The editors of JCAD are pleased to present this biannual column as a means to recognize select medical students, PhD candidates, and other young investigators in the field of dermatology for their efforts in scientific writing. We hope that the publication of their work encourages these and other emerging authors to continue their efforts in seeking new and better methods of diagnosis and treatments for patients in dermatology.

ABSTRACT

Psoriasis is an inflammatory skin disease that is associated with many comorbidities. Several psoriasis treatments approved by the United States Food and Drug Administration have been shown to have beneficial effects on these comorbidities, while others might lead to an exacerbation of these conditions. In this article, we review studies of psoriasis treatments and their level of evidence for use in co-occurring diseases. An awareness of the multifaceted effects of certain psoriasis medications can enable physicians to provide more personalized treatment to their most complicated patients.

KEYWORDS: Psoriasis, comorbidities, cardiovascular disease, metabolic syndrome, depression, psoriatic arthritis, ulcerative colitis, Crohn's disease, nephrotoxicity, liver disease, methotrexate, acitretin, cyclosporine, apremilast, etanercept, adalimumab, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab

REVIEW

Systemic Psoriasis Therapies and Comorbid Disease in Patients with Psoriasis: A Review of Potential Risks and Benefits

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Psoriasis is a chronic, immune-mediated, inflammatory, multisystem disease that affects about two percent of the adult population.[1] In addition to its effects on the skin, psoriasis is associated with several comorbidities, including cardiovascular disease (CVD), metabolic syndrome (defined as the combination of obesity, hypertriglyceridemia, reduced high-density lipoprotein [HDL], hypertension, and high fasting glucose), psoriatic arthritis (PsA), depression, Crohn's disease, ulcerative colitis, drug-induced nephrotoxicity, chronic kidney disease, and nonalcoholic fatty liver disease (NAFLD).[1–5] Therefore, patients with psoriasis often have higher mortality and hospitalization rates than those of the general population.[2]

Many psoriatic comorbidities have been linked with the chronic inflammatory nature of psoriasis as well as side effects from psoriasis medications.[6] For example, patients with psoriasis often have increased inflammatory mediators in the blood, such as high-sensitivity C-reactive protein, which are predictive of cardiovascular risk. Furthermore, patients

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with psoriasis often have dysregulation of inflammatory and lipid metabolism genes that have been shown to be related to atherosclerotic CVD.[1] In addition, certain psoriasis medications can increase the risk of CVD.[7]

PsA also shares specific immunopathologic and genetic pathways with psoriasis, providing a possible explanation for the frequent co-occurrence of these diseases. Specifically, patients with psoriasis often demonstrate the upregulation of tumor necrosis factor-alpha (TNF-α), a proinflammatory marker that is central to psoriasis pathogenesis. The upregulation of TNF-α results in the infiltration of T-cells and proliferation of keratinocytes in psoriatic plaques. TNF-α is often upregulated in the synovium of PsA patients. Polymorphisms in the TNF-α promoter have been shown to increase susceptibility of both psoriasis and PsA.[8]

Psoriasis-associated metabolic syndrome is also believed to be caused by increased levels of psoriasis proinflammatory factors, including TNF-α.[6] There is evidence suggesting that the psoriasis proinflammatory mediators TNF-α and interleukin (IL)-6 are linked with depression.[6] In addition, inflammatory bowel disease (IBD) most likely co-occurs in patients with psoriasis because it shares many genetic risks and inflammatory pathways with psoriasis.[2] As an example, patients with psoriasis and IBD often have genetic polymorphisms in IL-23R, which lead to changes in the IL-12/23 pathway.[4]

In addition, kidney disease is directly related to risk factors that are common in patients with psoriasis, such as hypertension, diabetes, obesity, dyslipidemia, and metabolic syndrome.[7] Since these risk factors put patients with psoriasis at higher risk for atherosclerosis, these individuals can become predisposed to developing chronic kidney disease and even end-stage renal disease.[5] Several psoriasis medications, such as methotrexate and cyclosporine, are nephrotoxic, thus increasing the likelihood of kidney disease or kidney function exacerbation.[7]

