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Psoriasis Comorbidities and Clinical Implications When Using Biologics
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Keywords: adverse effect, biologics, comorbidities, prevalence, psoriasis

Disclosures
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Abstract
Background: Psoriasis is a cutaneous inflammatory disorder with associated comorbidities which can influence treatment options. Biologics are immune-modifying agents that can improve or worsen pre-existing psoriasis comorbidities. The risks associated with a particular biologic agent and its effects on a comorbidity can guide treatment decisions and direct further workup to screen for markers of these comorbidities.

Methods: A literature search was performed to develop treatment recommendations for psoriasis patients in the background of common comorbidities when considering biologic agents.

Results: Psoriatic arthritis, inflammatory bowel disease, metabolic syndrome, non-alcoholic fatty liver disease, depression, and malignancies are comorbidities associated with psoriasis that can be affected by certain biologic agents.

Conclusion: Considerations to make when treating a patient with psoriasis include the severity of disease, the presence of comorbidities, and symptomology that can interact with biologics agents.

Keywords: adverse effect, biologics, comorbidities, prevalence, psoriasis

Introduction
Psoriasis is a common, chronic inflammatory skin disorder characterized by well-demarcated, indurated plaques with silvery scale. Pathogenesis of the immune-mediated disease

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is influenced by genetic and environmental factors. Psoriasis reduces quality of life, has many associated morbidities, and is a significant public health problem.\(^1,2\)

Psoriasis treatments generally fall into one of two categories – local treatments, including topicals and phototherapy, or systemic treatments. Biologics are revolutionary systemic agents that differ from older systemic drugs, such as methotrexate or cyclosporine, which are designed to suppress the immune system as a whole. In contrast, biologics are immune modifying agents that target specific signaling molecules in the inflammatory cascade, thereby making the therapy selective for the inflammatory pathways that contribute towards psoriasis.

Treatments for psoriasis may interact, either positively or negatively, with comorbidities found in patients with psoriasis. This review summarizes the comorbidities that occur in patients with psoriasis and describes their clinical implications when treating with biologic agents. Although increased relative risk of having a comorbidity does not necessarily mean that screening is warranted, the risks associated with a particular biologic agent and its effects on a comorbidity can guide treatment decisions and direct further workup to screen for markers of these comorbidities.

**Methods**

A literature search was performed according to an evidence-based model using PubMed and Medline databases of publications from November of 1984 to February of 2021 concerning comorbidities in psoriasis patients and how they affect the use of biologic agents to treat psoriasis. The reference lists included in the publications were also manually searched to ultimately find a total of 3 systematic literature reviews, 7 case reports, and 70 original articles that were relevant to this topic. Keywords used were “adverse effect”, “biologics”, “comorbidities”, “prevalence”, and “psoriasis” to find a total of 179 articles. Out of the entire search, 61 articles were used for this review. Articles were limited to those published in the English language. Statistically significant findings were reported in terms of relative risk, which is not as strong of a measure to determine clinical significance as absolute risk or risk-benefit analysis.\(^3\) Therefore, clinical suggestions made in this review should be further analyzed before decision-making.

**Results**

**Psoriatic Arthritis**

Psoriatic Arthritis (PsA) is a rheumatologic disease of the joints commonly associated with psoriasis. In addition to psoriatic plaques, the chronic inflammatory disorder presents with arthritis, bony erosions, syndesmophytes, dactylitis, and enthesitis. There is a higher risk of developing PsA among people with psoriasis compared to those without psoriasis. In a cross-sectional observational study from 2006 in Europe, the incidence of PsA among study participants with psoriasis was 74/1000 person-years and remained constant over time, resulting in a steady increase in prevalence up to 20.5% over 30 years after the initial diagnosis of psoriasis. The prevalence of PsA was higher in study participants who had a higher body surface area involvement of psoriasis.\(^4\) In a cross-sectional observational study from 2005 in the United States, the prevalence of PsA among patients with psoriasis was 11% (71/601 patients).\(^5\) In a 2013 study, 29% of patients with psoriasis had undiagnosed PsA.\(^6\) In a 1984 study, 34.4% of participants with psoriasis studied had PsA,\(^7\) and in a 1995 study in Italy, 36% of the participants with psoriasis had PsA.\(^8\) Variability in prevalence across these studies may be due to biological differences such as genetic predisposition or environmental factors that may exacerbate symptoms or promote the development of this comorbidity.

