include tender joint count, swollen joint count and five additional core set measures: physician

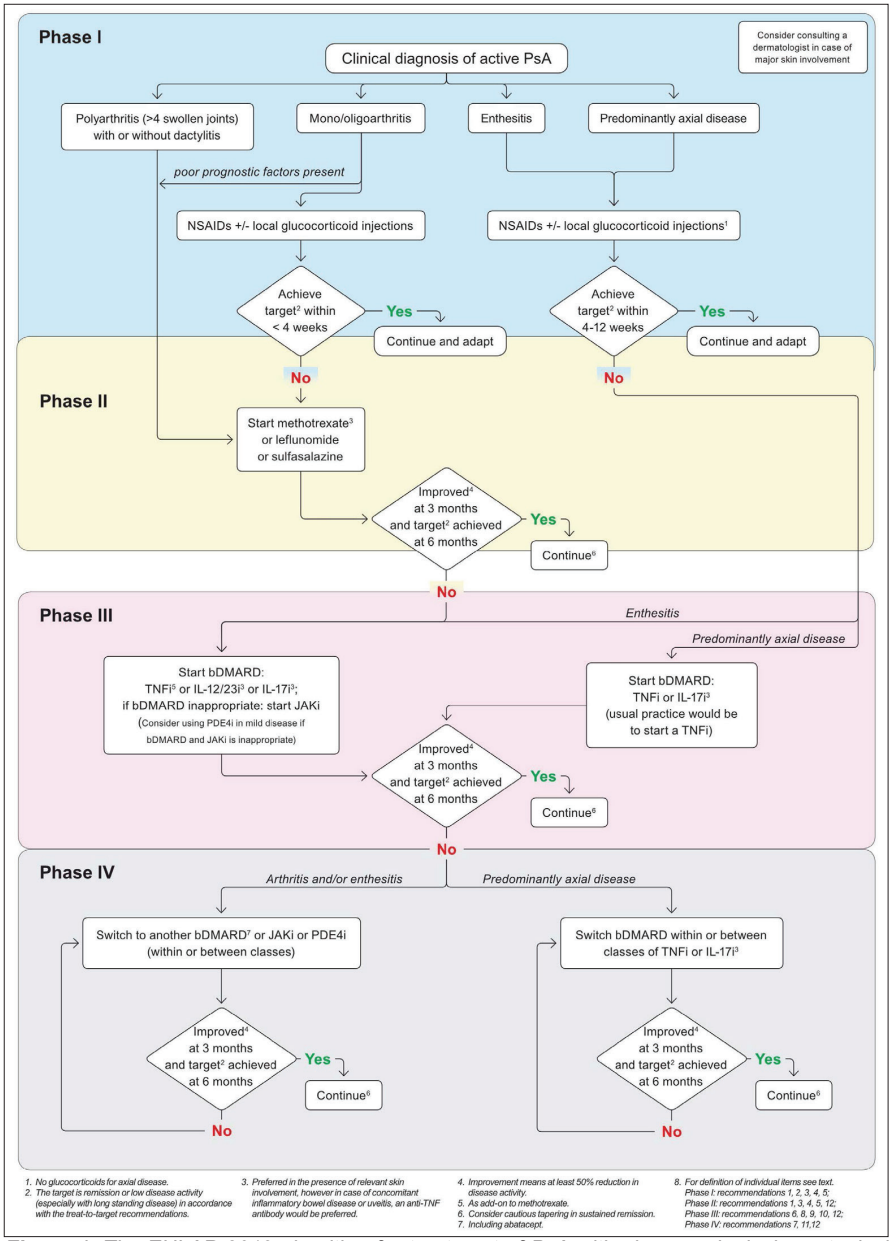

***Figure 1**: The EULAR 2019 algorithm for treatment of PsA with pharmacological non-topical treatments*

assessment of disease activity, patient assessment of disease activity, pain, physical function, and levels of an acute-phase reactant (referring to either CRP level or ESR).[11] An ACR20 response is defined as at least 20% improvement in both the tender joint and swollen joint count and at least 20% improvement in 3 of the 5 core set measures. Some studies also use ACR 50 and ACR70 as outcomes measurements (i.e., 50% or 70% improvement in the ACR response criteria respectively). Common outcome measures used to assess drug response in PsA trials are shown in **table 1**.[11]

Table 1. Selected Outcome Measures in Psoriatic Arthritis

Category	Outcome Measure(s)
Arthritis Response	• American College of Rheumatology (ACR) response criteria • Psoriatic Arthritis Response Criteria (PsARC)
Skin Severity	• Psoriasis Area and Severity Index (PASI)
Patient Function and Quality of Life	• Health Assessment Questionnaire - Disability Index (HAQ-DI) • Short Form-36 health survey (SF-36)

Different drug therapies for PsA treatment will be discussed in the following sections.

