Psoriatic Arthritis: The Influence of Co-morbidities on Drug Choice

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ABSTRACT

Psoriatic arthritis (PsA) is associated with a higher burden of co-morbidities such as obesity, cardiovascular disease, non-alcoholic fatty liver disease, inflammatory eye disease, inflammatory bowel disease, skin cancer and depression compared to the general population. In the last 20 years, the therapeutic options for PsA have increased exponentially with the availability of tumor necrosis factor-alpha (TNF) inhibitors, interleukin (IL)-17 inhibitors, IL-12/23 inhibitors and Janus kinases/signal transducer and activator of transcription proteins (JAK/STAT) inhibitors. The articular and extra-articular manifestations of PsA usually dictate the treatment choice but important consideration must be given to the corresponding co-morbidities while deciding the drug therapy due to associated safety profile, effect on disease activity, etc. This review provides a comprehensive review of common co-morbidities in PsA and how they can influence treatment choices.

Keywords: Psoriatic arthritis; Co-morbidities; Drug therapy

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INTRODUCTION

Psoriatic arthritis (PsA) is a complex heterogeneous condition which shares clinical, genetic and etiopathogenic features with other forms of spondyloarthritis (SpA). PsA affects around 10–30% of patients with psoriasis (PsO), and management of PsA relies on careful evaluation of disease activity, extra-articular features and associated co-morbid conditions [1]. Prevalent co-morbidities in PsA include metabolic syndrome (hypertension, diabetes mellitus, hyperlipidemia), cardiovascular disease, obesity, non-alcoholic fatty liver disease (NAFLD), malignancy, depression and extra-articular manifestations: psoriasis, inflammatory eye disease and inflammatory bowel disease (IBD) [2–5]. A large proportion of PsA patients have at least one comorbidity, and around 40% of patients can have three or more co-morbidities [6, 7]. Therapies can directly and indirectly impact co-morbid conditions despite having anticipated goals of improving PsA disease activity.

PsA treatment is focused on reducing inflammation and disease progression by utilizing non-steroidal anti-inflammatory (NSAID), glucocorticosteroids (GCs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD), biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). The therapeutic options for PsA have increased substantially over the years with available bDMARD therapies targeting tumor necrosis factor alfa (TNF-α), interleukin (IL)-17A, IL-12/23 and tsDMARD therapies targeting Janus kinases/signal transducer and activator of transcription proteins (JAK/STAT). Non-pharmacologic treatment includes physical therapy, smoking cessation, weight loss, behavioral therapy and exercise, which are extremely crucial [8].

The 2018 American College of Rheumatology (ACR)/National Psoriasis Foundation (NPF) guidelines for the treatment of PsA as well as the updated 2019 European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of PsA provide an excellent framework regarding treatment options for PsA [9, 10]. When applying to individual clinical care, all recommendations should be based on a risk-benefit assessment for the patient and a shared decision. It is imperative to consider existing co-morbidities when choosing drug therapy for PsA as co-morbidities can influence the treatment choice, disease activity and outcomes.

This narrative provides a review of the burden of the prevalent associated conditions in PsA and how the drug therapies for PsA affect these co-morbidities and vice versa. This article is based on previously conducted studies and does not contain any studies with human
ASSOCIATED CO-MORBIDITIES

Cardiovascular Disease

PsA is known to increase the risk of cardiovascular disease (CVD) and major adverse cardiovascular events (MACE) compared to the general population [11, 12]. Oxidative stress and subsequent pro-inflammatory cytokine production, such as tumor necrosis factor alpha (TNFα), interleukin (IL) 1Beta, IL-6, IL-1 and IL-17, are a few of the mechanisms implicated in plaque development within PsA [11]. Certain therapies can impact cardiovascular risk although PsA patients are already at an increased risk, secondary to traditional risk factors: age, smoking history, hyperlipidemia, hypertension and diabetes [13].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first-line therapy in patients with mild disease, predominant enthesitis and axial spondylitis [10, 14]. Cyclooxygenase (COX) inhibition, specifically COX-2 inhibition, increases risk of atherogenesis, hypertension, arrhythmias and heart failure. Certain nonselective COX inhibitors, such as naproxen, carry less cardiovascular risk compared to COX-2 inhibitors [15].

Corticosteroids are used in most immune-related rheumatic diseases to control inflammation temporarily. In psoriatic arthritis, corticosteroids are used with caution secondary to concern of cutaneous flare; however, studies have shown that moderate doses of corticosteroids (methylprednisolone < 16 mg/day) were not associated with erythroderma, severe pustular psoriasis or severe flares [16]. Local glucocorticoid injections can be used for mono/oligoarthritis and enthesitis [10]. There is a concern for CV risk in PsA patients on corticosteroids in rheumatic disease. A cohort study of CVD patients with and without PsA found that treatment with corticosteroids was associated with marginal increased risk of CVD and MACE with an incidence rate (IR) of 33.6/1000 person-years (PYs) (CI 13.5–69.2) compared to those on bDMARDs and csDMARDs, which had an IR of 15.6/1000PY (CI 13.3–18.1) [17].

The risk of CVD with csDMARD and bDMARD use in PsA appears to be low based on several studies. One study revealed that the risk of MACE in PsA patients on no DMARD therapy (methotrexate, sulfasalazine, leflunomide, TNF inhibitors [TNFi]) was high with a hazard ratio (HR) of 1.24 (confidence interval [CI] 1.03–1.49) compared to 1.17 (CI 0.95–1.46) for PsA patients on DMARDs [11]. A systematic review of PsA/PsO studies concluded that systemic therapy (TNFi, methotrexate, NSAIDs and corticosteroids) was associated with a significant decrease in risk of all CV events in PsA or PsO (RR, 0.75; 95% CI 0.63–0.91) [18]. Although methotrexate has also been shown to improve endothelial function, low-dose methotrexate failed to show reduction in pro-inflammatory cardiovascular cytokines [19, 20]. In a longitudinal cohort study, patients with severe PsO on methotrexate had an IR of 4.16 per 1000 patient-years for CV events but reduced the risk of events relative to other therapies with HR 0.53 (CI 0.34–0.83) [21]. Overall, methotrexate continues to be a useful therapy in uncontrolled PsA and is recommended relatively first line in polyarthritis based on EULAR recommendations and for mild disease based on ACR recommendations [10, 14].