NAFLD is another disease associated with psoriasis and ranges from simple steatosis to cirrhosis.[9] It is thought that the chronic inflammation in psoriasis, caused by proinflammatory adipokines or skin-derived cytokines, can trigger NAFLD by increasing insulin resistance and leading to hepatic lipid accumulation.[10]

Systemic therapies that target psoriasis can reduce the risk of systemic comorbidities. These effects are possible because psoriasis shares many of the mechanisms of disease and inflammation with those of its comorbid conditions.[1] In this article, we review United States Food and Drug Administration (FDA)-approved systemic treatments available for psoriasis, with a focus on their multisystem benefits as well as possible exacerbating characteristics. Knowledge about these treatment options for patients with psoriatic comorbidities can help physicians better individualize care for their most complex patients.

METHODS

To investigate the systemic effects of FDA-approved psoriasis treatments on well-documented psoriasis comorbidities, we conducted a PubMed search of articles using the term *psoriasis* combined with each of the following: *systemic treatment, comorbidities, cardiovascular disease, metabolic syndrome, depression, psoriatic arthritis, ulcerative colitis, Crohn's disease, nephrotoxicity, liver disease, methotrexate, acitretin, cyclosporine, apremilast, etanercept, adalimumab, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab*, and *guselkumab*. For each article, the type of study and endpoints were noted. Phase III clinical trials and meta-analyses of randomized, controlled studies were preferentially chosen, but, if none existed, lower-evidence studies, such as cohort studies, case reports, and case-control studies were used. Some additional sources were found by looking at the references of the articles identified during the initial search.

We used the guidelines by Shekelle et al[11] to document the highest level of available evidence for each medication and indication. Level IA indicates evidence for meta-analysis of randomized, controlled trials (RCTs). Level IB represents evidence from at least one RCT. Level IIA represents evidence from at least one controlled study without randomization. Level IIB represents evidence from at least one other type of quasi-experimental study. Level III represents evidence from nonexperimental descriptive studies, including comparative studies, correlation studies, and case-control studies. Lastly, Level IV represents evidence from expert committee reports, opinions, or clinical experience of respected authorities.

NONBIOLOGIC SYSTEMIC MEDICATIONS

Nonbiologic systemic medications that are FDA-approved for psoriasis include methotrexate, acitretin, cyclosporine, and apremilast. A summary of these medications and their level of evidence for psoriatic comorbidities can be found in Table 1.

Methotrexate. Methotrexate is an antimetabolite that inhibits the synthesis of deoxyribonucleic acid (DNA) by blocking dihydrofolate reductase and thymidylate reductase.[12] Methotrexate has been shown to have several systemic effects on patients with psoriasis. For example, a large, five-year cohort study showed a decrease in the incidence of cerebrovascular disease and atherosclerosis in patients with psoriasis and rheumatoid arthritis taking a low cumulative dose of methotrexate.[13] Another large cohort study showed that patients with severe psoriasis who were treated with methotrexate had a lower risk of cardiovascular death, myocardial infarction (MI), and stroke as compared to patients treated with topicals, phototherapy, and climate therapy.[14] In contrast, a retrospective study showed that methotrexate does not significantly improve metabolic syndrome in patients with PsA.[15] Another study associated methotrexate treatment with an increase in triglycerides and a decrease in HDL in patients with psoriasis.[16] One meta-analysis showed methotrexate's efficacy in treating PsA,[17] while another demonstrated its benefit in maintaining remission from Crohn's disease.[18] However, a different meta-analysis revealed no benefit in inducing remission from ulcerative colitis relative to placebo.[19] Methotrexate has also been shown to lead to renal damage and even acute renal failure; therefore, patients should be well hydrated and monitored for drug-drug interactions and creatinine levels while taking methotrexate.[20] Methotrexate has also been shown to decrease renal and creatinine clearance, and thus should be used with caution in patients with renal disease.[21] Patients with NAFLD or any chronic liver disease are at an increased risk for methotrexate-induced hepatotoxicity and hepatic fibrosis.[22] A retrospective case series showed that preexisting liver pathology in patients with psoriasis might be a risk factor for severe hepatotoxicity.[23] In this study, 62.5 percent of the patients with preexisting periportal fibrosis progressed to bridging fibrosis or cirrhosis upon methotrexate treatment. Due to the potential for