THERAPEUTIC AGENTS – NSAID

Non-steroidal anti-inflammatory drugs may be used to relieve musculoskeletal signs and symptoms.[9] The benefit to risk ratio of NSAIDs must always be considered carefully, especially in this population with frequent cardiovascular comorbidities.[9]

For patients with mild synovitis in PsA or axial symptoms, NSAIDs alone may be sufficient to control symptoms.[9] In patients with active peripheral arthritis, NSAIDs should be combined rapidly with DMARDs if needed. NSAID monotherapy should not exceed 1 month if disease activity persists, and other treatment possibilities should be considered.[9]

THERAPEUTIC AGENTS – GLUCOCORTICOIDS

As recommended in EULAR 2019 guideline, local injection of glucocorticoids should be considered as adjunctive therapy in mild PsA for symptomatic control. For systemic glucocorticoids, it may be used with caution at the lowest effective dose and for a short period of time.[9] A systematic review indicates that systematic glucocorticoids are frequently prescribed for PsA patients, and the use of systemic glucocorticoids should be considered if a patient needs rapid anti-inflammatory therapy.[12] However, in 2023, EULAR has announced the removal of the use of systemic glucocorticoids from its recommendations for the management of psoriatic arthritis.[13]

THERAPEUTIC AGENTS – CONVENTIONAL DMARDS

Conventional DMARDs (csDMARDs), including methotrexate, leflunomide and sulfasalazine, are recommended in the management of PsA as first-line DMARDs.

Methotrexate (MTX) is a folate antimetabolite that inhibits DNA synthesis, repair and cellular replication. This drug has a labeled indication for treatment of psoriasis but not for PsA. Although it is commonly recommended as the first-line csDMARD, data supporting its efficacy is limited. 'SEAM-PsA' study (n=851) evaluates the efficacy of MTX monotherapy, etanercept monotherapy, or methotrexate/etanercept in combination for early PsA. At week 24, ACR20 response rates were significantly greater in etanercept monotherapy compared to MTX monotherapy (60.9% versus 50.7%, p=0.029).[14] Another RESPOND study, an open-label comparison of MTX and combination therapy of infliximab plus MTX , shows clear superiority of infliximab plus MTX group in achieving ACR20 response rate at week 16 when compared to MTX group (86.3% vs 66.7%, p<0.02).[15] Although efficacy might be inferior to newer targeted therapies, both low cost and widespread availability are important factors that contribute to the prominent role of MTX in treatment of PsA. Targeted dose of MTX should be 25mg per week with folate supplementation.

Leflunomide is an immunomodulatory agent that inhibits pyrimidine synthesis, resulting in anti-proliferative and anti-inflammatory effects. A double-blind, randomized, placebo-controlled trial (n=190) studies the efficacy of leflunomide (100mg/day for 3 day follow by 20mg/day) versus placebo in PsA patients. At week 24, leflunomide showed better response with a higher PsARC rate when compared to placebo (59% leflunomide vs 30% placebo, p<0.0001).[16] Major safety concerns with leflunomide include hypertension, diarrhea, nausea, and hepatotoxicity. The dosage of leflunomide is 20mg daily orally.

Sulfasalazine contains 5-aminosalicylic acid (5-ASA) as the active component. While the specific mechanism of action is unknown, it is suggested that it modulate local chemical mediators of the inflammatory response. A retrospective cohort study (n=187) showed that for DMARD-naïve PsA patient prescribed csDMARD as monotherapy, MTX performs better than sulfasalazine

with respect to drug retention (median 34.5months for MTX, 12 months for sulfasalazine).[17] Major adverse reactions include GI side effects, blood dyscrasia and delayed hypersensitivity. The usual dose of sulfasalazine is 2-3g per day in divided doses.