American College of Rheumatology/National Psoriasis Foundation Guideline from 2018 generally recommends anti-tumor necrosis factor (TNF) agents for the treatment of active PsA due to its efficacy relative to alternative treatment options. However, the recommendation is conditional to severity of the disease, preference for the route of medication, and concerns over adverse effects of the medication. The FDA-approved TNF-inhibitors for the treatment of PsA include adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Anti-TNF
agents are contraindicated in patients with congestive heart failure, demyelinating disease, or history of serious infections.\textsuperscript{9} Other biologics approved for the treatment of PsA include T-cell inhibitor abatacept, interleukin (IL)-12/23 inhibitor ustekinumab, IL-23 inhibitor guselkumab, and IL-17 inhibitors ixekizumab and secukinumab. Biosimilars, a subset of biologics that are FDA-approved for the treatment of PsA include: adalimumab-atto, adalimumab-afzb, adalimumab-adbm, adalimumab-bwwd, adalimumab-fkjp, adalimumab-adaz, etanercept-szxs, etanercept-ykro, infliximab-axq4, infliximab-dyxb, infliximab-qbtx, and infliximab-abda.

There are also biologics not yet FDA-approved for the treatment of PsA that have been effective in reducing symptoms of PsA. Brodalumab is an IL-17 receptor subunit A inhibitor that rapidly and significantly improved PsA symptoms compared to placebo (p < 0.01).\textsuperscript{10} Tofacitinib is a Janus Kinase inhibitor that significantly reduced disease activity in patients with PsA who inadequately responded to TNF-inhibitors compared to placebo (p < 0.001).\textsuperscript{11} Bimekizumab inhibits IL-17A and IL-17F, and more patients treated with bimekizumab achieved improvement in their PsA symptoms compared to patients treated with placebo (p = 0.0004).\textsuperscript{12} These yet-to-be-approved biologics may also be considered as treatment options by providers for patients with PsA based on their efficacy. Some considerations to make when treating a patient with PsA include the severity of the disease, previous treatments and reasons for treatment failure, and the presence of comorbidities. The recommendation is to perform routine screening for PsA among patients with psoriasis for early detection and treatment to prevent disability from the progression of joint disease. Importantly, providers should educate patients of the disease association and how to detect the onset of symptoms for prompt evaluation. In addition, providers should consider whether medications approved specifically for PsA or marketed for the prevention of the progression of joint disease are necessary in patients with PsA and joint pain if they are not experiencing or showing early signs of progression of joint disease.

**Inflammatory Bowel Disease**

Inflammatory bowel disease (IBD) is a psoriasis comorbidity that has similarities to psoriasis in genetic background and pathogenesis. Some gene loci have been linked to both psoriasis and IBD,\textsuperscript{13} and both conditions have inflammatory pathway involvement in which levels of IL-23, IL-17, and T-helper cell 17 cells are increased.\textsuperscript{14,15} There is a higher prevalence of IBD in individuals with psoriasis compared to those without psoriasis. In a retrospective chart review of a psoriasis cohort, 1.6% of psoriasis patients studied had IBD, including Crohn’s disease and ulcerative colitis. Of the 1.6% of psoriasis patients with IBD, 0.7% had Crohn’s disease, and 0.8% of those patients had ulcerative colitis. There was also a higher prevalence of IBD in patients with both psoriasis and PsA compared to psoriasis patients without PsA.\textsuperscript{16}

Adalimumab, certolizumab pegol, etanercept, and infliximab have been associated with excessive weight gain in pediatric IBD cases.\textsuperscript{17} In a retrospective analysis, infliximab was associated with rapid weight gain in Crohn’s disease patients, where 59% of patients gained weight in 6 weeks, and 73% of patients gained weight in 3 months.\textsuperscript{18} Psoriasis patients on these medications should be monitored for excessive weight gain, as these patients have a higher risk for both IBD and obesity.