TABLE 1. FDA-approved non-biologic medications for psoriasis and their level of evidence for psoriatic comorbidities

MEDICATION	VASCULAR/ CARDIOVASCULAR	METABOLIC SYNDROME/ DIABETES	PSORIATIC ARTHRITIS EFFECTS (ACR 20)	DEPRESSION*	CROHN'S DISEASE	ULCERATIVE COLITIS	DRUG-INDUCED NEPHROTOXICITY/ RENAL DISEASE	NAFLD OR ANY CHRONIC LIVER DISEASE
Methotrexate	Reduced CVD, cerebrovascular disease, and atherosclerosis incidence; level III;[13] decreased risk of cardiovascular death, MI, and stroke; level III[14]	No changes in metabolic syndrome distribution; level III;[15] HDL decreased and triglycerides increased; level III[16]	Improved PsA; level IA[17]	**	Maintains remission; level IA[18]	No benefit on remission; level IA[19]	Decreases renal and creatinine clearance; level III[21]	Higher risk of progression to bridging fibrosis or cirrhosis in patients with preexisting liver disease; level IV;[23] contraindicated in the presence of preexisting chronic liver disease[20]
Acitretin	Effect on CVD in humans is unclear; level III[27]	Increased risk of hypercholesterolemia, hypertriglyceridemia; level III;[27] associated with hyperlipidemia; level III[27]	**	**	**	**	Contraindicated in patients with kidney disease[28]	Increased liver enzymes, but did not show hepatotoxicity on liver biopsy; level III;[30] hepatotoxicity is rare; level III;[31] should be avoided in NAFLD due to hyperlipidemia[32]
Cyclosporine	Did not reduce CVD; level III[14]	Increased triglyceride levels and risks of hypercholesterolemia and diabetes; level III;[27] provoked new-onset hypertension; level III[34]	Improved PsA; level IA[17]	**	High doses resulted in clinical improvements; level IA[35]	Moderate efficacy; level IA[36]	Increased risk of renal dysfunction in patients with preexisting kidney disease; level III[38]	Associated with hepatotoxicity and liver injury in some cases[33]
Apremilast	No increased risk of MACE for short-term treatment, but longer-term studies are needed; level IA[40]	**	Improved PsA; level IA;[41] FDA-approved[4]	**	**	**	Patients with severe renal impairment had changes in renal elimination; dosage reduction is needed in these patients; level III[42]	No liver-related serious adverse events; level IB[43]

CVD: cardiovascular disease; FDA: Food and Drug Administration; HDL: high-density lipoprotein; MACE: major adverse cardiovascular effects; NAFLD: nonalcoholic fatty liver disease; MI: myocardial infarction; PsA: psoriatic arthritis
*HADS, HAMS, BDI, and ZDS are different types of depression rating scales
**These medications were either not studied in clinical trials for the noted comorbidity or no significant studies were found during our search

acute and chronic hepatotoxicity, the package insert cautions against use of methotrexate in the presence of preexisting chronic liver disease.[20]

Acitretin. Acitretin is an oral retinoid that is approved for psoriasis treatment.[24] In addition to its effectiveness in psoriasis, several studies in both humans and animals have shown that retinoids such as acitretin slow atherosclerotic disease progression.[25,26] However, a cohort study revealed that, in a subset of patients with psoriasis, acitretin was associated with an increased risk of hyperlipidemia.[27] Therefore, these patients should have regular lipid screenings and should be treated for hyperlipidemia to avoid increased CVD risk. More studies are needed to determine the effect of acitretin on CVD risk.[25] Dermatologists should use caution when prescribing acitretin to patients with obesity and/or high blood lipid levels.[28,29] Acitretin is considered ineffective for PsA, and the package insert cautions against use in patients with kidney disease.[28] Regarding hepatotoxicity, a study linked acitretin with transaminitis, but there was no evidence of hepatotoxicity in biopsies after two years of treatment.[30] Furthermore, acitretin rarely results in severe hepatotoxic reactions (0.26%).[31] However, since acitretin can cause hyperlipidemia, it should be avoided in patients with psoriasis and NAFLD.[32]