THERAPEUTIC AGENTS – BIOLOGICAL DMARDs

Tumor Necrosis Factor inhibitors (TNFi)

Tumor Necrosis Factor inhibitors (TNFi), including etanercept, infliximab, adalimumab, certolizumab pegol and golimumab, have been the mainstays of moderate to severe PsA treatment. TNF inhibitors block interaction of TNF with cell surface receptors to block pro-inflammatory cytokines. These agents are recommended for patients who have had inadequate response to non-biologic DMARDS. Under American College of Rheumatology/ National Psoriasis Foundation (ACR/NPF) Guideline (2018) for the Treatment of PsA, TNFi is recommended over an oral small molecule (OSM) as a first-line agent.[18] Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendation (2021) also stated that data supported the superiority of TNFi over csDMARDs as first-line therapy, particularly in patients with early disease, mainly due to the higher efficacy achieved by TNFi as observed in studies.[10] Major adverse effects of TNFi include injection site reactions, infusion reactions, increased risk of infection, increased risk of malignancies and heart failure.

Etanercept is a human TNFi, the first of the class approved by FDA in 2002 for PsA. There are 2 double-blinded, placebo-controlled RCTs of etanercept in adults with active PsA, namely Mease 2000 (n=60) and Mease 2004 (n=205).[19,20,21] In both trials, patients with active PsA not responding adequately to NSAIDs were randomized to receive 25 mg etanercept subcutaneously every 2 weeks and placebo. The primary outcome in the Mease 2000 trial was Psoriatic Arthritis Response Criteria (PsARC) at week 12, with 87% of etanercept patients achieving PsARC compared to 23% in placebo group.[20] In Mease 2004, etanercept showed a significantly better ACR20 response compared to placebo (59% vs 15% placebo, p<0.0001); the results were sustained at 24 and 48 weeks.[21] Etanercept is administered subcutaneously as a 50mg once weekly or 25mg twice weekly injection.

Golimumab is a human monoclonal antibody that prevents the binding of TNF to its receptors. It is FDA approved for treatment of psoriatic arthritis in patients ≥ 2years old in 2009. Based on a randomized trial GO-REVEAL(n=405), patients with PsA were randomized to receive subcutaneous golimumab 50mg every 4 weeks, 100mg every 4 weeks and placebo. At week 14, both treatment arms showed significantly better ACR20 response compared to placebo (51% for 50mg, 45% for 100mg, 9% placebo, p<0.001 vs placebo).[22] In a follow-up trial, the efficacy was maintained at 1 year.[23] Efficacy of IV golimumab is demonstrated in GO-VIBRANT trial (n=480). PsA patients receiving golimumab (2mg/kg IV at week 0,4,12,20) and placebo were compared at week 14. IV golimumab is associated with better outcomes, including ACR20 response (75.1% vs 21.8%, p<0.001), ACR 50 response (43.6% vs 6.3%, p<0.001), ≥ 75% improvement by PASI in 59.2% vs. 13.6% (p < 0.001) in subgroup with ≥ 3% body surface area involvement at baseline.[24] A follow-up study demonstrated a high ACR20 response rate for up to 1 year (77%), with discontinuation rate due to adverse events standing at 3.7% overall.[25] Golimumab is available as IV and subcutaneous formulation. Subcutaneous route is only licensed for adult use. For subcutaneous route, the recommended dose is 50mg once a month. For IV route, it is administered as 2mg/kg at week 0, 4, then every 8 weeks.

Adalimumab is a recombinant monoclonal antibody that binds to TNF and neutralizes its function. It is FDA approved for treatment of psoriatic arthritis in 2005. Efficacy of adalimumab is demonstrated in a RCT Genovese 2007 (n=100), where adalimumab was superior to placebo in terms of ACR20 response rate (39% vs 16%, p=0.012), ACR50 (25% vs 2%, p<0.001), ACR70 (14% vs 2%, p<0.05) and PsARC (51% vs 24%, p=0.007).[26] A more recent study ,EXCEED trial (n=853) in 2020, evaluated the efficacy and safety of secukinumab versus adalimumab; results showed that at week 52, ACR20 response was comparable between two drugs (secukinumab 67% vs. adalimumab 62%), and adverse events were 77% vs. 79% respectively (no p value reported).[27] The recommended dose for adalimumab is 40mg every 2 weeks.

