

Association between the systemic treatment of psoriasis and cardiovascular risk

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Psoriasis is a chronic inflammatory disease that involves complex pathogenic interactions between the innate and adaptive immune systems, affecting approximately 2% of the population. In patients with psoriasis, the incidence of several important diseases is reportedly higher than that observed in the general population. Among them, cardiovascular diseases (CVDs) are the most common cause of morbidity and mortality in patients with psoriasis. Hence, effective and safe treatments are critical in lowering cardiovascular risk in this patient group.

Systemic treatment of psoriasis and major adverse cardiovascular events (MACE)

It has been identified that psoriasis is an independent risk factor for CVDs and is associated with an increased risk of MACE (a composite endpoint of myocardial infarction (MI), cerebrovascular accident, or cardiovascular death). Although the risk of MACE in patients with mild psoriasis remains relatively low, it could increase depending on disease severity and psoriasis duration.^[1] The influence of various systemic psoriasis treatments on altering cardiovascular risks remains uncertain.

Reportedly, the short-term risk of MACE did not substantially differ in patients with psoriasis treated with biologics when compared with a placebo. The impact of systemic psoriasis treatments on cardiovascular risks mainly depends on long-term effects.

It has been reported that tumor necrosis factor-alpha (TNF- α) inhibitors and methotrexate (MTX) could reduce the risk of MACE in patients with psoriasis, whereas acitretin failed to demonstrate a notable impact. Cyclosporine A (CsA) is known to cause myocardial damage by

generating reactive oxygen species. In the case of interleukin (IL)-12/23 inhibitors, ustekinumab reported some concerns of increased MACE during the initial analysis. However, in recent years, several studies have identified no increased or even a decreased risk of MACE with long-term ustekinumab therapy. Notably, another IL-12/23 inhibitor, briakinumab, increased the risk of MACE in 5 studies, resulting in the discontinuation of all briakinumab trials in 2011.

Tofacitinib, a Janus kinase inhibitor, has been approved for use in psoriasis and is associated with a low incidence of MACE.^[2,3] This lowered cardiovascular risk could be attributed to the inhibition of inflammation by reducing oxidized low-density lipoprotein (LDL)-mediated cytotoxicity and improving endothelial viability. In the case of IL-23 and IL-17 inhibitors, no increase in the rate of MACE was observed in patients with psoriasis treated with tildrakizumab, guselkumab, risankizumab, secukinumab, or ixekizumab. In an established mouse model of psoriasis, IL-23 and IL-17 inhibitors improved skin inflammation, decreased the number of circulating neutrophils, and increased thrombosis clotting times, suggesting that they might improve CVD. Further investigations are warranted to confirm whether these agents possess cardioprotective effects.

In patients treated with MTX and TNF- α inhibitors, the incidence of MACE was compared among four studies, revealing controversial results. Two studies reported that TNF- α inhibitors presented a greater cardioprotective effect, whereas the other two studies reported that MTX and TNF- α inhibitors demonstrated similar effects. Three clinical trials revealed that MACE rates did not signifi-

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cantly differ in patients with psoriasis treated with ustekinumab and TNF- α inhibitors, guselkumab and adalimumab, secukinumab, and etanercept, respectively.^[4]

In terms of the mechanism of action, tofacitinib and etanercept predominantly reduce inflammatory and cardiovascular proteins such as IL-6, chemokine (C-C motif) ligand 20, and C-X-C motif chemokine ligand 10, with IL-17A significantly reduced only in responders to either treatment, which was reported as a potential mechanistic link between psoriasis and CVDs. This could explain why only responders to TNF- α inhibitor therapy demonstrated a reduced MI rate when compared with non-responders. Based on current evidence, the ranking of cardioprotective effects among different anti-psoriatic therapies remains unclear. However, if systemic therapy is considered within the setting of CVDs or risks, TNF- α inhibitors and MTX demonstrate the best evidence of beneficial effects.

It is believed that anti-psoriatic treatments can block the common pathway of CVDs and psoriasis or reduce circulating inflammatory and other proteins associated with cardiovascular risks. However, the specific mechanism has not been comprehensively elucidated.

Systemic treatment of psoriasis and cardiovascular burden

It is speculated that psoriasis may induce systemic inflammation, endothelial dysfunction, and atherosclerosis, which are associated with higher incidences of ischemic heart disease, peripheral vascular disease, and atrial fibrillation in psoriasis. Currently, there is no consensus on whether systemic psoriasis treatment can improve or worsen arterial plaques, vascular function, and vascular inflammation.

Systemic treatment of psoriasis was associated with a reduced non-calcified coronary plaque burden, suggesting that modulating remote sites of inflammation may translate into a reduced risk of coronary artery disease.^[5] Conversely, a significant progression in carotid intima-media thickness (IMT) was observed in patients treated with TNF- α inhibitors, revealing the occurrence of arterial remodeling in patients with psoriasis despite improvement in clinical status. In a group of patients without initial calcified atherosclerotic plaques and treated with TNF- α inhibitors, a significant decrease in IMT was observed, whereas the other group with initial plaques showed an increasing IMT tendency, suggesting that TNF- α inhibitors could decrease IMT in patients with psoriasis specifically presenting no irreversible atherosclerotic plaques. Additionally, tofacitinib reportedly decreased carotid IMT.

The effects of MTX, IL-17, and IL-12/23 inhibitors on IMT need to be further investigated to validate previous findings. No significant changes in IMT values were observed in patients with psoriasis treated with biologics targeting the IL-23/IL-17 axis (ustekinumab, secukinumab, ixekizumab), indicating that anti-IL-23/IL-17 might have a neutral effect on atherosclerosis. However, another study revealed that the IMT decreased significantly after treatment with anti-IL-12/23 and MTX in patients with moderate and severe psoriasis.^[6]

Additionally, IL-17 inhibitors reportedly demonstrate a beneficial effect on CVD risk by improving endothelial and coronary microcirculatory functions; however, whether TNF- α inhibitors demonstrate these effects remains controversial.