Some biologics induce or worsen IBD in psoriasis patients. In phase three trials of infliximab, the adverse events reported included ulcerative colitis and Crohn’s disease.\textsuperscript{19} Secukinumab has been associated with new-onset cases of IBD in psoriasis patients. In a retrospective analysis of pooled data from 21 clinical trials of secukinumab, there were 14 new-onset cases of IBD out of 5181 psoriasis patients and seven new-onset IBD cases out of 1380 PsA patients.\textsuperscript{20} There is also a reported case of a patient with chronic plaque psoriasis and PsA who presented with new-onset IBD 14 months after switching from methotrexate to secukinumab.\textsuperscript{21} In another reported case, a patient with psoriasis and episodes of abdominal pain was diagnosed with ileocolic Crohn’s disease two months after starting secukinumab due to progressively worsening gastrointestinal symptoms.\textsuperscript{22} In a clinical trial of secukinumab for Crohn’s disease, the reduction in Crohn’s Disease Activity Index was greater in the placebo group. Four out of the five
cases of worsening of Crohn’s disease were from the experimental group, and 74% of patients in the group treated with secukinumab experienced adverse effects, compared to only 50% of patients in the control group.23 Ixekizumab has been associated with new-onset IBD in a psoriasis patient.24 Brodalumab has been associated with worsening Crohn’s disease; the odds ratio compared to the placebo group was 6.64 (confidence interval (CI) 1.48-29.88), and the Crohn’s Disease Activity Index (CDAI) was worse in the brodalumab treatment group, which had a mean CDAI of 75 +/- 75, compared to the placebo group, which had a mean CDAI of -37 +/- 43, (p = 0.06).25 Because IL-17 inhibitors have the potential to induce or worsen IBD in psoriasis patients, screening for symptoms of IBD in psoriasis patients may be considered before starting treatment. For psoriasis patients at risk for or who are simultaneously affected by IBD, ustekinumab may be offered as an alternative FDA-approved biologic for the treatment of plaque psoriasis because its adverse effects are unrelated to IBD. Infliximab and adalimumab are FDA-approved TNF inhibitors that are also options available for use in both IBD and psoriasis. Tildrakizumab and risankizumab target the p19 subunit of IL-23, and although they are FDA-approved only for the treatment of plaque psoriasis, these biologics have been used to improve IBD symptoms. Tildrakizumab not only improved symptoms of a patient’s plaque psoriasis and PsA, but also completely resolved their IBD.21 Risankizumab helped achieve higher rates of clinical remission in patients with moderate to severely active Crohn’s disease compared to placebo: 31% of patients on risankizumab had clinical remission whereas only 15% of patients on placebo had clinical remission (p = 0.0489).26 Therefore, tildrakizumab and risankizumab may be considered as treatment options for psoriasis patients with concurrent IBD.