Certolizumab pegol is a pegylated humanized antibody Fab fragment of TNF monoclonal antibody. Pegylation of certolizumab allows delayed elimination and therefore an extended half-life. It was FDA approved for treatment of active PsA in 2013. In RAPID-PsA trial (n=409), PsA patients were randomized to certolizumab 400mg once every 4 weeks, 200mg once every 2 week and placebo. The ACR20 response at 12 weeks was significantly higher in certolizumab groups versus placebo (51.9% in 400mg, 58% in 200mg, 24.3% with placebo, p<0.001). Better ACR20 response at 24 weeks (p<0.001 vs placebo), ACR50 response at 12 and 24 weeks (p ≤ 0.001 vs placebo) were also observed for both certolizumab groups. Treatment-emergent adverse

events were comparable (71.1% with 400mg, 68.1% with 200mg, 67.6% with placebo, no p value reported).[28] The dosage of certolizumab is 400mg SC at week 0,2,4, followed by maintenance dose of 200mg every 2 weeks or 400mg every 4 weeks.

Infliximab is a chimeric human-murine monoclonal antibody that inhibits the functional activity of TNF-alpha. It was FDA approved in 2005 for PsA. In IMPACT 2 trial (n=200) which compared infliximab and placebo in PsA patients unresponsive to conventional treatment, infliximab achieved a better ACR20 response at week 14 compared to placebo (58% vs 11%, p<0.001). Infliximab group also showed significantly better results than placebo group in terms of ACR50 at 14 weeks (36% vs 3%), ACR 70 at 14 weeks (15% vs 1%) and PsARC met at 14 weeks (77% vs 27%).[29] Another trial RESPOND comparing infliximab plus methotrexate versus methotrexate in methotrexate-naïve patients showed that combination therapy is associated with better ACR20 response rate at week 16 (86.3% vs 66.7%, p<0.02).[15]

The recommended route of infliximab administration is IV. The recommended dosage is 5mg/kg at 0, 2, 6 weeks, followed by 5mg/kg every 8 weeks.

IL-12/23 INHIBITORS

Ustekinumab is a human monoclonal antibody that inhibits IL-12 and IL-23 cytokines. IL-12 and IL-23 are naturally occurring proinflammatory cytokines that are involved in natural killer (NK) cell activation, CD4+ T-cell differentiation and activation. Ustekinumab is FDA approved for treatment of PsA in 2013. The safety and efficacy of Ustekinumab are supported by 2 trials, PSUMMIT 1 and PSUMMIT 2. In PSUMMIT 1 (n=615), patients with active PsA for ≥6 months with no prior biologic anti-TNF therapy were randomized to ustekinumab 45mg, 90mg and placebo. At week 24, the ACR20 response rates in both treatment arms were significantly higher when compared to placebo (45mg group 42.4%, 90mg group 49.5%, placebo 22.8%, p<0.0001 vs placebo). Treatment responses were maintained at 1 year, while no significant differences in adverse events were found between groups at week 16.[30] In PSUMMIT 2 trial (n=312), the patients enrolled had ≥ 3 months of DMARDs, ≥ 4 weeks of NSAIDs, and/or ≥ 8 continuous weeks of biological anti-TNF therapy. The study arms included ustekinumab 45mg, 90mg, and placebo. A significantly higher proportion of patients on ustekinumab achieved ACR20 response at week 24 (45mg group 43.7%, 90mg group 43.8%, placebo 20.2%, p<0.001 versus placebo).[31] Common side-effects include arthralgia, asthenia, diarrhea, nausea and vomiting. The major safety concerns of ustekinumab include an increased risk of infections and hypersensitivity reaction. Ustekinumab may increase the risk of malignancy but data are conflicting.[32] The recommended dose is subcutaneous injection 45mg at 0 and 4 weeks, then 45mg every 12 weeks. For patients with coexisting moderate-severe plaque psoriasis weighing >100kg, administer 90mg SC at week 0 and 4, followed by every 12 weeks. Some patients with inadequate response may require maintenance dosing every 8 weeks.