Cyclosporine. Cyclosporine is an immunosuppressive medication that is approved for psoriasis and has both positive and negative effects on certain psoriatic comorbidities.[33] In a nationwide cohort study, cyclosporine failed to reduce cardiovascular events in patients with psoriasis.[14] Another cohort study showed an association with increased triglyceride levels, increased risk of hypercholesterolemia (odds ratio: 1.34), and increased relative risk for developing arterial hypertension and diabetes (odds ratios: 3.31 and 2.88, respectively) in patients with psoriasis.[27] A separate study found that 12 percent of patients with psoriasis treated with cyclosporine developed new-onset hypertension.[34] It is therefore advised that cyclosporine be used only for a short duration, with alternative medications started once the patient's skin has improved.[25]

A meta-analysis demonstrated that cyclosporine was effective in the treatment of PsA.[17] One meta-analysis showed that high doses or cyclosporine resulted in clinical

improvements in Crohn's disease, and another showed moderate efficacy of cyclosporine for ulcerative colitis.[35,36] Cyclosporine should be avoided in patients with renal abnormalities due to nephrotoxicity.[37] A recent study reported that cyclosporine increased the risk of renal dysfunction in patients with psoriasis and preexisting kidney disease.[38] According to expert opinion, the length of treatment with cyclosporine correlates with nephrotoxicity. Intermittent treatment with 12-week courses decreases nephrotoxic risk when compared to continuous or long-term therapy.[37] Additionally, the package insert notes associations with hepatotoxicity and liver injury in some cases, especially in patients with psoriasis and underlying comorbidities.[33] Specifically, since cyclosporine increases lipid levels, it can potentially exacerbate NAFLD.[32]

Apremilast. Apremilast is an oral phosphodiesterase-4 inhibitor approved for use in patients with psoriasis and PsA.[39] It has also been shown to be generally safe in patients with psoriasis and certain comorbidities. A safety analysis that was pooled from two Phase III RCTs showed that patients with psoriasis treated with apremilast for up to 156 weeks did not demonstrate an increased risk of major adverse cardiovascular effects (MACE).[40] However, additional long-term studies are needed to evaluate the definitive effects on cardiovascular risk reduction in patients with psoriasis.[25] A meta-analysis showed that apremilast is highly effective in treating PsA.[41] In regards to kidney disease, one study reported that patients with mild-to-moderate renal impairment did not exhibit changes in renal elimination upon apremilast treatment, while those with severe renal impairment did; therefore, dose reduction is recommended in patients with severe renal dysfunction.[42] In a Phase III RCT in patients with psoriasis, serum alanine transaminases (ALTs) were elevated three times the upper limit of normal in 0.2 percent of the apremilast group and 0.4 percent of the placebo, and there were no liver-related serious adverse events. Therefore, apremilast might be suitable for patients with psoriasis and comorbid NAFLD.[43]

TNF-α INHIBITORS

Etanercept, adalimumab, infliximab, and certolizumab pegol are TNF-α inhibitors that are FDA-approved for psoriasis and PsA. In addition to these indications, adalimumab and infliximab are approved for Crohn's disease and ulcerative colitis, while certolizumab pegol is approved for Crohn's disease.[4,44] However, with regard to cardiovascular comorbidities, it remains unclear as to whether TNF-α inhibitors significantly reduce the risk of CVD. Some studies have associated TNF-α inhibitors with a decrease in the risks of MI and CVD in patients with psoriasis.[25,45] In comparison, other studies indicate that TNF-α inhibitors cause no change in MACE.[46] There is conflicting evidence for individual TNF-α inhibitors, suggesting that additional studies are needed before firm conclusions can be made regarding effects on the cardiovascular system. A summary of these TNF-α inhibitors and their level of evidence for psoriatic comorbidities can be found in Table 2.

