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The Psoriasis Decision Tree

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Abstract

Psoriasis, an inflammatory disorder of the skin, is associated with an increased risk of systemic diseases, such as psoriatic arthritis, psychiatric disorders, malignancy, and cardiometabolic and inflammatory bowel diseases. Careful consideration of the presence of these comorbidities should guide selection of appropriate therapy. The evolution of therapeutic targets for the treatment of psoriasis has significantly advanced available treatment options, potentially leading to uncertainty when selecting the optimal treatment for each patient. In this article, we review evidence-based guidelines for the use of psoriasis treatments in patients with distinct comorbidities, and group appropriate therapeutic options into a visual aid. An easy-to-use visual tool incorporating treatment options best suited for specific comorbidities can increase physicians' confidence when selecting the most appropriate treatment on an individualized basis.

Keywords: Psoriasis, comorbidities, multiple sclerosis, inflammatory bowel disease, depression, pregnancy, psoriatic arthritis, liver disease, kidney disease, biologics, secukinumab, ixekizumab, brodalumab, ustekinumab, guselkumab, tildrakizumab, risankizumab, methotrexate, cyclosporine, acitretin

Psoriasis is a chronic, inflammatory skin disorder known to affect 2 to 4 percent of adults in the United States.[1] The association between psoriasis and comorbid conditions, such as cardiometabolic, gastrointestinal, and kidney disorders, is well established.[2] In addition, malignancy, infection, inflammatory arthritis, and mood disorders are prevalent among patients with psoriasis.[2] The evolution of therapeutic targets for the treatment of psoriasis has significantly advanced available treatment options. Presently, there are 10 biologic medications approved by the United States Food and Drug Administration for use in the treatment of mild-to-moderate psoriasis, as well as several oral small-molecule and systemic therapies. With the increase in therapeutic options available, many dermatologists experience uncertainty when deciding which psoriasis therapy is appropriate to achieve optimal patient outcomes on an individualized basis. Here, we introduce the Psoriasis Decision Tree, a useful tool for navigating through the complicated sea of psoriasis treatments. The tree was developed as a visual aid to guide the busy clinician in selecting the most appropriate treatment for each individual patient. We reviewed select comorbidities associated with psoriasis and designated each branch individually, highlighting optimal treatment options using evidence-based guidelines. The recommendations made are not absolute, as therapeutic options should be considered on a case-by-case basis.

BIOLOGIC AGENTS

The decision-making tree for the selection of biologic agents for psoriasis is illustrated in Figure 1.

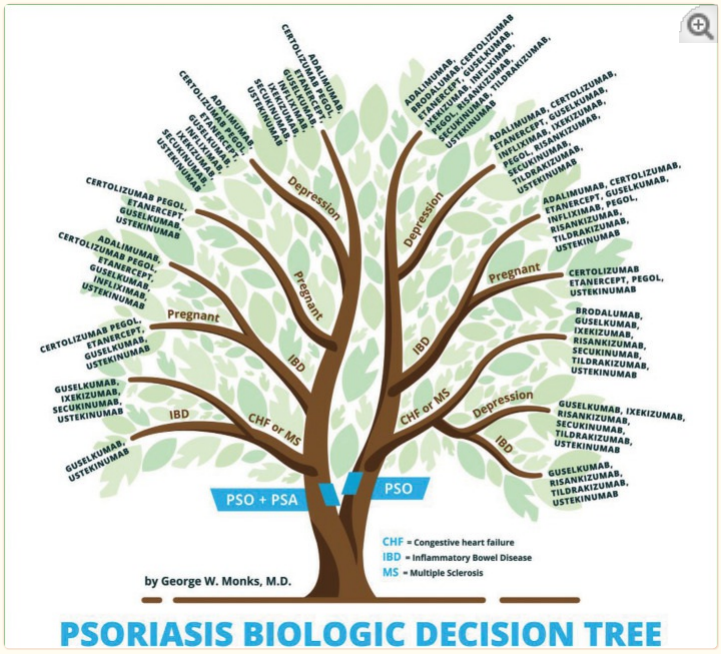

FIGURE 1.