IL-23 INHIBITORS

Interleukin (IL)-23 inhibitors are monoclonal antibodies that bind and inhibit cytokine IL-23, a proinflammatory cytokine. The IL-23 inhibitors approved by FDA for use in PsA are guselkumab (2020) and risankizumab (2022). Their approval provides more therapeutic choices for patient with PsA. Common adverse events associated with the use of IL-23 inhibitors include risk of infections (include upper respiratory tract infection), arthralgia, diarrhea, headache, hypersensitivity reaction and elevated liver enzymes.

Guselkumab is a monoclonal antibody that inhibits inflammatory and immune responses by selectively binding and inhibiting the p19 unit of IL-23. The efficacy of guselkumab is based on 2 trials DISCOVER-1 trial (n=382) and DICSOVER-2(n=741). Patients in both trials were randomized to receive placebo, guselkumab 100mg at week 0, 4 then every 8 weeks, and guselkumab SC 100mg every 4 week. In DISCOVER-1 which involved PsA patients who were either naive to biologic DMARDs or had had previous TNF inhibitor treatment, results showed that guselkumab treatment arms were associated with better ACR20 response at week 24 (59% in guselkumab Q4W, 52% in guselkumab Q8W, 22% placebo, p<0.0001 vs placebo respectively).[33] In DISCOVER-2, recruited patients were naïve to biologic DMARDs. Again both gulsekumab treatment arms achieved a significantly higher ACR20 response rate at week 24 (64% Q4W, 64% Q8W, 33% placebo, p<0.0001 vs. placebo).[34] Guselkumab is administered as subcutaneous injection of 100mg at week 0, 4 and every 8 weeks. A maintenance dose of 100mg every 4 weeks may be considered in patients at high risk of joint damage.[35]

Risankizumab is a humanized monoclonal antibody that binds selectively to interleukin-23. The efficacy of risankizumab for treating active PsA was established in two trials, KEEPsAKE 1 and KEEPsAKE 2. In KEEPsAKE 1, patients with active PsA who have responded inadequately or are intolerant to ≥1 csDMARD were included in the trial, while for KEEPsAKE 2 study, PsA patients with a history of inadequate response or intolerance to csDMARDs and/or bDMARDs were

recruited. Both studies evaluated the efficacy and safety of Risankizumab 150mg versus placebo over 24weeks, with a long-term extension for up to additional 204 weeks. In KEEPsAKE1, risankizumab treatment achieved a significantly better ACR20 response at week 24 when compared to placebo (57.3% vs 33.5%, p<0.001). It also demonstrated a significantly better response in ACR50 (33.4% vs 11.3%, p<0.001) and PASI 90 response (52.3% vs. 9.9%, p < 0.001).[36] In KEEPsAKE2, again a greater proportion of patients in risankizumab group achieved ACR20 response at week 24 (51.3% vs 26.5%, p<0.001).[37] The recommended dosage is 150 mg subcutaneously at week 0, week 4, and every 12 weeks.

IL-17 INHIBITORS

Interleukin (IL)-17 inhibitors are monoclonal antibodies that bind and inhibit cytokine IL-17, thereby blocking the inflammatory pathway of IL-17. The IL-17 inhibitors approved by FDA for PsA include secukinumab (2016) and ixekizumab (2017). Common adverse events associated with the use of IL-17 inhibitors include upper respiratory infections, arthralgia, diarrhea, headache, tinea infections and herpes simplex infections. Under EULAR recommendation (2019), in patients with peripheral arthritis with inadequate response to ≥1 csDMARD and relevant skin involvement, IL-17 inhibitors may be preferred over TNF inhibitors.[9]

Ixekizumab is a humanized monoclonal antibody that selectively binds to interleukin 17A (IL-17) cytokine and inhibits its interaction with IL-17 receptor, thereby inhibiting the release of proinflammatory cytokines and chemokines. In SPIRIT P2 trial (n=363), patients with active PsA who were intolerant or had inadequate response to TNF inhibitors were randomized to ixekizumab 80mg SC every 4 weeks, ixekizumab 80mg SC every 2 weeks and placebo. Both ixekizumab treatment arms achieved significantly better ACR20 response (53% for Q4W, 48% for Q2W, 20% placebo, p<0.0001 vs placebo) and ACR50 response (33% for Q4W, 35% for Q2W, 5% placebo, p<0.0001 vs placebo) at week 24. Ixekizumab groups were also associated with improved PASI 75 in patients with psoriasis in ≥ 3% of body surface area at baseline.[38] Dosing of Ixekizumab is 160 mg subcutaneously at week 0, followed by 80 mg every 4 weeks.