Etanercept. There are mixed reports on the effects of etanercept on the cardiovascular system. A retrospective cohort study showed that etanercept decreased the risk of MI, compared to topical agents in patients with psoriasis.[47] However, a meta-analysis showed no change in the risk of MACE relative to placebo.[46] A retrospective study reported that etanercept improved metabolic syndrome components (waist circumference, triglycerides, HDL, and glucose) in patients with PsA.[15] In addition, most studies report that etanercept improves PsA.[48] However, etanercept does not appear to be effective in treating Crohn's disease.[49] A large retrospective study found that etanercept can actually induce or worsen IBD in some patients.[50] Therefore, physicians should be careful when prescribing etanercept to patients with psoriasis and comorbid IBD.[4] Etanercept might also help with depression. A Phase III RCT showed that patients with psoriasis who were treated with etanercept had improvements in both depressive symptoms and fatigue as shown on the Hamilton Depression Rating Scale (HAM-D) and Beck's depression inventory (BDI).[51] Additionally, a study showed that etanercept treatment for six months did not affect the glomerular filtration rate in patients with psoriasis.[52] Another study comparing etanercept to phototherapy in patients with psoriasis, NAFLD, and metabolic syndrome found significant reductions ($p<0.05$) in aspartate transaminase to alanine aminotransferase ratio (AST/ALT) and significant increases in insulin sensitivity after 24 weeks of treatment. As insulin resistance is directly correlated with hepatic fibrosis, this study highlights that etanercept seems to be more effective in reducing the risk of hepatic fibrosis than psoralen and ultraviolet A (PUVA) light therapy in patients with psoriasis and NAFLD.[53]

Adalimumab. There are conflicting findings on the effects of adalimumab on the cardiovascular system. A meta-analysis reported that adalimumab does not appear to cause a change in the risk of MACE.[46] Another study showed no difference in vascular inflammation in the carotids of patients with psoriasis after 52-week treatment with adalimumab.[54] However, observational studies have shown reductions in MIs in patients treated with TNF-α inhibitors such as adalimumab. Therefore, further studies are needed to definitively conclude the effect of adalimumab on heart disease in patients with psoriasis.[55]

A retrospective study showed that adalimumab improved metabolic syndrome components in PsA patients.[15] Meta-analyses have also shown that adalimumab is effective in both PsA and Crohn's disease.[48,56] Furthermore, a meta-analysis demonstrated that adalimumab has a moderate efficacy in ulcerative colitis, but that biologics, such as infliximab, might be more effective.[57] With regard to depression, an RCT in patients with psoriasis treated with adalimumab showed a significant reduction in depression symptoms, as measured by the Zung Self-rating Depression Scale (ZDS) ($p<0.001$).[58] Furthermore, another study reported that adalimumab and other TNF-α inhibitors did not have a negative effect on renal function in patients with kidney disease.[59] A retrospective investigation indicated that, in patients with psoriasis and liver disease who were treated with adalimumab for five years, including three patients with NAFLD, none had progression of liver disease.[60]

Infliximab. A meta-analysis found no change in the risk of MACE in patients with psoriasis after treatment with infliximab compared to placebo.[46] However, a pretest–post-test study revealed that infliximab increased body mass index (BMI), as well as HDL and leptin levels, suggesting that lipid profiles and weight should be monitored in patients receiving this treatment.[61] A meta-analysis showed efficacy in patients with obesity, as infliximab response is independent of BMI, unlike response with other biologics.[62] Infliximab has been found to benefit patients

TABLE 2. FDA-approved TNF-α inhibitors for psoriasis and their level of evidence for psoriatic comorbidities