The bDMARDs, including TNFi, anti-IL-17, anti-IL-12/23, anti-IL-23 and JAK/STAT inhibitors, can be used in patients naive to treatment, resistant to initial treatment or with specific comorbidities [10, 14]. While EULAR considers bDMARDs as third line, ACR recommends TNFi in active PsA naïve to treatment [10, 14]. Multiple cohort studies suggest that bDMARDs may have a cardio-protective effect in PsO patients, with an almost 50% reduction in the rate of myocardial infarction [22, 23]. TNF-mediated inflammation has been thought to play a role in CV disease [24]. In a cohort study of > 60,000 PsA patients treated with different bDMARDs and csDMARDs, IR for myocardial infarction was lowest for patients on TNFi (1.4 per 1000 PY) [25]. In a meta-analysis of 5 studies of 50,000 PsA patients, TNFi reduced risk of cardiovascular events compared to placebo and reduced incidence of myocardial infarction.
compared to individuals on methotrexate alone [26]. In another study with a 5-year follow-up, TNFi reduced risk of cardiovascular events with HR 0.46 (CI 0.22–0.98) [21] (Table 1).

The safety and use of TNFi with advanced heart failure are controversial. TNFi therapies should be used with caution in class III/IV heart failure. In moderate-severe heart failure, stable class III/IV, use of infliximab, independent of inflammatory arthritis, did not improve clinical status. The risk of death from any cause or hospitalization from heart failure was increased in those patients on 10 mg/kg infliximab dosing [27]. Contrarily, etanercept therapy for 3 months was safe and well tolerated in advanced heart failure [28].

The role of IL-17 inhibition and IL-12/23 inhibition in atherosclerotic disease is still unclear. Based on ACR guidelines, IL-17 inhibition is typically recommended after failure of TNFi therapy [14]. In the CARIMA (Evaluation of Cardiovascular Risk Markers in Psoriasis Patients Treated with Secukinumab) study, flow-mediated dilation (a measure of endothelial function) improved at week 52 of secukinumab use at dose of 300 mg weekly (+2.1%, CI 0.8–3.3; \(P = 0.0022\)) while this was not seen at week 12 (+1.2, \(P = 0.223\)). The 150 mg dose did not reach statistical significance in either group [29]. The pooled exposure-adjusted IR of MACE across MEASURE-1 and MEASURE-2 studies evaluating use of secukinumab in ankylosing spondylitis (AS) was 0.4 events per

#### Table 1 Immunomodulators in PsA with specific co-morbidities

| Co-morbidity                  | csDMARD      | bDMARD                  | tsDMARD |
|------------------------------|--------------|--------------------------|---------|
| Psoriasis                    | Mtx, Apr     | TNFi, IL-17i, *IL 12/23i, IL-23i | *JAKi   |
| Inflammatory bowel disease   | SSZ, Mtx     | TNFi, *IL-17i, IL 12/23i |         |
| Uveitis                      | Mtx, SSZ     | $TNFi, *IL-17i, *IL 12/23i|         |
| Cardiovascular disease       | Mtx, Lef, SSZ| TNFi, *IL-17i, IL 12/23i, IL-23i |         |
| Malignancy                   | *Mtx         | *TNFi, IL-17i, IL 12/23i |         |
| Obesity                      | Mtx, Lef, SSZ, Apr | TNFi, IL-17i, IL 12/23i | JAKi    |
| Diabetes                     | Mtx, Lef, SSZ, Apr | TNFi, *IL-17i, IL 12/23i |         |
| Multiple sclerosis           | Lef          | IL17i, *IL12/23i         |         |
| Psychiatric illnesses        | Mtx, Lef, SSZ | TNFi, IL 17i, IL 12/23i |         |
| Pregnancy                    | SSZ          | TNFi                     |         |
| Renal disease (non-infectious)| SSZ, +Lef, *Mtx | TNFi, IL-17i, IL 12/23i, IL-23i | **JAKi |
| Hepatic disease (non-infectious)| *SSZ, +Lef, +Mtx | *TNFi, IL-17i, IL 12/23i, IL-23i | **JAKi |

*csDMARD conventional synthetic disease-modifying anti-rheumatic drugs, bDMARD biologic disease-modifying anti-rheumatic drugs, tsDMARD targeted synthetic disease-modifying anti-rheumatic drugs, Mtx methotrexate, Lef leflunomide, SSZ sulfasalazine, Apr apremilast, TNFi TNF inhibitors (adalimumab, infliximab, golimumab, certolizumab, etanercept), IL-17i IL-17 inhibitors (secukinumab, ixekizumab), IL-12/23-i IL 12/23 inhibitors (ustekinumab), IL-23i IL 23 inhibitors (guselkumab), JAKi Janus kinase inhibitors (tofacitinib)

*Relatively safe but must be used with caution after a shared decision
+Dose adjustment required
$Low quality and/or insufficient data
#Only adalimumab and infliximab
*Only secukinumab
^Only ustekinumab