Secukinumab is a recombinant humanized monoclonal antibody that selectively binds to interleukin 17A (IL-17). Efficacy of secukinumab is evaluated in 2 major trials, FUTURE-1 and FUTURE-2. Patients with previous treatment including NSAIDs, csDMARDs, or TNF inhibitors were included. FUTURE-1 (n=606), patients were randomized to IV secukinumab 10mg/kg at week 0, 2, 4, followed by either subcutaneous secukinumab 150mg or 75mg every 4 weeks or placebo. Results showed that secukinumab groups achieved significantly better ACR20 response at week 24 (50% 150mg, 50.5% 75mg, 17.3% placebo, p<0.001 vs placebo), with sustained improvement at week 52.[39] In FUTURE 2 trial (n=397), patients were randomized to subcutaneous secukinumab 300mg, 150mg, 75mg and placebo respectively for once weekly for 5 weeks followed by every 4 weeks. At week 24, significantly better ACR20 response rates were achieved in secukinumab 300mg and 150mg group (54% and 51%, p<0.0001 vs placebo), but not in 75mg group.[40]

Another study EXCEED trial comparing efficacy of secukinumab and adalimumab without concurrent use of csDMARD showed that two drugs achieved a similar ACR20 response rate at week 52 (67% vs 62%), while secukinumab showed a better PASI90 response rate (65% vs 43%, p<0.0001).[27] Recommended dose of subcutaneous secukinumab is a loading dose of 150mg every week for 5 weeks, followed by maintenance dose of 150mg-300mg every 4 weeks, or without loading dose 150mg -300mg every 4 weeks. For IV route, a loading dose of 6mg/kg is given at week 0 followed by 1.75mg/kg (not exceeding 300mg) every 4 weeks. Another IV regimen without loading dose can also be considered at 1.75mg/kg (not exceeding 300mg) every 4 weeks.

SELECTIVE T-CELL COSTIMULATION BLOCKER

Abatacept is a soluble, selective fusion protein that binds to CD80/86 receptor on antigen-presenting cells, blocking activation of T-cells. It was approved by FDA in 2017 for treatment of PsA. A randomized trial (n=170) evaluated efficacy of abatacept versus placebo in PsA patients previously treated with DMARDs. Patients were randomized to abatacept 3mg/kg, 10mg/kg, a titrating dose of abatacept, and placebo, given on day 1, 15, 29, then every 28 days. Results showed that abatacept is associated with significantly greater ACR20 response on day 169 for 10mg/kg group (48%, p=0.006 vs placebo 19%) and titrating-dose group (42%, p=0.022 vs placebo 19%). Abatacept 3mg/kg group achieved ACR20 response of 33% which is not significantly different from placebo.[41] Abatacept may be used with or without nonbiologic DMARDS. It can be administered by weekly subcutaneous injection or by monthly IV infusion. Given its low efficacy, EULAR treatment guideline (2019) suggested that abatacept should be limited to potential use after other bDMARDs have failed.[9] Dosing of IV abatacept is weight-based, ranging from 500mg (<60kg), 750mg (60-100kg) or 1g (>100kg) at week 0, 2, 4, then every 4 weeks. For subcutaneous abatacept, the recommended dose is 125mg once weekly.