MEDICATION	VASCULAR/ CARDIOVASCULAR	METABOLIC SYNDROME/ DIABETES	PSORIATIC ARTHRITIS EFFECTS (ACR 20)	DEPRESSION*	CROHN'S DISEASE	ULCERATIVE COLITIS	DRUG-INDUCED NEPHROTOXICITY/ RENAL DISEASE	NAFLD OR ANY CHRONIC LIVER DISEASE
Etanercept	No change in risk of MACE; level IA;[46] cohort study showed reduction in MI risk, further studies are needed[47]	Improvement in metabolic syndrome; level III[15]	Improved psoriatic arthritis; level IA;[48] FDA-approved[4]	Decreased depression symptoms and fatigue; level IIB[51]	No efficacy; level IB;[49] potential risk of worsening/induction of Crohn's disease; level III[50]	Potential risk of worsening/ induction of ulcerative colitis; level III[50]	Treatment for six months did not affect the glomerular filtration rate; level III[52]	Reduces AST/ALT ratio and lowers risk for hepatic fibrosis; level III[53]
Adalimumab	No change in risk of MACE of RCTs; level IA;[46]observational studies of large registries show favorable effects, further studies are needed[55]	Improvement in metabolic syndrome; level III[15]	Improved PsA; level IA;[48] FDA-approved[4]	Reduced depression symptoms; level IB[58]	Maintains remission; level IA;[56] FDA-approved[4]	Moderate efficacy; level IA;[57] FDA-approved[4]	No negative effects on renal function in patients with kidney disease; level III[59]	No progression of liver disease in patients with preexisting liver pathology; level III[60]
Infliximab	No change in risk of MACE; level IA[46]	Increases BMI, HDL, and leptin levels; level III;[61] Infliximab response was same regardless of patients BMI; level IA[62]	Improved PsA; level IA;[48] FDA-approved[4]	Stabilized or improved manifestations of psychiatric comorbidities; level IV[63]	Induced and maintained remission; level IA;[56] FDA-approved[4]	Induced and maintained remission; level IA;[57] FDA-approved[4]	No negative effects on renal function in patients with kidney disease; level III[59]	Persistent ALT elevations after six infusions of infliximab and chronic hepatitis and mild fibrosis on biopsy; level IV[65]
Certolizumab pegol	Risk of MACE with certolizumab pegol did not increase with increased exposure duration; level IA[66]	**	Improved signs and symptoms of PsA; level IB;[67] FDA-approved[44]	**	Modestly improved response rates, but did not significantly improve remission rates; level IB;[68] FDA-approved[44]	Currently being investigated in a Phase II clinical trial[69]	**	**

ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; FDA: United States Food and Drug Administration; HDL: high-density lipoprotein; MACE: major adverse cardiovascular effects; NAFLD: nonalcoholic fatty liver disease; MI: myocardial infarction; PsA: psoriatic arthritis
*HADS, HAMS, BDI, and ZDS are different types of depression rating scales
**These medications were either not studied in clinical trials for the noted comorbidity or no significant studies were found during our search

with PsA, ulcerative colitis, and Crohn's disease.[4] Meta-analyses have demonstrated that infliximab improves PsA, as well as reduces and maintains remission of Crohn's disease and ulcerative colitis.[48,56,57]

Infliximab can also have beneficial effects on psychiatric disorders, although the level of evidence is weak. A case series reported three cases of psoriasis and comorbid depression in which infliximab was effective in stabilizing or symptoms of depression.[63]

A separate study showed that infliximab and other TNF-α inhibitors do not have a negative effect on renal function in patients with kidney disease.[59] Furthermore, severe liver toxicity is rare in infliximab treatment.[64] A case report of a 53-year old patient with PsA revealed persistent ALT elevations after six infusions of infliximab, as well as chronic hepatitis and mild fibrosis on biopsy.[65]

Certolizumab pegol. A meta-analysis conducted in patients with rheumatoid arthritis showed that the risk of MACE with certolizumab pegol treatment did not increase with increased drug exposure duration.[66] A Phase III RCT in patients with PsA showed improvements in symptoms of PsA upon certolizumab pegol treatment.[67] Another Phase III RCT conducted in patients with Crohn's disease showed modest improvement in response rates, but no significant improvement in remission rates upon certolizumab pegol treatment.[68] Certolizumab pegol is currently being investigated in a Phase II clinical trial for its potential use in patients with ulcerative colitis.[69]

OTHER BIOLOGIC MEDICATIONS

Other biologic medications that are FDA-approved for psoriasis include ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, and tildrakizumab. A summary of these medications and their level of evidence for psoriatic comorbidities can be found in Table 3.