Decision-making tree for the selection of biologic agents for psoriasis

Congestive heart failure. According to a nationwide cohort study, psoriasis was associated with a disease severity-dependent increased risk of new-onset heart failure.[3] The ATTACH trial evaluated the efficacy and safety of infliximab in patients with moderate-to-severe congestive heart failure (CHF). The combined risk of death from any cause or hospitalization for heart failure through 28 weeks was increased in patients receiving high doses (10mg/kg) of infliximab (hazard ratio: 2.84, 95% confidence interval: 1.01–7.97; p<0.043) relative to the placebo group.[4] In addition, there are multiple case reports demonstrating both new-onset heart failure and exacerbations after initiation of tumor necrosis factor (TNF) antagonist therapy.[5] Differently, a study with etanercept in patients with advanced heart failure resulted in a significant dose-dependent improvement in left ventricular structure and function.[6] Long-term safety data on both ustekinumab and secukinumab did not report any cases of heart failure.[7,8] Additional data are limited regarding the safety of other interleukin (IL)-23 and IL-17 blockers in patients with heart failure, although no cases have been reported in the trials.

Based on the evidence, ustekinumab and secukinumab are the first-line treatment options, followed by the other IL-17 and IL-23 blockers in patients with psoriasis with concomitant heart failure. TNF inhibitors should be avoided in patients with moderate-to-severe heart failure, but can be used with caution in mild disease.

Multiple sclerosis. Both psoriasis and multiple sclerosis are immune-mediated diseases of the body. Although the mechanism is unclear, a significant association has recently been observed in a retrospective cross-sectional study.[9] TNF inhibitor use has been associated with increased incidence of both exacerbations and new-onset multiple sclerosis (MS).[10,11] Multiple case reports and one Phase II study have reported no worsening neurologic disease after treatment with ustekinumab.[12,13] Although limited, there are data suggesting secukinumab and its IL-17 blockade in patients with psoriasis and MS is associated with a reduction in the number of lesions seen with magnetic resonance imaging.[14] The effect that IL-23 inhibitors have on patients with MS is yet to be studied.

Ustekinumab and secukinumab can be considered first-line treatment options, followed by the other IL-17 and IL-23 blockers, as no neurological adverse events have been reported. TNF inhibitors should be avoided completely.

Inflammatory bowel disease. Psoriasis is associated with both ulcerative colitis (UC) and Crohn's disease (CD), collectively referred to as inflammatory bowel disease (IBD).[15] A Danish nationwide cohort study reported both a psoriasis severity-dependent increased risk of CD and UC and an increased risk of psoriasis in patients with IBD.[16] TNF inhibitors are effective in the treatment of psoriasis and IBD.[17] Aside from being safe, etanercept demonstrated insufficient efficacy in the treatment of CD.[18] Long-term safety data suggest that infliximab is a safe treatment option for managing IBD.[19] It has also proved to be highly efficacious in the treatment of IBD, as evidenced by two key trials (ACCENT-1 and -2).[20,21] In a randomized, controlled trial (RCT), adalimumab induced remission with greater frequency than placebo in patients with active CD despite them previously being treated with infliximab or an intolerance to it.[22] Efficacy of certolizumab was demonstrated in a Phase III RCT where induction and maintenance therapy were associated with modest improvements in response rates relative to the placebo.[23] Ustekinumab has been approved for the treatment of CD based on favorable outcomes of three Phase III induction and maintenance trials (UNIT-1 and -2 and IM-UNIT1).[24]

In a proof-of-concept trial, secukinumab's blockade of IL-17 was both ineffective and led to greater rates of adverse events relative to the placebo.[25] A careful analysis of 10 Phase II and III clinical trials for secukinumab reported the exposure-adjusted incidence rates for both CD and UC to be 0.11 and 0.15, respectively.[26] Data from an integrated database of seven ixekizumab trials proposed that CD and UC cases were uncommon (<1%).[27] Only one case of IBD was reported during one of three Phase III trials for brodalumab in the treatment of plaque psoriasis (AMAGINE-1, -2, and -3).[28,29] Importantly, during a Phase II RCT evaluating brodalumab's efficacy in treating CD, 30 percent of patients exposed to brodalumab developed exacerbations, which led to it being contraindicated in CD.[30] In a short-term Phase II study, significantly more patients with CD achieved clinical remission with risankizumab relative to the placebo.[31]

Infliximab, adalimumab, certolizumab, and ustekinumab are indicated for the treatment of CD. Although safe, etanercept has limited efficacy. Secukinumab and ixekizumab can be used with caution. Brodalumab is contraindicated in CD. Risankizumab and IL-23 have demonstrated encouraging data, although more are needed.