THERAPEUTIC AGENTS– TARGETED SYNTHETIC DMARDS

PDE-4inhibitors

Apremilast is a phosphodiesterase-4 inhibitor. It inhibits the activity of phosphodiesterase type-4 (PDE4) which results in suppression of pro-inflammatory mediator synthesis and promotes anti-inflammatory mediators. This oral drug was FDA approved in 2014 for treatment of PsA in adults. In PALACE 3 trial (n=505), patients with active PsA and skin involvement despite a prior therapy with conventional or biologic DMARDs were randomized to apremilast (20mg BD and 30mg BD) versus placebo. A significantly higher proportion of patients in apremilast 20 mg and 30 mg groups achieved ACR20 response versus placebo (28% 20mg group, p=0.0295 vs. placebo, 41% with 30mg, p=0.0001 vs. placebo, 18% with placebo). However, there is no significant difference among groups in ACR50 and ACR70 response.[42] Under EULAR treatment recommendation (2019), apremilast may be considered in patients with mild disease and an inadequate response to at least 1 csDMARD, for whom neither a bDMARD nor a JAK inhibitor is appropriate.[9] Apremilast is generally well tolerated; common adverse events include diarrhea, nausea, vomiting, weight loss, headache and nasopharyngitis. There is an increased risk of depression. Targeted dosage of apremilast is 30mg twice daily, with a titration schedule of 5 days starting from 10mg in the morning to reduce risk of gastrointestinal symptoms.

Janus kinase inhibitor (JAK inhibitors)

JAK inhibitors are small and orally active drugs that inhibit the protein tyrosine kinases Janus kinases (JAKs) and suppress multiple cytokine and growth factor receptor signaling pathways involved in inflammatory response. Currently, two orally active JAK inhibitors tofacitinib (2017) and upadacitinib (2021) are FDA approved for treatment of PsA. Both drugs carry a FDA boxed warning of the risk of serious infections, increased rate of mortality, malignancies, cardiovascular events, and thrombosis. Healthcare professionals should assess and use with caution in patients with risk factors for above conditions.[43] Under EULAR treatment guideline (2019), JAK inhibitors may be considered in patients with peripheral arthritis and an inadequate response to at least one csDMARD and at least one bDMARD, or when a bDMARD is not appropriate.[9]

Tofacitinib selectively inhibits the Janus tyrosine kinases JAK1 and JAK3. In OPAL trial (n=422), patients with PsA ≥6 months, previous inadequate response to ≥ 1 csDMARD, and not previously treated with TNF inhibitor were randomized to receive tofacitinib, adalimumab, and placebo while receiving a stable dose of csDMARD. Tofacitinib achieved a significantly better ACR20 response than placebo at 3 months, with 50% with tofacitinib 5mg ($p<0.01$ vs placebo), 61% with tofacitinib 10mg ($p<0.001$ vs placebo), 52% with adalimumab (no p value reported), and 33% with placebo. Patients in tofacitinib groups also achieved a better result in mean reduction in HAQ-DI scores at 3 months.[44] The dosage of tofacitinib is 5mg BD for immediate release tablet and 11mg once daily for modified release tablet.

Upadacitinib is another JAK inhibitor for treatment of PsA. Efficacy of upadacitinib were assessed in SELECT-PsA 1 (n=1705) and SELECT-PsA2 (n=642) trials. In SELECT-PsA2, patients with active PsA for ≥ 6 months and inadequate response or intolerance to ≥ 1 bDMARD were randomized to upadacitinib and placebo. At 12 weeks, both upadacitinib groups (15mg and 30mg) were associated with a significantly better ACR20 response rate compared to placebo, with 56.9% for 15mg group ($p<0.001$ vs placebo 24.1%) and 63.8% with 30mg group ($p<0.001$ vs placebo 24.1%).[45] In SELECT-PsA1 (n=1,705), PsA patients with previous inadequate response to ≥ 1 nonbiologic DMARD, and not previously treated with biologic therapies or JAK inhibitors were randomized to receive upadacitinib, adalimumab and placebo. The ACR20 response rates at week 12 were better for upadacitinib 30mg (78.5%, $p<0.001$ vs placebo) and upadacitinib 15mg group (70.6% $p<0.001$ vs placebo) when compared to 36.2% with placebo group.[46] This study also showed a significantly better response rate for PASI 75 at week 16 for upadacitinib groups (62% with 30mg, 63% with 15mg, 21% with placebo, $p<0.001$ vs placebo). The recommended dosage of upadacitinib is 15mg once daily.