Ustekinumab. Ustekinumab is an IL-12/23 inhibitor that offers systemic effects that can be beneficial to patients with psoriasis and certain comorbidities.[70] The drug has also been FDA-approved for use in patients with PsA, Crohn's disease, and ulcerative colitis.[4] However, ustekinumab's effect on the vascular system is unclear. A meta-analysis showed that patients with psoriasis treated with ustekinumab had no change in the risk of MACE relative to placebo (Table 3).[46] Conversely, a recent RCT indicated that ustekinumab might improve myocardial and coronary function in patients with psoriasis,[71] while a cohort study reported that its use increased fasting sugar and triglyceride levels.[72] However, a separate study reported

TABLE 3. Other FDA-approved biologic medications for psoriasis and their level of evidence for psoriatic comorbidities

MEDICATION	VASCULAR/ CARDIOVASCULAR	METABOLIC SYNDROME/ DIABETES	PSORIATIC ARTHRITIS EFFECTS (ACR 20)	DEPRESSION*	CROHN'S DISEASE	ULCERATIVE COLITIS	DRUG-INDUCED NEPHROTOXICITY/ RENAL DISEASE	NAFLD/ANY CHRONIC LIVER DISEASE
Ustekinumab	No change in risk of MACE; level IA;[46] improved myocardial and coronary function; level IB;[71] more studies needed to determine whether long-term use is beneficial or detrimental[25]	Increased fasting sugar and triglyceride levels; level III;[72] does not increase BMI; level III[73]	Improved PsA; level IA;[41] FDA-approved[4]	Reduced depression and anxiety; level IB[77]	Strong efficacy; level IB;[74] FDA-approved[4]	**	Good clinical response and stable renal function in one patient with psoriasis on hemodialysis; level IV[79]	Safe for patients with preexisting liver disease; level III[80]
Secukinumab	No change in risk of MACE; level IA[46]	Risk of hypercholesterolemia[81]	Improved PsA; level IA;[41] FDA-approved[4]	**	No efficacy and potential risk of exacerbation; level IB[82]	**	**	**
Ixekizumab	No change in risk of MACE; level IA[46]	No effect on total cholesterol, HDL, triglyceride, fasting glucose level, or blood pressure at 60 weeks; level IA[83]	Improved PsA; level IB;[84] FDA-approved[94]	**	**	**	**	**
Brodalumab	No increased cardiovascular risk; level IB[85]	**	PsA; level IB[86,87]	Increased risk of suicide in patients with history of depression or suicidality;[88] no causality between brodalumab and suicidality; level IA[89]	Exacerbated Crohn's disease; level IB[90]	**	**	**
Guselkumab	No increased risk of MACE; level IB[91]	**	**	**	**	**	**	**
Tildrakizumab	**	**	**	**	No new cases or exacerbation of Crohn's disease; level IA[93]	No new cases or exacerbation of ulcerative colitis; level IA[93]	**	**

ALT: alanine transaminase; AST: aspartate transaminase; BMI: body mass index; FDA: United States Food and Drug Administration; HDL: high-density lipoprotein; MACE: major adverse cardiovascular effects; NAFLD: nonalcoholic fatty liver disease
*HADS, HAMS, BDI, and ZDS are different types of depression rating scales
**These medications were either not studied in clinical trials for the noted comorbidity or no significant studies were found during our search

that ustekinumab did not increase BMI in patients with chronic plaque psoriasis.[73] These conflicting findings demonstrate the need for further research investigating ustekinumab's effects on the cardiovascular system.[25]

