Targeting inflammation in the prevention of cardiovascular disease in patients with inflammatory arthritis

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Patients with inflammatory arthritis have increased risk of cardiovascular diseases (CVDs) compared with the general population. Subclinical carotid atherosclerosis and increased arterial stiffness are also common in these patients, which may serve as surrogate end points for cardiovascular (CV) events in clinical trials. Although exact mechanisms are still unclear, persistent systemic inflammation in patients with inflammatory arthritis may contribute to the development of CVD. Dysregulated innate immunity pathways in these patients may also play a role in accelerating atherosclerosis. During the last decade, effective suppression of inflammation by biological disease-modifying antirheumatic drugs has improved the disease outcome dramatically in patients with inflammatory arthritis. Growing evidence suggests that antitumor necrosis factor (TNF) therapy may prevent CVD in patients with rheumatoid arthritis. Nonetheless, data on non-TNF biologics are limited. Whether anti-TNF therapy may prevent CVD in patients with spondyloarthritis also remained unclear. In this review, we summarized the effect of both anti-TNF and non-TNF biologics on the CV system, including traditional CVD risk factors, endothelial function, arterial stiffness, subclinical atherosclerosis, and clinical CVD in patients with inflammatory arthritis. (Translational Research 2016;167:138–151)

Abbreviations: ABA = abatacept; ADA = adalimumab; AIx = augmentation index; AMI = acute myocardial infarction; ANA = anakinra; Apo = apolipoprotein; AS = ankylosing spondylitis; CTZ = certolizumab pegol; CV = cardiovascular; CVD = cardiovascular disease; DMARD = disease-modifying antirheumatic drug; ETN = etanercept; FMD = flow-mediated vasodilation; GOL = golimumab; HDL = high-density lipoprotein; IFX = infliximab; IL = interleukin; IMT = intima-media thickness; LDL = low-density lipoprotein; MACE = major adverse cardiovascular event; MI = myocardial infarction; MMPs = matrix metalloproteinases; MTX = methotrexate; PsA = psoriatic arthritis; PWV = pulse wave velocity; RA = rheumatoid arthritis; RAGE = receptor for advanced glycation end product; RCT = randomized controlled trial; RTX = rituximab; sRAGE = soluble RAGE; TC = total cholesterol; TCZ = tocilizumab; TG = triglyceride; TNF = tumor necrosis factor; TOF = tofacitinib

INTRODUCTION

Patients with inflammatory arthritis have increased risk of cardiovascular diseases (CVDs) compared with the general population.[1-3] Effective suppression of inflammation by biological disease-modifying antirheumatic drugs (DMARDs) or biologics has improved the disease outcome dramatically during the last decade. Systemic inflammation is the cornerstone of both inflammatory arthritis and atherosclerosis. However, whether effective suppression of inflammation by biologics can ameliorate this increased risk in inflammatory arthritis

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is still controversial. In this review, we first summarized the epidemiologic evidence and underlying mechanism of increased CVD in these patients. Next, we focused on the effects of both antitumor necrosis factor (anti-TNF) and non-TNF biologics on the cardiovascular (CV) system, including clinical CVD and the possible underlying mechanisms, which may contribute to the change in CV events in these patients.

Increased prevalence of clinical and subclinical CVDs in patients with inflammatory arthritis. Rheumatoid arthritis (RA) is associated with premature death primarily because of CVD,[1,4] even at the early phase of the disease.[5,6] In a meta-analysis, which pooled 24 cohort studies (111,758 patients), the risk of incident CVD was increased by 50% in patients with RA.[1] An increased risk of major adverse cardiovascular events (MACEs) was also observed in a recent population-based study by Ogdie et al[2] comparing 41,752 patients with RA and 81,573 control subjects. Patients with RA had a significant increase in MACE (no DMARDs, 39%; DMARDs, 58%) after adjusting for traditional CV risk factors. The authors hypothesized that patients on DMARDs could have more severe RA.[2]