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100 patient-years of exposure to secukinumab and 0.3 per 100 patient-years in the secukinumab trial in PsA [30, 31]. In a 5-year follow-up of ixekizumab users, MACE ranged from 0.3 to 0.7/100 patient-years [32]. In a cohort of 9071 ustekinumab users, overall MACE events were 6.2 (95% CI, 4.9–7.8) compared to 6.1 (95% CI 5.5–6.7) for TNFi [33]. The combined hazard ratio for MACE among ustekinumab initiators was 1.10 (95% CI, 0.80–1.52) [33]. In another cohort of patients with severe PsO, while methotrexate and TNFi agents were associated with lowered cardiovascular risk, ustekinumab was not (HR 1.52; CI 0.47–4.94) [21]. A meta-analysis of RCTs of patients with PsA and psoriasis did not find any significant difference of MACE or congestive heart failure seen in patients receiving TNFi (adalimumab, certolizumab, etanercept, golimumab, infliximab), anti-IL17 (brodalumab, ixekizumab, secukinumab), anti-IL12/23 (briakinumab, ustekinumab) and antiIL23 (guselkumab, risankizumab, tildrakizumab) compared to placebo [34]. Although there does not appear to be an increased MACE with ustekinumab, another meta-analysis found a trend for an increased risk in MACE in patients exposed to an anti-IL 12/23, which was not statistically significant [33, 34].

In 2017, tsDMARD tofacitinib was approved for use in PsA; upadacitinib is approved in the European Union. There has been a growing concern surrounding the safety of JAK inhibitors (JAKi) due to reported MACE and venous thromboembolism (VTE). Recent FDA warnings have been placed for increased risk of MACE with JAKi [35]. In one study, although limited to rheumatoid arthritis (RA) patients, the incidence rate of MACE with JAKi use was 0.4 patients with events per 100 patient-years [13]. Baseline age, hypertension and the total cholesterol to high-density lipoprotein (HDL) cholesterol ratio was associated with risk of MACE, and there was increased risk of MACE with elevated sedimentation rate [13]. In a post-hoc analysis of 783 PsA patients treated with tofacitinib, increases in all lipid parameters including both LDL and HLD levels with no change in total cholesterol to HDL ratio were noted. Five (0.6%) patients of the 783 included had MACE with incidence ratio 0.24 (CI 0.05–0.70), and 2 were fatal [36]. In a phase 3 study evaluating upadacitinib for PsA, one event (0.5%) of MACE and VTE was reported, respectively [37]. Thus, caution should be exercised when considering JAKi therapy and a history of VTE or MACE.

PsA inherently increases the risk of cardiovascular disease, and therefore choice of therapeutic agent requires a proper risk assessment based on traditional risk factors and associated co-morbidities. The use of TNFi, IL-17 and IL-12/23 inhibitors does not seem to increase the risk of adverse CV outcomes but JAKi should be used cautiously in patients with higher cardiovascular co-morbidities or VTE.

Malignancy

The overall incidence of malignancy including non-melanoma skin cancer (NMSC) is increased in patients with severe PsO [38, 39]. The increased risk of cancer with PsA is unclear. The Toronto PsA cohort study of 665 patients reported a malignancy risk of 10.2%, which is similar to that of the general population [40]. Contrarily, in a study of 217 PsA patients, the incidence of overall malignancy, excluding NMSC, was found to be higher with HR ratio of 1.64 (CI 1.03–2.61), and breast cancer had HR of 3.59 with a wide CI (1.22–10.61) [41]. A systematic review of 112 articles did not find an increased risk of cancer in PsA patients [38].

The data regarding malignancy risk with csDMARDs and bDMARDs are unclear. In one study of 248 methotrexate-treated PsO patients, 10 malignant neoplasms were found; the risk was not higher than that of the general population, and the study found that methotrexate therapy did not contribute to the development of neoplasm [42]. Another study of > 12,000 PsO patients found no increased risk for overall or frequently observed malignancies with any duration of treatment with methotrexate [43].

TNFi may increase risk of non-melanoma skin cancers, which is concerning in patients with known active PsO. In an analysis of 6 studies with 123,031 patients, rheumatoid arthritis patients on TNFi therapy had increased
risk of NMSC with relative risk of 1.28 (CI 1.19–1.38, $P = 0.056$) [44]. Another study in patients on TNFi showed odds ratio for malignancy of 1.48 (CI 0.71–3.09) and 1.28 (CI 0.39–4.15) when non-melanoma skin cancer was excluded [45]. Bonovas et al. revealed no clear association between TNFi and cancer in a systemic review of a randomized controlled trial (RCT) with an odds ratio of 1.31 (CI 0.89–1.95) [46]. In another study of 618 PsA patients, 296 of whom were on TNFi and 322 on csDMARD, there was no statistically significant association between bDMARDs or csDMARDs and malignancy [47] (Table 1). In the same study, 44 patients had a diagnosis of malignancy; 14 of these patients were on TNFi and 30 were on csDMARDs (azathioprine, methotrexate, leflunomide, sulfasalazine); however, the difference was not statically significant after adjusting for clinical and demographic factors [47]. Data from two large Swedish registries, ARTIC (Anti-Rheumatic Therapy in Sweden [ARTIS]) and DANBIO (Danish biologics registries), also studied the cancer risk in > 8500 spondyloarthritis patients and found that TNFi was not associated with an increased risk of cancer, including the six most common cancer types [48]. In those with pre-existing history of cancer, there was no increased risk of secondary malignant neoplasms in those on bDMARD (TNFi) use compared to those with non-bDMARD use with HR of 1.11 (CI 0.74–1.67). The HR for death for bDMARD use before primary cancer was 1.20 (CI 0.88–1.63) and HR 1.36 (CI 0.78–2.39) after cancer [49]. Therefore, treatment with certain bDMARDs was not conclusively associated with increased risk of secondary malignancy.