Depression. Recent studies have reported that individuals with psoriasis are 2 to 3 times more likely to develop depression than the general population.[32,33] In addition, studies have shown that, if left untreated, depression in patients with psoriasis or psoriatic arthritis can lead to higher rates of suicidality and self-harm.[34,35] During the pivotal trials for etanercept, adalimumab, infliximab, and ustekinumab, depressive symptoms were decreased.[31,36] Similarly, Strober et al[37] found adalimumab to have the strongest association with a lower risk of developing depression when analyzing

data from patients in the Psoriasis Longitudinal Assessment and Registry (PSOLAR). Importantly, patients on ustekinumab and infliximab also trended toward a lower risk of depression but did not reach statistical significance.[37]

Strober et al[38] analyzed pooled data from 10 clinical studies of secukinumab and reported no elevated risk for depression, anxiety, or suicidality in patients with psoriasis. Similarly, ixekizumab therapy resulted in the remission of depression for approximately 40 percent of patients in an integrated analysis of three Phase III clinical studies.[39] The safety of brodalumab has been a controversial topic due to the suicidal ideation and behaviors (SIB) events observed in the brodalumab trials. In-depth analysis of the trials by Lebwohl et al[40] revealed no causal association between brodalumab therapy and SIB events. Although four completed suicides occurred during the studies and long-term follow-up, there was no increase in the rates of suicidal behavior or completed suicides in the brodalumab treatment group.[40] In a Phase III RCT (VOYAGE 2), guselkumab treatment was associated with greater improvements in symptoms of anxiety and depression in patients with psoriasis compared to the placebo and adalimumab.[41] An analysis of pivotal trials for tildrakizumab and rizankizumab revealed no adverse psychiatric events.[42,43]

Etanercept, adalimumab, infliximab, and ustekinumb reduce depressive symptoms in patients with psoriasis. No increased risk for depression has been reported for secukinumab or ixekizumab. Brodalumab should increase physicians' awareness of psychiatric comorbidities, but can be used with caution. Guselkumab appears to improve depressive symptoms. Risankizumab and tildrakizumab have not been shown to increase depression risk.

Pregnancy. Pregnancy generally improves psoriatic symptoms, yet some patients actually experience clinical deterioration.[44] Patients with mild psoriasis have the option of discontinuing treatment. However, in cases of moderate-to-severe psoriasis, continuation of therapy might sometimes be necessary.[45] Limited data exist on proper management of psoriasis in pregnant patients because of the ethical concerns of including this patient population in clinical trials and is limited to case reports and small case series, among others.[46]

A prospective comparator study suggested that TNF inhibitor treatment does not pose a major teratogenic risk in humans, although the conclusion was based on a relatively small number of pregnancies.[47] Differently, a large prospective multicenter cohort study concluded that TNF inhibitors might carry a risk of adverse pregnancy outcomes, as evidenced by a statistically significant increase in risk of major birth defects, preterm birth, and low birth weight compared to the placebo.[48] The use of etanercept in pregnancy has generally been well tolerated, as evidenced by multiple studies.[49,50] Contrarily, one study suggested an association between etanercept and VACTERL syndrome, although this has since been largely rejected.[51,52] Adalimumab has triggered no increase in the rate in miscarriage, malformations, or preterm birth, although data are limited to case reports and letters.[53,54] Recent data from the TREAT Safety Registry reported no increase in adverse pregnancy outcomes for patients being treated with infliximab.[55] Alarmingly, a case of neonatal death after being exposed to infliximab following an injection of the Bacillus Calmette-Guérin vaccine at the age of three months has been reported, although a study of pregnant women enrolled in Crohn's and Colitis Foundation PIANO registry found that routine vaccination in infants exposed to biologic therapy did not affect their ability to mount an immune response.[56,57] Certolizumab has been shown to cause minimal placental transfer from mother to infant due to its PEGylated structure and absence of an Fc portion, as highlighted by CRIB, a prospective pharmacokinetic study.[58] Additionally, an analysis of 339 pregnancies exposed to certolizumab suggested a lack of harmful effects on pregnancy outcomes.[59]