In patients with psoriatic arthritis (PsA), increased mortality has been demonstrated in some[7,8] but not all[9,10] observational cohort studies and population-based studies. Nonetheless, data have consistently indicated an increased prevalence of CVD and related mortality.[2,11,12] In addition to the higher prevalence of traditional CV risk factors,[12,13] uncontrolled low-grade inflammation may account for the 24% increased risk of MACE in patients with PsA (N = 4174) not prescribed a DMARD compared with control subjects.[2]

A 20%–40% increase in CVD mortality was observed in patients with ankylosing spondylitis (AS) compared with controls.[3,7,14] A meta-analysis showed a significant increase in myocardial infarction (Odd ratio [OR], 1.60 [95% confidence interval [CI], 1.32–1.93]) and stroke (OR, 1.50 [95% CI, 1.39–1.62]) in patients with AS.[15] The most recent population-based cohort study reported an increased age-adjusted risk of developing ischemic heart disease only in female patients with AS.[16] However, after adjustment for nonsteroidal anti-inflammatory drug use, only a nonsignificant trend toward increased risk was found.[16]The discrepancy can be explained by the different study design, outcome measurement, and adjustment by nonsteroidal anti-inflammatory drug usage.

As a first step toward more accurate CVD risk prediction, it was proposed in the European League Against Rheumatism recommendations for CVD risk management in RA to apply a multiplication factor of 1.5 to the calculated CVD risk by Systematic Coronary Risk Evaluation algorithm in selected patients to enhance the risk estimates.[17] However, risk assessment by original or adapted CVD risk models such as Systematic Coronary Risk Evaluation appears to be suboptimal.[18,19] The use of other CVD-related parameters not incorporated in the present CVD risk algorithms, such as carotid artery intima-media thickness (IMT) and, or the presence of atherosclerotic carotid plaques in these patients may be considered.

IMT has been shown to improve risk prediction for incident CVD over what was achieved by a model with Framingham risk factors alone in the general population,[20] and to improve CV risk stratification in patients with RA[21] and PsA.[22,23] Arterial stiffness is also associated with atherosclerotic diseases and is increasingly recognized as a surrogate end point for CVD.[24] Arterial stiffness can be determined noninvasively by different methods including pulse wave velocity (PWV) and augmentation index (AIx). Subclinical atherosclerosis and arterial stiffness were more prevalent in patients with RA[22,25-30] and PsA.[31-39] In patients with AS, an increased prevalence of subclinical atherosclerosis[40-42] and arterial stiffness[42-46] has been demonstrated in some but not all studies.[47-49]

The increased prevalence of both clinical CVD and subclinical atherosclerosis has already drawn great attention. Although exact mechanisms are still unclear, growing evidence suggest that the persistent systemic inflammation in patients with inflammatory arthritis may contribute to the development of CVD.

Mechanism of inflammation in CVD in inflammatory arthritis. The precise nature of the relationship between local and systemic inflammation, their interactions with traditional CV risk factors, and their role in promoting CVD remains unresolved.[50,51] Although monocytes, $CD4^+$ T lymphocytes, and proinflammatory cytokines including TNF-α, interleukin (IL)-1, and IL-6 play a central role in the pathogenesis of inflammatory arthritis, the inflammatory milieu enhances the expression of adhesion molecules (intercellular adhesion molecule 1, vascular cell adhesion molecule 1, and E-selectin), promotes endothelial dysfunction,[52,53] and subsequently leads to atherosclerotic plaque formation.[53] Matrix metalloproteinases (MMPs) released from activated leukocytes degrade the extracellular matrix, whereas proinflammatory cytokines decrease new collagen synthesis. These changes lead to plaque remodeling and fibrous cap thinning, which increases plaque vulnerability and finally leads to plaque rupture, resulting in acute myocardial infarction (AMI) (Fig 1).[54] Endothelial dysfunction and the excessive expression of proinflammatory cytokines and MMPs are also key promoters for increasing arterial stiffness by altering the balance of elastin and collagen.[55] Chronic