Metabolic Syndrome and Cardiovascular Events

Psoriasis is strongly associated with metabolic syndrome, a collection of cardiovascular risk factors that is defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) as the simultaneous presence of at least three of the following conditions: high waist circumference, hypertension, hypertriglyceridemia, hypercholesterolemia, and hyperglycemia.27 An observational case-control study in Singapore identified common human leukocyte antigen alleles that put patients at risk for hyperlipidemia, hypertension, and psoriasis.28 In a 2020 study, there was a higher prevalence of greater waist circumference, higher blood pressure, higher fasting blood glucose, and higher serum level of angiotensin-like protein 2 in study participants with psoriasis compared to those without psoriasis.29 Patients with psoriasis also have an increased odds ratio for metabolic syndrome starting at age 40-49.30 In a hospital based case-control study, the prevalence of metabolic syndrome among patients with psoriasis was 30.1%, whereas the prevalence of metabolic syndrome in patients without psoriasis was only 20.6% (p = 0.005) in patients older than 40 years.31 In a 2017 study at a tertiary care hospital in India, all individual metabolic abnormalities were more prevalent in patients with psoriasis compared to patients without psoriasis. The prevalence of metabolic syndrome among patients with psoriasis based on the modified NCEP ATP III criteria was 40.9% compared to just 12.2% in patients without psoriasis (univariate analysis odds ratio was 5.04 (CI 3.19-7.96)). After adjusting for age, sex, BMI, tobacco smoking, and alcohol consumption, the odds ratio of metabolic syndrome in psoriasis patients was 6.00 (CI 3.34-10.52). Compared to non-psoriasis patients, psoriasis patients had higher prevalence of abdominal obesity (66.2% versus 47%; p < 0.001), hypertriglyceridemia (40.4% versus 29.6%; p = 0.009), systolic blood pressure ≥ 130 mmHg (25.1% versus 7.4%; p < 0.001), diastolic blood pressure ≥ 85 mmHg (30.2% versus 12.2%; p < 0.001), and fasting plasma glucose ≥ 100 mg/dl (17.4% versus 9.1%; p = 0.005). Psoriasis patients had higher levels of IL-6 and TNF-alpha compared to the normal population, alluding to the overlapping pathogenesis of psoriasis and metabolic syndrome. In psoriasis patients with metabolic syndrome, the mean +/- standard deviation of IL-6 was 76.7 +/- 73.9 pg/ml compared to 1.79 +/- 2.03 in the normal population (p < 0.0001). In psoriasis patients with metabolic syndrome, the mean +/- standard deviation of TNF-alpha was 234.3 +/- 273.9 compared to 2.74 +/- 0.94 in the normal population (p < 0.0001).32
Obesity is another common psoriasis comorbidity. In a cross-sectional study in Germany, 30.6% of studied psoriasis patients were obese or morbidly obese, while only 15.7% of the general population without psoriasis were obese or morbidly obese. \(p<0.0001\). In a prospective study, obese individuals had almost twice the relative risk of psoriasis (relative risk was 1.87 (CI 1.38-2.52)) compared to normal weight individuals. \(^{34}\) There was an improved response to treatment of psoriasis with cyclosporine in patients who lost weight through a low-calorie diet \(p<0.001\) compared to patients treated with cyclosporine without the low-calorie diet who did not lose as much weight. \(^{35}\)

Cardiovascular disease, stroke, and myocardial infarction are also psoriasis comorbidities. There was a higher frequency of a major adverse cardiac event in patients with severe psoriasis compared to those without psoriasis (4.5% vs 2.95%). Even after adjusting for risk factors such as age, hyperlipidemia, hypertension, smoking, and diabetes, severe psoriasis had a hazard ratio of 1.53 (CI 1.26-1.85) for major cardiac effects. \(^{36}\) In an observational study, the odds ratio for ischemic heart disease was 1.78 (CI 1.51-2.11), and the odds ratio for cerebrovascular disease was 1.70 (CI 1.33-2.17). \(^{37}\) Within a cohort study in US women, women with psoriasis had a higher hazard ratio for non-fatal cardiovascular disease compared to women without psoriasis. \(^{38}\)

Given the elevated risk of metabolic syndrome, obesity, and cardiovascular events, patients with psoriasis should get at least standard age-appropriate recommended screening for components of metabolic syndrome at regular intervals based on the severity of their risk factors and overall health. Measurements could include a fasting blood glucose, two consecutive blood pressure measurements, BMI, waist circumference, and fasting blood lipids.

The effect of certain biologic agents on metabolic syndrome and obesity may need to be kept in mind when using them to treat psoriasis. Etanercept and infliximab have been associated with fat mass gain in psoriasis vulgaris patients, where 60% of the study participants experienced weight gain on the medications. \(^{39}\) In a retrospective analysis, infliximab was associated with rapid weight gain in Crohn’s disease patients, where 59% of patients gained weight in 6 weeks, and 73% of patients gained weight in 3 months. \(^{18}\) Because psoriasis patients are at risk for metabolic syndrome, obesity, and IBD, it may be prudent to monitor weight gain in certain higher risk patients when using these specific anti-TNF medications.

Although etanercept is an anti-TNF agent that can improve heart function, some anti-TNF agents have been associated with adverse cardiovascular events. In a clinical trial, patients with advanced heart failure were administered etanercept and had significantly improved systemic endothelial vasodilator capacity compared to the control group \(p<0.05\). \(^{40}\) However, high doses of infliximab worsened the clinical status of patients with heart failure in a randomized clinical trial. Patients treated with high-dose infliximab had a higher risk of dying or being hospitalized for heart failure compared to patients in the placebo group \(p=0.043\). \(^{41}\) Although clinical trials carry more weight, case reports with adalimumab use have also been associated with new-onset heart failure and cardiomyopathy in patients treated for HS and Crohn’s, respectively. \(^{42, 43}\) Because anti-TNF agents may have cardiovascular effects on those with psoriasis due to higher prevalence of cardiovascular risk factors in psoriasis patients, providers may consider avoiding these medications and consider screening patients who are at risk.