A meta-analysis of RCTs showed that ustekinumab is effective in PsA.[41] Other RCTs have also reported efficacy of ustekinumab use in Crohn's disease.[74–76] Ustekinumab has also been demonstrated to help with depression and anxiety in patients with psoriasis. A Phase III RCT that investigated ustekinumab treatment in patients with psoriasis reported significant reductions in the Hospital Anxiety and Depression Scale scores ($p<0.001$ for both depression and anxiety).[77] According to the package insert, nephrotoxicity has not been reported or formally studied for ustekinumab.[78] A recent case report described a patient with psoriasis and end-stage renal disease who was on hemodialysis that showed a good clinical response and renal stabilization after ustekinumab treatment.[79] Furthermore, a retrospective study reported that ustekinumab-induced liver injury was rare and mild in patients with psoriasis, and that ustekinumab is safe for patients with psoriasis and preexisting liver disease.[80]

Secukinumab. Secukinumab is an IL-17A inhibitor that is approved for psoriasis and PsA,[4] and has been shown to have variable effects on different comorbidities in patients with psoriasis. For example, a meta-analysis showed no difference in the risk of MACE in patients with psoriasis treated with secukinumab compared to placebo.[46] On the other hand, according to the package insert, clinical trials have reported that a higher percent of patients on secukinumab developed hypercholesterolemia compared to those on placebo.[81] Another meta-analysis suggested that secukinumab is effective in treating PsA.[41] Importantly, a Phase II clinical

trial found that secukinumab exacerbated Crohn's disease.[82] Therefore, secukinumab should be prescribed with caution in patients with psoriasis and comorbid IBD.

Ixekizumab. Ixekizumab is another IL-17A inhibitor approved for psoriasis and PsA treatment.[4] A meta-analysis showed no difference in the risk of MACE in patients with psoriasis treated with ixekizumab compared to placebo.[46] Similarly, a meta-analysis showed no significant changes between patients with psoriasis treated with ixekizumab or placebo for total cholesterol, HDL, triglyceride, fasting glucose levels or for blood pressure at 60 weeks.[83] However, a Phase III clinical trial suggests that ixekizumab is effective for treating PsA.[84]

Brodalumab. Brodalumab, a human immunoglobulin (Ig) G2 monoclonal antibody, inhibits the human IL-17 receptor A and is approved for use in patients psoriasis.[4] Regarding psoriatic comorbidities, brodalumab was studied in Phase II and III trials and did not appear to increase cardiovascular risk.[85] In addition, multiple Phase II trials have found that brodalumab is effective in patients with PsA.[86,87] On the other hand, according to the package insert, brodalumab has a suicide and depression warning and should be carefully considered before prescribing to patients with a history of suicidality or depression.[88] However, a recent study that analyzed several psoriasis clinical trials did not find causality between suicide and brodalumab treatment.[89] Thus, more research is needed regarding the safety of brodalumab use in patients with psoriasis and comorbid depression. In addition, a Phase II trial that was conducted for treatment of Crohn's disease with brodalumab was terminated early because it exacerbated the disease.[90] Therefore, brodalumab is contraindicated in patients with Crohn's disease.

Guselkumab. Guselkumab is a human IgG1 monoclonal antibody that inhibits the p19 subunit of IL-23, and is approved for use in patients with psoriasis.[4] Phase III trials have shown that guselkumab does not appear to be associated with an increased risk of MACE as compared with placebo.[91]

Tildrakizumab. Tildrakizumab is a humanized IgG1 κ monoclonal antibody that inhibits IL-23 p19 and has been recently gained FDA approval for use in psoriasis.[92] A recent analysis of three large clinical trials reported that no new cases of IBD or exacerbation of IBD occurred in patients with psoriasis who were taking tildrakizumab.[93]

CONCLUSION

Psoriasis is associated with numerous comorbidities, and selecting the proper treatment can be challenging. Some medications can help with one comorbidity and exacerbate another. Studies of psoriasis medications should continue to explore the effects of study drugs on comorbid disease among patients with psoriasis to help minimize the number of medications required for these patients and to help ensure the application of more personalized therapies that avoid adverse events.

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