The impact of traditional psoriasis treatments on vascular inflammation remains unclear, and the effects of biologics are controversial. Reportedly, biologic therapy is associated with a significant decrease in the fat attenuation index (FAI), a novel imaging biomarker that assesses coronary inflammation. Associations with FAI were consistent among patients receiving different biologic agents, including anti-TNF- α and anti-IL-12/23, or anti-IL-17 therapy.^[7] Furthermore, ustekinumab treatment was significantly associated with decreased systemic and vascular inflammation measured via ¹⁸F-fluorodeoxyglucose positron emission tomography-computed tomography (¹⁸F-FDG PET/CT) in patients with psoriasis.^[8] Conversely, three studies showed no difference in vascular inflammation measured using ¹⁸F-FDG PET/CT in patients treated with TNF- α inhibitors, ustekinumab, and secukinumab, respectively.^[9,10] Tofacitinib effectively suppressed tissue-resident memory T cells and inhibited core vasculogenic effector pathways; however, real-world data is currently scarce.

Systemic treatment of psoriasis and cardiovascular risk factors/markers

In patients with psoriasis, especially those with moderate-to-severe psoriasis requiring systemic treatment, the prevalence rates of cardiovascular risk factors are significantly increased. A meta-analysis showed that patients with psoriasis presented higher values of total cholesterol, LDL, triglycerides, systolic blood pressure, diastolic blood pressure, body mass index (BMI), waist circumference, fasting glucose, non-fasting glucose, and hemoglobin A1c (HbA1c). Herein, we summarized evidence demonstrating that the systemic treatment of psoriasis could reduce or increase these cardiovascular risks.

Obesity

During conventional therapy, MTX did not increase the body weight and BMI of patients with psoriasis. Regarding biological agents, TNF- α inhibitors were associated with increased body weight and BMI; however, IL-12/23 and IL-17 inhibitors and apremilast could induce weight loss. Interestingly, patients receiving MTX during infliximab treatment are reportedly leaner, indicating that the simultaneous use of MTX could limit the weight gain caused by TNF- α inhibitors. Furthermore, it has been reported that obesity can compromise the effectiveness of systemic psoriasis treatments (conventional and biological therapies), and in obese patients, weight loss could improve metabolic parameters, as well as the responsiveness to psoriasis therapies.

Diabetes mellitus

Apremilast reportedly improved glucose metabolism, whereas CsA is known to increase the risk of diabetes. In a study utilizing TNF- α inhibitors and ustekinumab,

insulin resistance and glycemia were reportedly improved. Other anti-psoriatic therapies have not been associated with significant differences in altered HbA1c or fasting glucose levels.

In recent years, some antidiabetic drugs, including metformin, pioglitazone, liraglutide, and acarbose, have been shown to alleviate psoriasis, whereas the regular use of insulin might worsen psoriasis. Notably, the combined administration of TNF- α inhibitors and some antidiabetic medications such as sulfonylureas, meglitinides, and insulin might increase the risk of hypoglycemia in patients with psoriasis.

Dyslipidemia

Based on the included studies, MTX, IL-17, and IL-12/23 inhibitors reportedly demonstrate a marginal effect on lipid metabolism, whereas CsA and acitretin are related to dyslipidemia. Acitretin and CsA have been associated with an elevated risk of hypercholesterolemia and hypertriglyceridemia. There remain several controversies regarding the effect of TNF- α inhibitors on lipid metabolism. Although tofacitinib increased total cholesterol, LDL, and high-density lipoprotein (HDL) levels in a dose-dependent manner, total cholesterol:HDL and LDL:HDL ratios, definite predictors of MACE, were unaltered.

Hypertension

Several studies have revealed that CsA could increase the risk of or even worsen hypertension. There is no evidence that other systemic psoriasis treatments affect blood pressure. CsA significantly elevated blood pressure when compared with a placebo in a dose-dependent manner, increasing the risk of stroke, MI, heart failure, and other CVDs. However, the increased blood pressure was reversible after ceasing CsA administration.

C-reactive protein (CRP)

CRP, which is a marker of systemic inflammation and CVD risk, was significantly increased in patients with moderate-to-severe psoriasis. It has been reported that biological agents, including TNF- α inhibitors, ustekinumab, ixekizumab, and tofacitinib, could reduce CRP, whereas secukinumab failed to reduce this biomarker. Moreover, patients with a lower response to etanercept and ustekinumab presented higher CRP levels. This relationship was not observed in groups treated with secukinumab, suggesting that higher CRP levels might be associated with the lower efficacy of etanercept and ustekinumab, while not affecting the efficacy of secukinumab.^[11]

Conclusions

Various anti-psoriasis drugs have different effects on CVDs and cardiovascular risk factors (Supplementary Table 1, <http://links.lww.com/CM9/A395>). The specific clinical situation of patients with psoriasis, especially cardiovascular complications, should be carefully consid-

ered when selecting appropriate treatment. For psoriasis patients with arterial plaques or a high risk of MACE, MTX and TNF- α inhibitors remain good options. Moreover, IL-17 and IL-12/23 inhibitors are effective in reducing arterial plaques. Patients with dyslipidemia should avoid CsA and acitretin. Similarly, CsA is not recommended in patients with hypertension, and obese patients should avoid TNF- α inhibitors.

Conflicts of interest

None.

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