Research progress in psoriatic arthritis-related cardiovascular damage

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To the Editor: Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, mainly manifested as peripheral arthritis, enthesitis, finger or toe inflammation, and spinal arthritis.[1] PsA may develop at any age, peaking at age of 30 to 50 years with no significant gender difference, but the spinal involvement is more frequent in men. The prevalence of PsA in China is about 1.23‰. About 75% of patients with PsA develop rash before arthritic onset whereas 10% after arthritis development.

PsA patients are closely associated with a variety of comorbidities, including obesity, metabolic syndrome, cardiovascular disease (CVD), cerebrovascular disease, and peripheral vascular disease. According to European League Against Rheumatism recommendations for the management of PsA with pharmacological therapies, non-musculoskeletal manifestations including skin, eyes, and gastrointestinal tract should be monitored during the treatment of PsA patients while complications such as metabolic syndrome, CVD or depression should also be considered.[2] In order to provide guidance for clinical practice, we summarize recent literatures on PsA-related cardiovascular damage.

PsA is a chronic recurrent inflammatory disease mainly mediated by T cells and other immune cells. A variety of effector cells and inflammatory mediators participate in PsA pathogenesis, among which proinflammatory adipocytokines produced by adipocytes such as resistin, leptin, and visfatin contribute to the disease progression. In addition to its inhibitory function on regulatory T cells, leptin has been shown to promote the proliferation of $CD4^+$ T cells and natural killer cells, increase neutrophil chemotaxis, and induce macrophages to produce tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-12. Consequently, TNF-α and IL-6 can inhibit adiponectin production by adipocytes, thus increasing the disease severity of cutaneous-only psoriasis (PsC).[3] On the other hand, increased TNF-α production leads to the elevation of serum leptin level, which promotes the local inflammatory response and enhances the progression of PsC. Notably, both body mass index (BMI) and leptin levels are found significantly higher in PsA patients than those in PsC patients. A close correlation between PsA and CVD is possibly due to the shared pathophysiological pathways between them. The increased levels of C-reactive protein (CRP), IL-6, TNF-α and other inflammatory mediators in CVD patients can affect vascular endothelial cells and lead to endothelial dysfunction, and promote the occurrence and progression of major vascular events. Currently, it is not clear whether certain specific inflammatory cytokines are involved in the development of PsA-CVD. It has been reported that human cartilage glycoprotein-39 (YKL-40), a biomarker of endothelial dysfunction, is significantly increased in PsA patients.[4] As a risk factor for CVD, the metabolic syndrome is characterized with endothelial dysfunction. Since YKL-40 is associated with adiponectin and leptin, key adipokines in the pathogenesis of psoriasis,[5] further studies are needed to determine whether increased YKL-40 levels can indicate a higher risk for CVD in PsA patients.

Patients with psoriasis are often presented with lipid metabolism disorder. The prevalence of metabolic syndrome or hyperglycemia, hypertension, atherosclerosis,

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and abnormal lipid metabolism in psoriasis patients is significantly higher than that of normal subjects, which may be possibly related to obesity and increased production of adipokines, TNF-α, and other inflammatory factors. Analysis of single nucleotide polymorphism of psoriasis, rheumatoid arthritis and other immune diseases revealed multiple risk loci in high density lipoprotein (HDL) and low density lipoprotein genes, providing a molecular basis for elucidating the mechanisms underlying PsA complicated with dyslipidemia.[6] However, current findings on the expression profile of blood lipid levels in PsA patients are not consistent. HDL levels in patients with PsA were lower than that in healthy controls and even increased after effective treatment.

In PsA, the classical risk factors for CVD include hypertension, dyslipidemia, BMI increase, subclinical cardiovascular risk factors such as carotid intima-media thickness and drug-related factors (non-steroidal anti-inflammatory drugs, glucocorticoid). Recent studies have found that CRP can serve as an important predictor of CVD in patients with inflammatory arthritis. In addition to the classical cardiovascular risk factors, PsA disease activity and systemic inflammatory response have been identified as independent risk factors of cardiovascular events.

The main manifestations of PsA involving CVD include ascending aorta arteritis, aortic valve lesions, and conduction disorders, while pericarditis, cardiomyopathy and mitral valve lesions are less common. Moreover, the incidence rate and mortality of CVD increase with the extension of course and aggravation of disease. Congestive heart failure, especially left ventricular congestive heart failure, may occur when heart disease becomes severe. A prospective follow-up study of 648 PsA patients showed that the incidence rate of myocardial infarction was significantly higher than that of healthy subjects.