In contrast, secukinumab may reduce cardiovascular risk by improving endothelial function in patients with plaque psoriasis: secukinumab increased baseline-adjusted mean flow-mediated dilation compared to placebo. \(^{44}\) Patients with plaque psoriasis and comorbid compromised endothelial function may benefit from secukinumab’s potential to increase flow-mediated vascular dilation if the medication is not otherwise contraindicated.

Non-Alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is a comorbidity associated with psoriasis and has greater prevalence in psoriasis patients than in the general population. NAFLD was diagnosed
In 59.2% of the psoriasis patients studied who did not have viral hepatitis or significant ethanol or methotrexate use compared to only 20% of NAFLD observed in the general population. In a cohort study, PsA was an independent predictor of NAFLD in psoriasis patients with an odds ratio of 3.94 (CI 1.07-14.46; p = <0.005). There was a higher prevalence of NAFLD in patients with chronic plaque psoriasis compared to study participants without psoriasis (47% versus 28%, p < 0.0001%). Patients with both chronic plaque psoriasis and NAFLD had higher C-reactive protein (CRP), liver enzymes, and serum triglycerides compared to patients with only chronic plaque psoriasis. This relationship may be due to the fact that that obesity is causative for NAFLD in addition to being a common comorbidity in psoriasis. There was also a higher prevalence of NAFLD in psoriasis patients with more severe psoriasis (psoriasis area and severity index >10) compared to patients with less severe psoriasis. 

Infliximab has been linked to drug induced autoimmune hepatitis. Due to the increased prevalence of NAFLD in psoriasis patients, it is advised to conduct liver function tests before beginning treatment with infliximab, after the first dose, and at minimum every four months throughout the course of treatment. It is also advised to consider avoiding infliximab in psoriasis patients with pre-existing liver conditions and discontinue treatment in patients whose transaminases are greater than three times the normal upper limit. 

Mental Health Disorders

Mental health disorders are common in patients with psoriasis. This may be due to the psychosocial impact of psoriasis. In addition, a physiological link between psoriasis and depression involving IL-6 is also possible. In a population-based psoriasis cohort study, the crude incidence of clinically diagnosed depression was 25.9%, anxiety was 20.9%, and suicidality was 0.9% per 1000 persons observed for 1 year. In an Italian survey of psoriasis patients, depressive symptomatology was present in 62% of participants. Self-reports of psoriasis severity directly correlated with depression scores. Patients may be informed about the association between psoriasis and depression and be regularly screened for anxiety and depression. Patients with depression may be less likely to be adherent than patients without depressive symptomology. In turn, physicians may consider using biologics with longer dosing intervals or in-office administration for patients diagnosed with depression who may have less motivation for more frequent injections.

Several biologics have been associated with a lower incidence rate of depression compared to conventional systemic agents such as methotrexate, cyclosporine, systemic corticosteroids, fumarates, mycophenolate mofetil, and oral retinoids. The incidence rate of depression among patients with moderate to severe psoriasis using these conventional systemic agents was 5.70 (CI 4.58-7.10), compared to adalimumab’s incidence rate of 2.62 (CI 2.15-3.19), etanercept’s incidence rate of 3.53 (CI 2.90-4.30), infliximab’s incidence rate of 3.01 (CI 2.24-4.05), and ustekinumab’s incidence rate of 3.01 (CI 2.60-3.50). Although brodalumab carries a boxed warning for suicidal ideation and behavior, a causal relationship between brodalumab use and suicides was not established, and there does not seem to be a clear increased risk. Four suicides occurred during the clinical trials of brodalumab, and it prompted the development of The Risk Evaluation and Mitigation Strategies program, which aims to reduce the risk of suicidal ideation and behavior in patients treated with brodalumab by ensuring that both providers and patients are educated about the risk observed with the therapy. Consider regular screening for depressive symptomology and suicidal ideology in psoriasis patients with pre-existing anxiety or depression being treated with brodalumab.