CONCLUSION

Psoriatic arthritis is a disease involving musculoskeletal and non-musculoskeletal manifestations associated with high disease burden and significant comorbidities. Treatment goal is to maximize health-related quality of life through control of symptoms and prevention of structural damage. Traditional treatments for PsA include csDMARD such as methotrexate, but in recent years an expanded list of drugs with a more targeted action to the underlying pathophysiology have developed. Biologic DMARDs including TNF inhibitors, IL-12/23 inhibitors, IL-23 inhibitors, IL-17 inhibitors, and targeted-synthetic DMARDs such as apremilast and JAK inhibitors prove to be efficacious in multiple trials. Treatment decisions should be tailored for individual patients and pharmacists play a critical role in appropriate patient education and medication adherence.

Author's background

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Questions for Pharmacy Central Continuing Education Committee Program

(Please be informed that this article and answer sheet will be available on PCCC website concurrently. Members may go to PCCC website (www.pccchk.com) to fill in their answers there.)

2 CE Units

Overview of the Drug Therapy of Psoriatic Arthritis

1. ***Which of the following is FALSE regarding psoriatic arthritis?***
   a. Psoriatic arthritis involves both musculoskeletal and non-musculoskeletal manifestations
   b. The prevalence of psoriatic arthritis in patients with psoriasis is around 90%
   c. Pathophysiology of psoriatic arthritis is thought to involve genetic, immunologic and environmental factors.
   d. All of the above

2. ***Which of the following cytokine(s) is/are the therapeutic target for treatment of psoriatic arthritis***?
   a. Interleukin-12
   b. Interleukin-23
   c. Tumor necrosis factor
   d. All of the above

3. ***Which of the following is NOT a common clinical manifestation of psoriatic arthritis?***
   a. Dactylitis
   b. Nail changes
   c. Enthesitis
   d. Watery diarrhea

4. ***Which of the following is TRUE regarding the treatment approach of psoriatic arthritis?***
   a. NSAID may be used alone as initial treatment in patient with active polyarticular disease
   b. Consider conventional DMARD when there is inadequate response to NSAID with or without local glucocorticoid after 3 months
   c. In patient with inadequate response to conventional DMARD, consider initiate another conventional DMARD and observe for 3 months
   d. In patient with inadequate response to conventional DMARD, a biologic DMARD should be considered

5. ***Which of the following is NOT a common adverse reaction of TNF inhibitors?***
   a. Injection site reactions
   b. Renal toxicity
   c. Hepatotoxicity
   d. Increased risk of infection

6. ***Which of the following is TRUE regarding abatacept***
   a. It is available as subcutaneous injection and intravenous infusion
   b. It is not recommended to be used with conventional DMARD
   c. It is recommended as a first line agent after inadequate response to conventional DMARD
   d. Because of its high efficacy, abatacept should be considered for severe disease with inadequate response to other bDMARDs

7. ***Which of the following is NOT a FDA boxed warning for JAK inhibitor Tofacitinib?***
   a. Increased risk of cardiovascular events
   b. Increased risk of serious infections
   c. Increased risk of severe liver injury
   d. Increased risk of malignancies

8. ***What is the mechanism of action of Ustekinumab?***
   a. It is a chimeric monoclonal antibody that inhibits IL-12 and IL-23 cytokines
   b. It is a humanized monoclonal antibody that inhibits IL-12 and IL-23
   c. It inhibits janus kinase and suppresses multiple cytokine and growth factor receptor signaling pathways
   d. It is a humanized monoclonal antibody that inhibits IL-12 and IL-17

9. ***Which of the following is the recommended dosing for ustekinumab in a patient with body weight of 60kg?***
   a. 45mg subcutaneously at week 0, 2, 4, followed by 45mg subcutaneously every 8 weeks
   b. 45mg subcutaneously at week 0, 4, followed by 45 mg subcutaneously every 12 weeks
   c. 90mg intravenously at week 0, 4, followed by 45mg subcutaneously every 12 weeks
   d. 90mg subcutaneously at week 0, 4, followed by 90mg subcutaneously every 12 weeks

10. ***Which of the following is FLASE regarding apremilast?***
    a. Apremilast is a phosphodiesterase-4 inhibitor
    b. A 5-day dose titration schedule is required on initiation of apremilast to reduce risk of gastrointestinal side effects
    c. Patients on apremilast should be monitored for increased risk of depression
    d. Apremilast should be considered as the drug of choice when patient has inadequate response to csDMARD

Answers will be released in the next issue of HKPJ.