In a small cohort study of 10 pregnant patients with plaque psoriasis, ustekinumab exposure during conception and pregnancy was not associated with any adverse events.[60] Additionally, multiple case reports have been published where no adverse pregnancy outcomes occurred, with the exception of one report of a spontaneous abortion.[61–64] Data regarding exposure to IL-17 and IL-23 during pregnancy are limited. No cases have been reported in the literature.

Certolizumab pegol should be the first-line therapy used in pregnant patients or in those of childbearing potential; existing data do not point to any birth defects associated with etanercept, adalimumab, or infliximab. Ustekinumab is a safe and effective alternative to TNF inhibitors. There are limited data for IL-17 and -23 inhibitors.

Psoriatic arthritis. Estimates of the prevalence of patients with psoriasis with associated psoriatic arthritis (PsA) range from 6 to 39 percent.[65–67] As many as 15 percent of patients with psoriasis have undiagnosed PsA. Early intervention and treatment of PsA is critical to prevent deforming, irreversible joint damage.

The role of TNF inhibitors in the treatment of PsA has been the subject of multiple studies. In a Phase III RCT, etanercept was significantly more effective in improving multiple study measures compared to the placebo.[68] Adalimumab was shown to significantly improve skin and joint symptoms, inhibit structural changes on radiographs, and improve quality of life compared to the placebo.[69] Similarly, infliximab and certolizumab have both been shown to significantly improve signs and symptoms of PsA and currently have approval for treatment.[70,71]

Secukinumab and ixekizumab have both been shown to be superior to placebo in improving signs and symptoms of PsA throughout multiple Phase III RCTs.[72,73] Although brodalumab is not currently approved for treatment of PsA, there have been Phase II studies that suggest significant and rapid clinically meaningful improvement in active PsA at week 24.[74]

Significant improvement in joint disease and delayed radiographic progression was observed in ustekinumab's two Phase III RCTs for the treatment of PsA.[75] Guselkumab has demonstrated its superior efficacy in the treatment of PsA in both Phase II and III RCTs.[76–78] Risankizumab and tildrakizumab currently have promising Phase II data for PsA, but larger Phase III studies assessing their efficacy are still needed.

Etanercept, adalimumab, infliximab, certolizumab, secukinumab, ixekizumab, and guselkumab are indicated for the treatment of PsA. Brodalumab, although not approved, has shown efficacy in treatment. In patients with severe skin disease and mild arthritis, ustekinumab may be considered. Limited data exist for other IL-23 inhibitors.

ORAL AGENTS

The decision-making tree for the selection of oral agents for psoriasis is illustrated in Figure 2.