Malignancy

In a nested case-control analysis, the incident rate of non-specific cancer diagnosis in psoriasis patients was 5.83 per 1,000 person years (CI 5.47-6.22), whereas the incident rate in patients without psoriasis was 5.18 per 1,000 person-years (CI 4.83-5.55). The risk of developing lymphohematopoietic malignancies and digestive tract cancer, specifically, was increased in
patients with psoriasis compared to patients without psoriasis.\textsuperscript{55} Psoriasis patients had 2.95
greater rate of lymphoma compared to patients without psoriasis, and there were additional cases of
lymphoma in patients aged 65 and older.\textsuperscript{56} There was also an increased incidence of squamous
cell skin carcinoma, non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, and laryngeal cancer in psoriasis patients compared to those without psoriasis. The overall cancer standardized incidence ratio in psoriasis patients was 1.3 (CI 1.2-1.4). Out of the malignancies studied, Hodgkin’s
disease and squamous cell skin carcinoma had the highest incidence in psoriasis patients,
followed by non-Hodgkin’s lymphoma, then laryngeal cancer. The standard incidence ratio in
psoriasis patients for Hodgkin’s disease, squamous cell skin carcinoma, non-Hodgkin’s
lymphoma, and laryngeal cancer was 3.3 (CI 1.4-6.4), 3.2 (CI 2.3-4.4), 2.2 (CI 1.4-3.4), and 2.9
(CI 1.5-5.0), respectively.\textsuperscript{57}

A few biologic agents have been associated with the development of malignancies. The
manufacturer of adalimumab noted lymphoma and hepatosplenic T-cell lymphoma in children
and adolescents who were simultaneously being treated with azathioprine or 6-mercaptopurine
and adalimumab. Adalimumab has also been associated with a higher incidence of non-melanoma
skin cancer in psoriasis patients.\textsuperscript{58} There was a higher tumor burden and incidence of
keratinocytic neoplasia in mice given etanercept compared to control mice when both groups
were treated with ultraviolet phototherapy.\textsuperscript{59} Ustekinumab, however, had malignancy rates
comparable to the control group.\textsuperscript{60, 61} Consider screening formalignancies regularly in psoriasis
patients being treated with either of these medications.

Other Psoriasis Comorbidities

Table 1 lists biologic agents that have a positive or negative effect on the psoriasis
comorbidities discussed in the prior sections of this review. Obstructive sleep apnea, sexual
dysfunction, chronic obstructive pulmonary disease (COPD), end-stage renal disease (ESRD),
uveitis, and Parkinson’s disease are also comorbidities associated with psoriasis but have no
known effect on the treatment of psoriasis with biologics. Table 2 describes details of each of
these psoriasis comorbidities that do not interact with biologic agents.

Discussion

PsA, IBD, metabolic syndrome, cardiovascular complications, NAFLD, depression, and
certain malignancies are some of the significant comorbidities in patients with psoriasis that
affect treatment decisions. In addition to the manufacturer-recommended screening for
tuberculosis when using biologics, providers should consider screening psoriasis patients for
cardiovascular risk factors, lymphoma, and non-melanoma skin cancers, as well as excessive
weight gain when treating with anti-TNF-alpha agents. Providers should also consider screening
psoriasis patients for transaminase elevations when treating with infliximab, for IBD before
treating with anti-IL-17 agents, and for suicidal ideation when treating with brodalumab.
Consider avoiding certain biologics and offer an alternative if the risk for adverse effects in an
individual due to the medication is higher than normal.