The malignancy risk associated with JAKi is also unclear with a study showing no increased malignancy risk in those on tofacitinib therapy with odds ratio of 1.15 (CI 0.24–5.47) [50, 51]. In another study the incidence ratio of non-NMSC malignancy in RA users on upadacitinib 15 mg was 1.05 (0.66–1.60), which was documented to be in range with the general population [52]. Recent FDA warnings have been issued for increased risk of malignancy with JAKi [35].

The observed rate of malignancies other than NMSC in ustekinumab-treated patients is like that of the general population with standardized incidence ratio 0.98 (CI 0.74–1.39), 0.60/100 patient-years (PY) (CI 0.45–0.78) [53]. Follow-up data from the PHOENIX1/2 studies and safety data from the Psoriasis Longitudinal Assessment and Registry demonstrated low or no overall increased risk for malignancy with long-term exposure to ustekinumab [43]. In a 5-year study, patients treated with secukinumab had low malignancy risk with the exposure-adjusted incidence rates of malignancy of 0.85 per 100 patient treatment years (CI 0.74–0.98), equivalent to 204 patients per 23,908 patient treatment years [54]. Similarly, in an analysis of 8228 patients with ixekizumab exposure, malignancy was rarely reported with an IR < 0.8 [55]. In another 5-year safety follow-up study of 2749 patients with > 4 years of ixekizumab exposure, rate of NMSC was 0.2/100 patient-years and other malignancy ranged from 0.4 to 0.6/100 patient-years [32]. Although the risk of malignancy with csDMARDs and bDMARDs appears low, a shared decision must be made about the therapeutic choice.

### Renal/Hepatic Dysfunction

Patients with PsA and treated PsO are at an increased risk of liver disease with a 32% prevalence of liver abnormalities and are twice as likely to develop liver injury, respectively [56, 57]. PsA and treated PsO are also risk factors for kidney disease with a hazard ratio of 7.60 and 1.19, respectively, of developing end-stage renal disease [58]. These associations are likely secondary to known risk of metabolic syndrome and concomitant hypertension, obesity and diabetes.

All csDMARDs can potentially elevate transaminases and require regular monitoring. Patients with known hepatotoxicity are at greater risk for developing severe liver injury. Methotrexate is avoided or used with caution in patients with underlying liver disease. Patients with PsA have a greater risk for NAFLD, and pre-existing moderate-to-severe hepatic fat deposition and obesity had an adjusted hazard ratio of
7.69 and 2.68, respectively, for developing elevated and persistent transaminitis [59]. Elevations in liver enzymes occur in 15–50% of patients treated with low-moderate dose methotrexate, and the incidence of severe hepatotoxicity in methotrexate treated PsO patients was as high as 23% [60]. Elevation in liver enzymes is seen in up to 15% of patients on leflunomide; however, these are usually mild and self-limiting. Again, patients who develop fibrosis appear to have risk factors for fatty liver disease [61]. Compared to rheumatoid arthritis, those with PsO and PsA are thought to be more susceptible to risk of liver disease with methotrexate use [62]. The use of combination leflunomide and methotrexate can increase the risk of silent fibrosis, thought to be influenced by the cumulative dose of leflunomide [63].

Rarely, sulfasalazine can cause significant liver injury, and pathogenesis is thought to be related to a drug allergy or generalized hypersensitivity reaction. This can be induced by sulfonamide allergy or secondary to the 5-aminosalicylic acid component of the drug, which can cause idiosyncratic liver injury [61]. Although rare, NSAID use can also cause liver injury with diclofenac and sulindac most reported [61].

TNFi seldom cause liver injury, but cases have been reported of worsening liver enzymes and drug-induced autoimmune hepatitis. One study included 226,555 incident patients with immune-related diseases, and during the median 1.5-year follow-up, there was an increased HR of composite liver disease, cirrhosis and NAFLD/NASH with TNFi agent (HR 1.47 [CI 1.27–1.70]; HR 1.47 [CI 0.96–2.23]; HR 1.53 [CI 1.32–1.77]), respectively [64]. Researchers reviewed cases from the US DILI (Drug-Induced Liver Injury) registry and PubMed of patients on TNFi and found 22 patients with liver injury and positive anti-nuclear/smooth muscle, 15/17 of whom had biopsy with autoimmune features [65]. Although elevated liver enzymes have been seen in tofacitinib use, in both tofacitinib and placebo groups, the incidence of transaminitis was higher in those with hepatic steatosis than in those without hepatic steatosis [66]. Grade 3 elevations in liver enzymes were seen in 2% or fewer patients in both 15 mg and 30 mg upadacitinib groups compared to adalimumab [67]. This speaks to the importance of treating underlying co-morbid conditions contributing to fatty liver disease. Apremilast, a tsDMARD targeting phosphodiesterase-4, has not been shown to alter liver enzymes or kidney function in clinical trials [68].

Chronic kidney disease also limits the use of NSAIDs and csDMARDs, particularly methotrexate. NSAIDs cause nephrotoxicity through COX inhibition, with increased risk in those with prior renal disease, cardiovascular risk factors and concomitant nephrotoxic medications, and is influenced by dose and duration of use [69]. Methotrexate in high doses can cause renal toxicity, and recommendations for using low-moderate dose methotrexate depend on glomerular filtration rate (GFR) [70]. Doses >12 mg/week were associated with a decrease in GFR of 0.25 over 1 year compared to 8–12 mg/week [71]. In an older study of 21 patients who received methotrexate 7.5 mg/week for 2 years, there was an 11% reduction in creatinine clearance after 6 months with reduction in clearance of methotrexate by 25% [72]. Extra care should be taken in those at higher risk for lower creatinine clearance including elderly patients and those on nephrotoxic medications. Both leflunomide and sulfasalazine typically do not need dose adjustment based on renal function [73]. TNFi agents have not been associated with renal injury and are safe to use in patients with renal disease [74]. IL-17 inhibition and IL12/23 inhibition have not been associated with liver or kidney dysfunction [68].