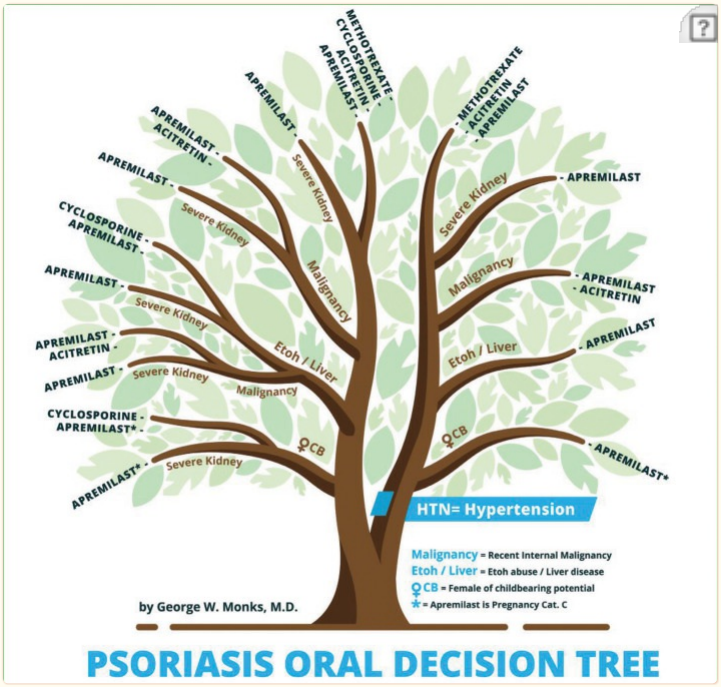

FIGURE 2.

Decision-making tree for the selection of oral agents for psoriasis

Hypertension/cardiac disease. Hypertension has been observed to be more prevalent in patients with psoriasis relative to those without. Several cohort studies have shown psoriasis is associated with an increased risk of incident hypertension.[79] Similarly, the pooled odds ratio for the association between psoriasis and hypertension was found to be significantly increased (1.58; 95% confidence interval: 1.42–1.76) in a large meta-analysis.[80]

The available evidence suggests that methotrexate might have beneficial effects on vascular homeostasis and blood pressure.[81] A five-year cohort study reported that treatment with methotrexate was associated with significantly lower rates of cardiometabolic events when compared with other therapies.[82] However, cyclosporine was found to increase the risk for developing hypertension, hyperlipidemia, and diabetes in a prospective cohort study, in addition to increasing the incidence of new-onset hypertension.[83,84] Hyperlipidemia has been associated with acitretin in patients with psoriasis.[83] Differently, several studies have shown a slowing in the progression of atherosclerotic disease in patients on acitretin therapy.[85,86] There was no increased risk of any major cardiovascular event in patients treated with apremilast when analyzing the safety data of two Phase III RCTs.[87]

Methotrexate can be used due to demonstrated cardioprotective benefits, while cyclosporine and acitretin should be avoided due to the elevated risk of hypertension and hyperlipidemia. Additional long-term data are required for apremilast.

Pregnancy. Most of the data on the adverse effects of treatment with methotrexate and cyclosporine during pregnancy have been obtained from patients undergoing therapy for cancer and organ transplant, respectively. Methotrexate is teratogenic and mutagenic, as well as an abortifactant. Therefore, it is contraindicated in pregnancy.[88] Although cyclosporine crosses the placental–blood barrier, there is no evidence of teratogenicity in humans, and it has been demonstrated to be a safe option for treating pregnant patients with psoriasis.[89–91] In a meta-analysis, the prevalence rate for malformations in cyclosporine-exposed live births was three percent, similar to in the general population.[92] In contrast, in a large retrospective case series, preterm deliveries and low birth weight were reported in cyclosporine-exposed individuals.[93] In-utero exposure to acitretin is associated with high risk of fetal malformations, involving craniofacial, thymic, cardiac and central nervous system structures.[94] Its use is therefore contraindicated in pregnant women. Although the risk of gastrointestinal upset may be a considerable nuisance for pregnant women already dealing with nausea and vomiting, there are no reported cases of apremilast-induced embryonal abnormalities.

Methotrexate and acitretin are contraindicated in pregnancy. Cyclosporine can be used if the potential benefit justifies the potential risk to the fetus. There are limited data for IL-17 and IL-23 inhibitors and apremilast.

Liver disease. Chronic liver diseases are a major cause of morbidity and mortality worldwide. The incidence of nonalcoholic fatty liver disease (NAFLD) has increased steadily in recent years.[95] Associations between psoriasis, NAFLD, chronic hepatitis, and alcoholic liver disease have been reported.[94] Methotrexate use in patients with preexisting liver pathology has been associated with an increased risk of methotrexate-induced hepatotoxicity across multiple studies.[97,98] For patients with psoriasis, an association with hepatotoxicity and liver injury is noted in the cyclosporine package insert. Although acitretin-induced hepatoxicity is rare, a study found that cholestasis might be more common than previously thought.[99] In a Phase III RCT, there were no hepatic adverse events in the apremilast-treated group.[100]

In the presence of preexisting liver disease, methotrexate, cyclosporine, and acitretin have potential disadvantages. Apremilast might be a suitable option.