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<table>
<thead>
<tr>
<th>Table 1. Biologic agents that have a positive or negative effect on psoriasis comorbidities.</th>
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<tbody>
<tr>
<td><strong>Comorbidity associated with psoriasis that can be affected by biologic agents</strong></td>
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<tr>
<td>PsA</td>
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<table>
<thead>
<tr>
<th>Condition</th>
<th>Inhibitors</th>
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<tr>
<td>T-cell inhibitor: abatacept</td>
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<tr>
<td>IL-12/23 inhibitor:</td>
<td>ustekinumab</td>
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<tr>
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<td></td>
<td>IL-23 inhibitors: tildrakizumab, risankizumab</td>
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<td></td>
<td>IL-17 inhibitors: secukinumab, ixekizumab, brodalumab</td>
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<td>Obesity</td>
<td>TNF-inhibitors: etanercept, infliximab</td>
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<tr>
<td>Cardiovascular disease</td>
<td>TNF-inhibitor: etanercept</td>
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<td></td>
<td>IL-17 inhibitor: secukinumab</td>
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<td></td>
<td>TNF-inhibitors: infliximab, adalimumab</td>
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<tr>
<td>NAFLD</td>
<td>TNF-inhibitor: infliximab</td>
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<tr>
<td>Depression, suicidal</td>
<td>TNF-inhibitors: adalimumab, etanercept, infliximab</td>
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<td>ideation and behavior</td>
<td>IL-12/23 inhibitor: ustekinumab</td>
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<td>IL-17 inhibitor: brodalumab</td>
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<tr>
<td>Malignancy</td>
<td>TNF-inhibitor: adalimumab, etanercept</td>
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</tbody>
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Key: PsA = psoriatic arthritis; IBD = inflammatory bowel disease; NAFLD = non-alcoholic fatty liver disease; TNF = tumor necrosis factor; IL = interleukin; JAK = Janus Kinase
Table 2. Psoriasis comorbidities associated with psoriasis that have no known effect on the treatment of psoriasis with biologics.

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Description</th>
</tr>
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| Obstructive sleep apnea      | - The frequency of obstructive sleep apnea in psoriasis patients is 54.5% (18 out of 33 patients)\(^{37}\)  
  - Obstructive sleep apnea patients have greater risk of psoriasis. Within a 3-year follow-up period, 0.49% of obstructive sleep apnea patients developed psoriasis compared to the 0.22% of patients who developed psoriasis without the pre-existing obstructive sleep apnea.\(^{58}\)  
  - There is severity-dependent bidirectional association of psoriasis and sleep apnea and their increased risks for one another.\(^{59}\) |
| Sexual dysfunction           | - 40.8% of psoriasis patients self-reported that their sexual activity has declined since their psoriasis. These affected patients had more joint pain and higher depression scores.\(^{60}\)  
  - Psoriasis patients experience more sexual dysfunction compared to control group. No difference with or without depression (p = 0.004).\(^{51}\)  
  - Significantly higher prevalence of erectile dysfunction in psoriasis patients compared to patients without psoriasis (p = 0.046).\(^{62}\)  
  - Questionnaire: control group had 23.33% of patients with erectile dysfunction, whereas the group with mild psoriasis had 56.67% erectile dysfunction, and the group with severe psoriasis had 46.68% of subjects with erectile dysfunction\(^ {63}\) |
| COPD                         | - Pathogenesis is similar in that both diseases involve chronic inflammation. Higher IL-6 and CRP found in COPD\(^ {64}\)  
  - Prevalence of COPD in psoriasis patients is 5.7% compared to 3.6% in patients without psoriasis (p<0.001)\(^ {65}\) |
| ESRD                         | - Indicators of renal impairment higher in psoriasis patients: urinary albumin excretion rate and microalbuminuria\(^ {66}, {67}\)  
  - Psoriasis patients had a higher risk of developing ESRD (p < 0.001). p < 0.001 after adjusting for age, gender, household income, region, diabetes, hypertension, and dyslipidemia.\(^ {68}\)  
  - Duration of psoriasis and severity correlated positively with urinary albumin to creatine ratio\(^ {69}\) |
| Uveitis                      | - Types of uveitis in PsA: insidious, chronic, posterior, bilaterally active\(^ {70}\)  
  - 2% incidence of uveitis in psoriasis patients\(^ {71}\) |
| Parkinson’s disease          | - 1.78% of psoriasis patients were diagnosed with Parkinson’s disease during the 5 years they were followed, whereas the control cohort had only 0.98% of participants diagnosed (p < 0.001).\(^ {72}\) |

Key: COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; ESRD = end-stage renal disease; IL = interleukin; PsA = psoriatic arthritis