**Obesity**

Obesity (body mass index [BMI] ≥ 30 kg/m²) is a state of chronic low-grade inflammation and is a major comorbidity in PsA [75, 76]. Multiple case control and cohort studies have established that obesity is not only a risk factor for development of PsA but can also affect disease activity and therapeutic choices [77–80]. It is a negative predictor of treatment response for csDMARDs and bDMARDs. Obesity is closely associated with simple steatosis, NAFLD and...
NAFLD-related cirrhosis [81]. Methotrexate does not affect body weight or BMI but it is important to consider the effects of obesity on the liver prior to treatment of PsA with methotrexate. PsA patients have higher burden of liver disease compared to the general population, which is increased with obesity. A cross-sectional study identified the prevalence of NAFLD to be significantly higher in patients with PsO compared to control (44% vs. 26%) [82]. Similarly, a population-based study of PsO and PsA patients demonstrated a significantly elevated risk of any liver disease (HR 1.37, 1.38), NAFLD (HR 2.23, 2.11) and risk of cirrhosis (HR 2.62, 3.15), respectively [83]. Contrarily, a prospective study of 54 PsO and PsA patients showed mild early fibrosis in 22% of the cases [84]. Obesity has been categorized as a risk factor for methotrexate-related liver toxicity, and the American Academy of Dermatology (AAD) guidelines proposed a liver biopsy when the cumulative dose approached 1.5 g [85]. Though there are no specific guidelines for toxicity monitoring in PsA patients on methotrexate from the ACR, liver function tests should be performed every 2–4 weeks for the first 3 months and then every 8–12 weeks [86]. Apremilast has a unique side effect of weight loss, and during the 52-week study period in PsA patients, weight loss [5% was observed in 32% of the study population [87].

Higher BMI can affect the volume of distribution of an administered drug, as well as its elimination, leading to insufficient dosing and limited efficacy [88, 89]. Infliximab and golimumab are the only TNFi routinely administered intravenously in a weight-based dose while other TNFi are usually administered in a fixed dose regimen. TNF-α induces muscle protein breakdown and downregulates the expression of anabolic hormones and growth factors [90]. TNFi suppresses TNF-α, and weight gain has been reported in PsO and PsA patients treated with TNFi for 12–48 weeks [91, 92]. Obese patients are at risk of having poor response to TNFi medications [93]. In a prospective cohort study of 135 obese and 135 normal-weight PsA patients treated with TNFi, obese patients were more likely to not achieve and maintain minimal disease activity (MDA) (HR: 4.90, [95% CI] 3.04–7.87; P < 0.001) [94]. Data from two large European registries suggest that there was no difference in TNFi doses between the obese and non-obese group, but obesity was associated with less adherence and response to TNFi [95]. In a systematic review with meta-analysis of 54 cohorts with 19,372 patients, obesity was associated with a 60% higher odds of failing TNFi therapy compared to non-obese and normal BMI patients across all forms of inflammatory immune-mediated diseases including PsA [93]. Ogdie et al. reported that obesity was among the strongest predictors with OR 0.51 (0.33–0.81) for not achieving Clinical Disease Activity Index (CDAI) remission [96]. Weight loss has been shown to improve disease activity in PsA [97]. In PsA patients treated with TNFi, the OR of achieving MDA was 6.67 with >10% weight loss compared to OR 3.75 with 5–10% weight loss and lower if weight loss is <5% [98].

IL-12/23 do not affect muscle breakdown, and the IL-12/IL-23 inhibitor, ustekinumab, was not associated with increased BMI or body weight (mean body weight increase 0.6 ± 1.1 kg) compared with infliximab (mean body weight increase 2.5 ± 3.3 kg) in patients with chronic plaque psoriasis treated over a 7-month period [99]. The dosing for ustekinumab is weight based with the 45-mg dose indicated for patients with body weight <100 kg, whereas the 90-mg dose for those weighing >100 kg. A study of 3800 patients with plaque psoriasis treated with ixekizumab and sub-grouped based on body weight did not find any difference in treatment effectiveness based on body weight [100]. Interestingly, Pantano et al. analyzed the effect of BMI on secukinumab response in 100 PsA patients and observed that a higher BMI was associated with lower disease activity score thus suggesting a better response to secukinumab [101]. Pooled data analysis of 710 PsA patients treated with tofacitinib demonstrated that tofacitinib is more effective than placebo, regardless of baseline BMI, but reduced efficacy was observed in patients with baseline BMI ≥ 35 kg/m² [102] (Table 1). There is no conclusive evidence that any PsA treatment is responsible for a significant
increase in weight though apremilast can cause weight loss in a certain subset of patients. A higher BMI can have a negative impact on certain treatments such as methotrexate and TNFi but does not affect response to treatment with IL-17A, IL12/23 or JAK/STAT inhibitors.

**Diabetes**

Diabetes mellitus (DM) is a prevalent comorbidity in PsA patients worldwide as seen from population-based and cohort studies [103, 104]. The prevalence of DM is higher in North American PsA patients, which is likely related to the higher burden of obesity and unhealthy lifestyle [2]. Systemic GCs, though not recommended by the ACR and recommended to be used at lowest dose in the European League Against Rheumatism (EULAR) treatment guidelines for PsA, are commonly used in clinical practice for acute flares of inflammatory arthritis [9, 10, 105]. The effects of GCs on glucose metabolism are well known, and they increase the risk of DM. Long-term use of low-dose steroids can cause hepatic insulin resistance, thus highlighting the importance of using steroids at the least possible doses for the shortest possible duration [106]. Methotrexate does not affect glucose metabolism and is considered safe in PsA patients with DM. Multiple studies looking at increases in hemoglobin A1c, fasting blood glucose or incident DM among methotrexate-treated PsA patients have found no effect on glucose metabolism [107–109]. It is important to note that NAFLD is common in DM, and methotrexate is associated with a significant increased risk of liver fibrosis in patients with DM compared to the group without DM, so close monitoring of LFTs is needed while on methotrexate [110]. There are no effects on glucose metabolism after treatment with leflunomide or sulfasalazine. Multiple studies have found a neutral impact of apremilast on glucose metabolism [111, 112].