Malignancy. The risk of malignancy attributable to psoriasis remains unclear. A meta-analysis evaluating the risk of malignancy in patients with psoriasis demonstrated and increased overall risk.[101] Specifically, patients with psoriasis were observed to have a persistently increased risk of lymphoma.[102] Interestingly, however, those being treated for severe psoriasis were at the greatest risk of developing malignancy.[103] Methotrexate's association with the development of malignancy in patients with psoriasis remains unclear, as studies have reported mixed results. Recent data showed that patients with psoriasis treated with low-dose methotrexate monotherapy were not at an increased risk for developing malignancy compared to the placebo.[104] Differently, a study found an elevated risk of lymphoma in patients treated with methotrexate for longer than 36 months relative to the general population (incidence rate ratio: 3.65; 95% confidence interval: 1.34–9.90).[105] In a prospective cohort study, there was a sixfold increase in the incidence of nonmelanoma skin malignancies, particularly squamous cell carcinoma, in patients with psoriasis treated with cyclosporine compared to in the general population. This was especially true in patients with a history of more than 200 psoralen and ultraviolet A radiation treatments.[106,107] With the exception of lymphoma, the incidence of internal malignancies in patients with psoriasis treated with cyclosporine was not significantly increased compared to the general population (1.7; 95% confidence interval: 0.7–3.5 vs. 1.2; 95% confidence interval: 0.7–1.9). In a nested cohort study, system retinoid use

significantly reduced the risk of developing squamous cell carcinoma in patients with psoriasis treated with psoralen and ultraviolet A radiation.[108] Similarly, acitretin therapy decreased the incidence of actinic keratoses in renal transplant recipients in a randomized trial.[109] Although a case of melanoma recurrence was reported during treatment with apremilast, no causality was established.

Methotrexate and cyclosporine should be avoided, while acitretin is protective against skin cancer. Limited data regarding apremilast.

Kidney disease. Moderate-to-severe psoriasis might be an independent risk factor for chronic kidney disease and end-stage renal disease.[2] Numerous studies have suggested an increased risk of death from kidney disease in patients with psoriasis.[110,111] Unsurprisingly, psoriasis was found to be a possible independent risk factor for chronic kidney disease as well as end-stage renal disease.[112] After six months of treatment, significant decreases in renal clearance and creatinine clearance were observed in patients treated with methotrexate in a pharmacokinetic testing study.[113] Nephrotoxicity is a well-known side-effect of cyclosporine use. Studies have demonstrated an increased risk of renal dysfunction in patients with psoriasis and concomitant renal disease.[17,114] The package insert advises against the use of acitretin in patients with kidney disease. Apremilast has been reported to exhibit changes in kidney function only in patients with severe renal disease. Conversely, no decrease in renal function was observed in those with mild renal impairment.[115]

Methotrexate should be used with caution in patients with renal disease. Cyclosporine and acitretin should be avoided in patients with significant renal impairment. Apremilast can be used, although dose reduction in patients with moderate-to-severe renal dysfunction is recommended.

CONCLUSION

In conclusion, when determining the optimal treatment for patients on an individual basis, the numerous comorbidities associated with psoriasis should be taken into consideration. A recent survey performed by the National Psoriasis Foundation concluded that undertreatment and nontreatment of psoriasis and PsA remain significant issues in the United States.[116] Another survey performed by Lebwohl et al[117] found physicians reporting the treatment and management of patients with psoriasis and/or PsA to be particularly complex and time-consuming, possibly contributing to undertreatment.Many factors must be considered when electing the optimal therapy for psoriasis patients.[118,119] The development of highly efficacious agents for treating psoriasis has transformed the way psoriasis is managed today. We hope our Psoriasis Decision Tree can help aid physicians in selecting the most appropriate treatment options in a time-efficient manner while taking into consideration the presence or absence of comorbidities, ultimately increasing their confidence when prescribing systemic therapies to a heterogeneous patient population.

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