Atherosclerosis begins with intimal involvement, which is caused by the interaction of chronic mild inflammatory reaction and metabolic abnormalities in the vascular wall. Initially, the local migration of smooth muscle cells, macrophages, and T lymphocytes occur in intima, followed by lipid accumulation in macrophages and smooth muscle cells and extracellular matrix. Finally, fibrous tissue hyperplasia and calcification result in the thickening and hardening of arterial wall. Compelling evidence indicates that immune dysregulations can directly lead to an increased incidence rate of atherosclerosis or subclinical atherosclerosis. The incidence of atherosclerosis in patients with PsA is higher than normal controls. Moreover, the higher coronary plaque burden in patients with PsA is not associated with metabolic syndrome, but is associated with the severity of underlying disease.[7]

Current treatment for PsA includes non-steroidal anti-inflammatory drugs (NSAIDs), conventional disease modifying anti-rheumatic drugs (cDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs). NSAIDs can inhibit inflammatory reaction and relieve joint pain, swelling, and morning stiffness in PsA patients. The long-term and continuous use of NSAIDs reduce radiographic progression in patients with ankylosing spondylitis. The cyclooxygenase-2 inhibitors can reduce the side effects of NSAIDs on gastrointestinal tract, but may increase the incidence rate of cardiovascular events such as thrombosis, hypertension, heart failure, and heart failure. However, other studies have reported that celecoxib does not increase the risk of cardiovascular events.[8]

In clinical applications, cDMARDs include methotrexate, acitretin and cyclosporin, and so on. The methotrexate can reduce the incidence of CVD while its long-term use may lead to higher risk of end organ toxicity. It is reported that acitretin often causes hyperlipidemia whereas cyclosporin can lead to hypertension, hyperlipidemia, and even cause myocardial damage through the production of reactive oxygen species. Therefore, more attention is needed to monitor the side effects of these drugs on cardiovascular system.

Both bDMARDs and tsDMARDs provide a new option for the treatment of PsA. Several studies have observed the effects of these new therapies on lipid metabolism disorder and cardiovascular events in patients with PsA. Spanakis *et al* compared the effect of infliximab on 60 patients with refractory rheumatism and found that HDL levels showed a long-term upward trend. Furthermore, anti-TNF-a therapy is beneficial in reducing the incidence rate of CVD in these patients. Recent studies show that IL-12/23 inhibitor ustekinumab has potential effects on cardiac protection and does not increase the risk of serious cardiovascular adverse events, but further studies with longer-term follow up are required to confirm this finding. In addition, IL-17A inhibitor secukinumab does not cause any significant changes in blood glucose, blood pressure, body mass index, and blood lipid in patients with PsA after

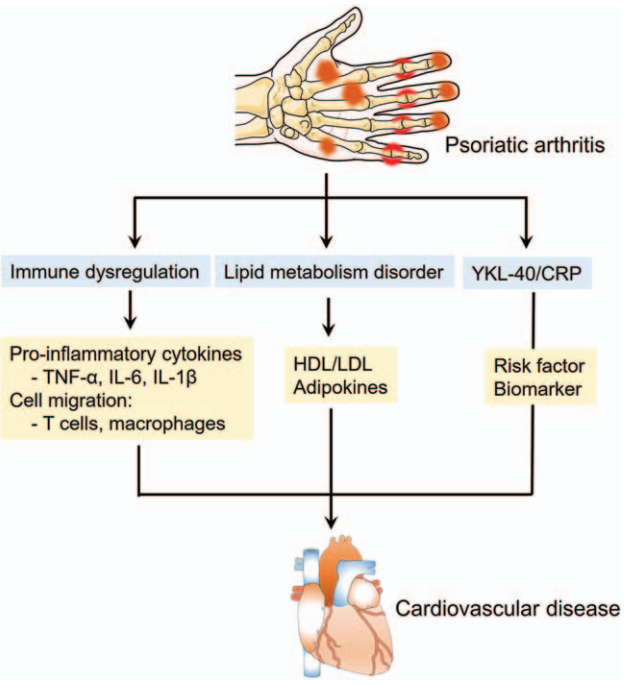

Figure 1: The schematic illustration shows proinflammatory factors and the molecular mechanisms underlying cardiovascular damage in PsA. YKL-40: Human cartilage glycoprotein-39; CRP: C-reactive protein; TNF-α: Tumor necrosis factor-α; IL: Interleukin; HDL: High density lipoprotein; LDL: Low density lipoprotein.

3 years of treatment. Since systemic inflammation may affect cardiac metabolism and increase the risk of CVD in patients with PsA during the natural course of disease, the observed cardiac safety of secukinumab from clinical studies supports its application as a new treatment option for patients with PsA accompanied with cardiac metabolic risk factors. A recent study has evaluated the influence of treatment with JAK inhibitors on cardiovascular events, in which the incidences of deep vein thrombosis and pulmonary embolism were higher in baricitinib treatment group than those in placebo.[9]

Patients with PsA often have metabolic diseases with increased mortality rate after serious cardiovascular complications [Figure 1]. Therefore, how to evaluate and control the cardiovascular risk of patients with PsA remains a challenge in clinical management. Moreover, further clinical trials are needed to determine the therapeutic potentials of newly developed JAK and phosphodiesterase-4 inhibitor in the treatment of PsA patients with CVD.

Conflicts of interest

None.

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