A small study of 18 PsA patients evaluated the effect of TNFi and found no change in mean glucose level [113]. Another large study of 1200 PsA patients treated with adalimumab found no difference in the mean glucose levels between the adalimumab vs. placebo group [114]. These findings suggest that TNFi do not increase blood glucose levels and are safe in PsA patients with DM. IL-17 is being actively investigated as a cytokine of interest in the development of DM with evidence supporting a role of Th17 cells in the etiology of type 1 DM and IL-17 playing a role in inflammation, insulin resistance and type 2 DM [115]. Egdeberg et al. studied the impact of ixekizumab for PsO on cardiovascular parameters and found no difference in fasting glucose at 60 weeks [116]. A pooled analysis of > 3000 PsA patients treated with secukinumab showed a neutral effect of secukinumab on fasting plasma glucose level at 52 weeks [117] (Table 1). There are very limited data to date on the relationship between IL-12/23 inhibitors and glucose metabolism apart from a single retrospective study of 93 ustekinumab-treated PsA patients reporting an increase in fasting glucose level at 24 weeks [118]. Though there are no specific studies addressing DM and tofacitinib use in PsA, a large market scan database study over 11 years tried to address this in RA patients. The study of > 10,000 patients with RA and DM found the risk of DM treatment intensification was lower in the tofacitinib cohort (HR 0.67, 95% CI: 0.50, 0.90) compared with abatacept [119]. Much of the lower risk appeared to be driven by non-insulin DM treatment intensification events for tofacitinib [119].

**Neurologic Disorders**

Neurologic disorders are not commonly associated with PsA. The most common neurologic disorder reported in the Toronto Psoriatic Arthritis Clinic cohort was seizure disorder followed by neuropathy and multiple sclerosis (MS) [7]. The association among PsO, PsA and MS is controversial but must be considered in deciding the therapeutic agents [120, 121]. TNFi are associated with demyelinating diseases such as MS, Guillain-Barré syndrome and neuromyelitis optica and thus cannot be used in patients with these conditions [122]. Teriflunomide, which is the active metabolite of leflunomide, is approved for the treatment for
MS and can be considered in patients with coexisting PsA [123]. Though there are reports of utility of methotrexate in MS, a Cochrane review found insufficient data to support the use of methotrexate in MS [124]. Blockade of IL-17A has generated interest as a treatment option for MS, with secukinumab showing effectiveness in patients with relapsing-remitting MS, by reducing unique brain lesions and gadolinium-enhancing T1 lesions by 49% and 67%, respectively [125]. Ustekinumab was not successful in reducing MS lesions and is not a feasible options for MS with PsA [126].

EXTRA-ARTICULAR MANIFESTATIONS

Psoriasis

PsA and PsO have a very high coexistence with PsA reported in 10–30% of psoriasis patients [1]. In a study of 20,936 person-year follow-up, rate of new-onset PsA was 2.7 per 1000 person-years (CI 2.1–3.5) with corresponding 5-year incidence of 1.7% (CI 1.0–2.3%) [127]. The major subtypes of psoriasis include plaque psoriasis, pustular psoriasis, guttate psoriasis, nail psoriasis, erythrodermic psoriasis and inverse psoriasis [128]. The most common type of psoriasis in a PsA cohort of 1593 patients was plaque psoriasis (79%), and the most common site at initial presentation was scalp (42%), followed by knees and elbows (35%) [127]. Features of psoriasis that increase risk of PsA include number of cutaneous sites affected and location of psoriasis [129]. There was a 2.24-fold increased risk of PsA in those with more than 3 body sites affected, 3.98 increased risk with scalp lesions and 2.93 increased risk with nail dystrophy [127]. In the same study, PsA patients who presented at the same time with psoriasis were younger, male and more likely to have a family history of psoriasis [127]. Studies have also found an increased trend of obesity, trauma, bacterial infection, smoking, family history of PsA and physically demanding vocations to be associated with the development of PsA in patients with psoriasis [79].

The treatment of PsO includes topical therapies, such as topical corticosteroids, vitamin D analogs, tazarotene, calcineurin inhibitors, etc., which are not useful in PsA. Fortunately, there is a significant overlap between biologic and non-biologic therapies for PsO and PsA based on the guidelines from respective societies [130, 131]. Methotrexate and apremilast are FDA approved for the treatment for PsO and can be used for PsA management [130, 131]. Tofacitinib has been shown to be efficacious for the treatment of PsO but is not yet FDA approved, though it is approved for the treatment of PsA [131, 132]. Five TNF inhibitors have been approved for the treatment for PsA and four for the treatment for PsO (golimumab is not approved for PsO) [131, 133]. In terms of IL-17 inhibitors, both secukinumab and ixekizumab are approved for treatment of PsO and PsA while brodalumab is only approved for treatment of PsO [133]. Ustekinumab and guselkumab have shown excellent efficacy results for treatment of PsO and PsA and are approved for treatment of both [133, 134]. Tildrakizumab and brodalumab are approved for PsO treatment but are not used in treating PsA.

Inflammatory Bowel Disease

Gastrointestinal diseases such as Crohn’s disease (CD) and ulcerative colitis (UC) are reportedly more common in PsA compared to PsO [135]. There are no specific guidelines differentiating treatment of PsA based on individual CD or UC diagnosis; however, the American College of Gastroenterology (ACG) has guidelines for each inflammatory bowel condition [136]. The ACG guidelines conditionally recommend avoiding NSAIDs in IBD. Certain csDMARDs such as sulfasalazine and methotrexate can be used in mild disease. Sulfasalazine can be used for treatment of mild-to-moderate colonic CD and UC. Methotrexate can also be used but typically given in doses up to 25 mg once weekly intramuscularly or
subcutaneously for those with steroid-dependent CD and for maintaining remission [136]. In UC, methotrexate is not recommended for induction or remission of moderate-severe disease.

Monoclonal TNFi (infliximab, adalimumab, certolizumab pegol) are used in moderate-severe CD and UC followed by IL-12/23 inhibition if there is failure of TNFi. Golimumab is approved for UC but not for CD and is effective in PsA. Vedolizumab, an integrin inhibitor, is approved for the treatment of CD and UC. It is not used for treatment of PsA but clinicians should be aware about the rare side effects of inflammatory arthritis and sacroiliitis reported with vedolizumab use [137]. Tofacitinib can also be used in those with moderate to severe UC [138]. Studies of tofacitinib use in CD have shown conflicting results [139]. Ustekinumab is typically reserved for patients who have failed TNFi therapy and csDMARD use. It can also be used in induction for moderate-severe CD with similar background therapy use or no prior exposure to TNFi as well as for maintenance of remission [136]. Similarly, ustekinumab was recently approved for inducing and maintaining remission for those with moderate-severe UC [140].

IL-17 inhibition works well for predominant cutaneous disease; however, there is caution in its use in patients with concomitant inflammatory bowel disease. Although rare, cases have been reported of patients who have had new onset or exacerbation of inflammatory bowel disease on IL-17 inhibition. In a 2-year span, 27 patients were identified in the literature to have IBD onset after IL-17 inhibition [141]. Causality however cannot be determined based on the nature of the review. Pooled cases from several studies involving 1380 PsA patients treated with secukinumab only revealed 7 new-onset cases of IBD [142]. In a safety follow-up study of ixekizumab users, incidence rate for IBD was 0.2/100 patient-years [32]. The pooled exposure-adjusted incidence rate of CD across MEASURE-1 and MEASURE-2 studies in ankylosing spondylitis was 0.7 events per 100 patient-years of exposure to secukinumab; these cases were seen in patients with already pre-existing CD [30].

As there is such an extensive overlap between the therapeutic options for PsA and IBD, close collaboration between rheumatology, dermatology and gastroenterology is necessary to decide the optimal therapeutic agent (Table 1).

**Ophthalmic Diseases**

Uveitis is a well-recognized extra-articular manifestation associated with human leucocyte angigen-B27 (HLA-B27)-associated spondyloarthritis including PsA [143, 144]. The risk of uveitis is significantly higher in PsA compared to patients with PsO and the general population [145]. A large systematic review of > 9500 uveitis patients predicted the prevalence of uveitis in PsA as 25% [144]. Although uveitis is frequently reported in PsA, other manifestations such as conjunctivitis, keratoconjunctivitis, etc., have been reported [146]. Multiple immunomodulators, such as methotrexate, mycophenolate, azathioprine and sulfasalazine, are used to treat non-infectious uveitis, though only a few are used in PsA [147, 148].

In recent years, biologic therapies have increased the treatment armamentarium for uveitis. While there are no specific data for uveitis in the PsA population, adalimumab and infliximab are effective in lowering the risk of uveitis flare or visual impairment [149, 150]. Etanercept is generally not effective in the treatment of uveitis while certolizumab and golimumab have shown lower risk of uveitis flares [151, 152]. In a pooled analysis of 3 clinical trials of 794 AS patients, there was no increased risk of uveitis with secukinumab use [153]. Ustekinumab has been reported to be successful in treatment of noninfectious uveitis associated with PsO, PsA and Crohn’s disease [154, 155]. As uveitis can be a vision-threatening manifestation of PsA, a collaborative approach among ophthalmology, rheumatology and dermatology is helpful in deciding a single agent that can control all manifestations of PsA (Table 1).
LINKED MANAGEMENT ISSUES

Chronic Infections

All patients must be screened for hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) and latent tuberculosis (LTBI) prior to starting csDMARD or bDMARD therapy. Methotrexate increases the risk of HBV reactivation and can cause liver fibrosis/cirrhosis according to very limited reports [156]. As methotrexate is widely used and there are only a few cases related to HBV reactivation, the risk of HBV reactivation is < 1% [157]. There is a known risk of opportunistic infections and reactivation of HIV and LTBI patients, respectively [158, 159]. TNF-α is crucial for clearance and containment of infections such as HBV and LTBI [160]. Inhibition of TNF-α can lead to HBV re-activation, and a meta-analysis of pooled dermatologic and rheumatic patients suggested that recurrence of HBV ranged from 4.2 to 6.8%, with higher HBV recurrences in HbsAg-positive patients [161]. HbsAg-positive patients are at higher re-activation of HBV compared to anti-Hbc-positive patients. Patients on TNFi with positive anti-Hbc antibody are at moderate risk of HBV re-activation, and treatment with anti-viral drugs or routine monitoring must be decided based on risk profile [157]. Etanercept appears safe, at least with short-term use, in the management of PsA patients with concomitant HCV [162]. Chiu et al. reported HCV and HBV re-activation in ustekinumab-treated patients while Abuchar et al. reported no reactivation of HCV [163, 164]. The data regarding safety of IL-12/23 inhibitors with HBV are limited but preliminary reports suggest they are safe to use [165, 166]. TNF-α is crucial for granuloma formation, and inhibition of TNF-α can lead to reactivation of LTBI [167]. The risk of LTBI is present with all TNFi but is highest with infliximab. It is recommended that patients be treated with LTBI prophylaxis for 4–6 weeks prior to commencing TNFi therapy. The IL-17 inhibitors and IL12/23 inhibitors have not been shown to substantially increase the risk of LTBI re-activation [168–170].

Psychiatric Illness

Mental health disorders such as depression and anxiety have a reported prevalence of 9–37% in PsA, which is higher than the general population [171, 172]. The relationship between depression and systemic inflammation is still unclear but is an important co-morbidities to consider as it can affect pain and the likelihood of disease remission [173]. Another challenge in patients with depression and PsA is treatment adherence, which can impact disease activity and quality of life [174]. Assessment of psychiatric co-morbidities is important as some treatment options such as brodalumab and apremilast come with FDA label warning of increased risk of mental health outcome such as self-harm [175, 176]. Similarly, studies have tried to evaluate the effect of csDMARD/bDMARD therapy and relevant mental health with favorable outcomes. A Swedish registry-based study looked at the use of anti-depressants in patients with PsA, RA and AS and found that the use of anti-depressants was reduced after starting treatment with DMARDs or TNFi [177]. Biologic medications have shown some encouraging results in the treatment of depression in patients with PsO without PsA [178]. A large cohort study of PsA or PsO patients from Taiwan examined the effects of biologic therapy on reducing depression and noted a 40% decrease in the prevalence after 2 years of biologic therapy [179]. An integrated pooled clinical trial safety dataset from 21 randomized controlled clinical trials of secukinumab in PsO, PsA and AS reported low incidence of suicide-related events in the treatment group [180]. Physicians must pay attention to psychiatric co-morbidities in PsA as it not only determines the treatment choice but can very well affect treatment adherence and clinical outcomes (Table 1).

Pregnancy

The burden of rheumatic disease is high among women, especially those of child-bearing age. The choice of therapy and disease activity can weigh heavily on conception and during

△ Adis
gestation. A retrospective analysis by Karma-
ccharya et al. showed a 3% increase in incidence
of females with PsA from 2000 to 2017, pri-
marily in age groups 40–59 years [181]. The goal
of therapy for successful gestation is to control
activity prior to and during pregnancy. A sys-
temic literature search of pregnant patients with
PsA revealed elevated disease activity port par-
tum and increased risk of preterm birth, pre-
eclampsia and elective cesarean section among
patients [182]. Another study showed a risk of
preterm delivery correlating to PsA disease
activity [184].

PsA medications typically safe to use in
pregnancy include NSAIDs prior to third tri-
mester, prednisone < 20 mg/daily, sulfasalazine
and TNFi [185] (Table 1). Medications including
steroids, non-bDMARDs, bDMARDs and
NSAIDs in the first or second trimester were not
associated with increased risk of preterm deliv-
ery [184]. There are limited data regarding use of
IL-17 inhibition, IL12/23 inhibition, IL-23
inhibition, PDE-4 inhibition and JAK/STAT
inhibition; therefore, consensus is to modify
therapy prior to planned pregnancy [185, 186].
Methotrexate and leflunomide are contraindi-
cated [185, 186]. In one retrospective case series,
discontinuation of biologics prior to pregnancy
was found to be associated with a flare in disease
activity during pregnancy with increased use of
steroids; there was no significant change in
disease activity in those continued on biologics
[187].

Fertility

The relationship between PsA and infertility is
unclear [188]. In a study of 74 PsA patients, the
diagnosis of infertility was not significantly
different compared to 74 healthy controls [188].
Infertility, defined as being unable to get preg-
nant after 12 months of trying or physician
diagnosis of infertility, was assessed based on a
questionnaire in 28 PsA patients, and 10
patients (36%) who had ever been pregnant or
attempted pregnancy reported infertility with
polycyclic ovarian syndrome being the pre-
dominant cause (5/10) [189].

Certain medications are thought to influence
fertility and pregnancy outcomes. Although
teratogenic, the risk of infertility with
methotrexate use appears low with one report
stating successful conception in women after
methotrexate cessation [190]. There are no clear
associations between methotrexate use and
male fertility [191]. Although not many human
models, animal studies show that leflunomide,
in its active form, does not influence fertility
however is embryotoxic and teratogenic [192].
If there is difficulty with conception and sig-
nificant NSAID use, NSAIDs are recommended
to be discontinued pre-conception because of
the risk of un-ruptured follicle syndrome
[185, 192]. Sulfasalazine has been found to
reduce male fertility in a setting of reversible
azoospermia but is safe in females [192, 193].
There are no clear recommendations for use of
JAKi and tsDMARDs due to lack of data [185].
No data are available regarding use of anti-IL-17
and anti-IL-12/23 in female fertility.

CONCLUSION

PsA is a complex disease, and there has been
tremendous progress in our understanding
about the associated co-morbidities. Individual
co-morbid conditions in PsA present a unique
challenge in deciding the treatment choice and
attaining successful treatment. The goal of
therapy is to control the immune-mediated
inflammation directed by active PsA and extra-
articular manifestations. Certain co-morbidities
help dictate treatment choices and can affect
the response to treatment. The burden of CV
disease is high in PsA, and treatment of under-
lying inflammatory arthritis has been shown to
improve CV outcomes. Obesity is a risk factor
for PsA development and has been shown to
adversely affect response to treatment. The risk
of malignancy is low with the available
bDMARD therapies, but patients should be
made aware about the risk. As PsA is a hetero-
genous disease that can have ocular, cutaneous
or gastrointestinal manifestations, close collab-
oration between specialties is crucial in deciding
the optimal drug therapy. Screening for chronic infections and renal and hepatic dysfunction is recommended prior to therapy initiation. A shared decision model must be utilized concerning the appropriate drug choice based on the disease presentation, associated co-morbidities and individual needs of a patient.

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