

## Editorial Comment

# Rheumatoid Arthritis and Atherosclerosis: Could Common Pathogenesis Translate Into Common Therapies?

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**R**heumatoid arthritis (RA) is an autoimmune condition that manifests clinically as a chronic inflammatory polyarthritis. It constitutes the most common inflammatory disease of the musculoskeletal system, affecting approximately 1% of the population.<sup>1</sup> RA exhibits a 2- to 3-fold higher incidence in women as compared with men and it appears most often in the 4th and 5th decades of life.<sup>2</sup> Apart from the resultant disabilities, which negatively affect the quality of life, RA has been associated with a reduced life expectancy, partly due to the associated comorbidities.<sup>3</sup>

Cardiovascular disease – and in particular ischemic heart disease, heart failure, and cerebrovascular disease – is included among the most common comorbidities in patients with RA, along with infections, malignancies and mental health conditions.<sup>4,5</sup> In the specific context of cardiovascular disease, patients with RA exhibit an approximately 2- or 3-fold increase in cardiovascular events (which is highest in those who have the disease for more than 10 years) and a 50% increase in cardiovascular mortality.<sup>4,5</sup> It should be emphasized that cardiovascular risk in RA patients is disproportionately increased when traditional risk factors are considered.<sup>6</sup> Accordingly, cardiovascular risk in RA patients is currently perceived as com-

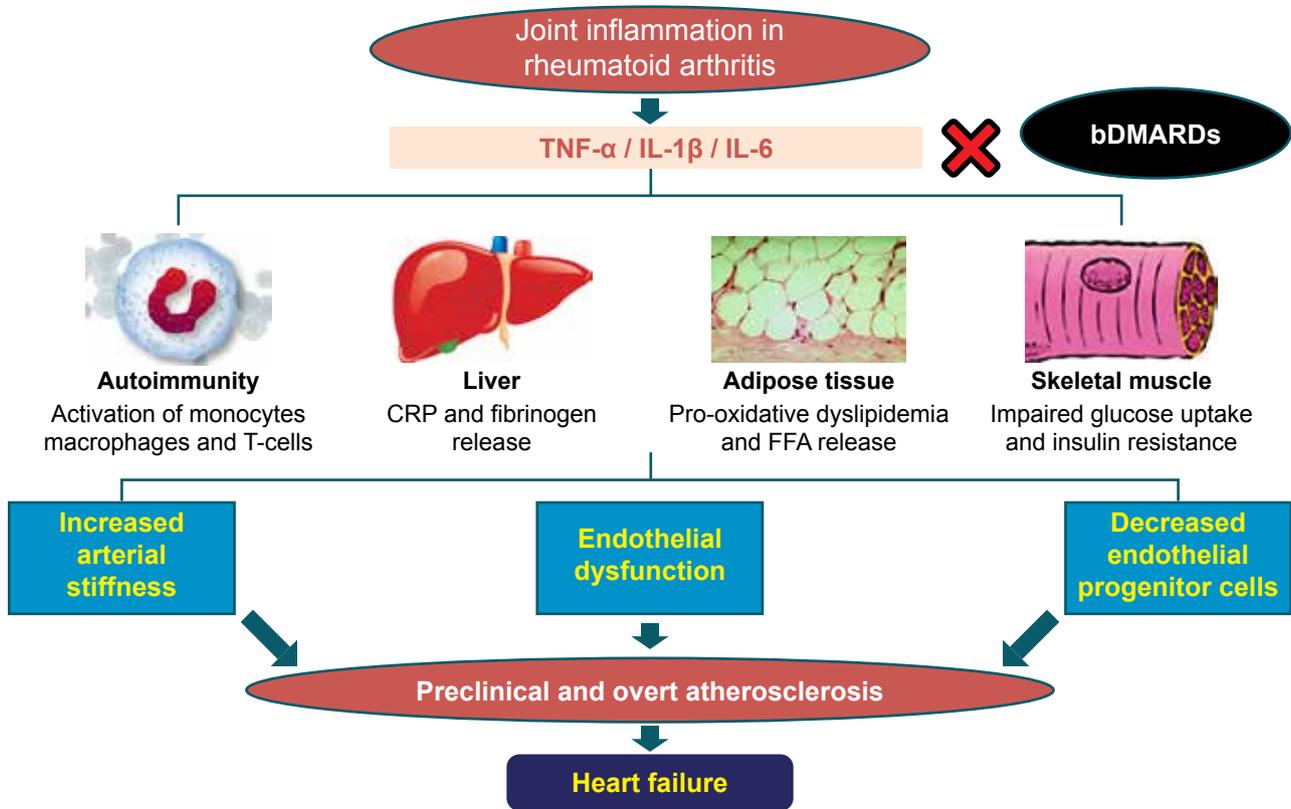
parable with the relevant risk attributable to diabetes mellitus; thus, RA has been included in the group of so-called coronary artery disease equivalents.<sup>1</sup>

The increased cardiovascular risk in RA is driven by several parameters, mostly due to the long-standing inflammation. Among traditional risk factors, an atherogenic pattern of pro-oxidative dyslipidemia (consisting of low levels of high-density lipoprotein cholesterol and high levels of low-density lipoprotein cholesterol, triglycerides and free fatty acids) is frequently encountered in this disorder.<sup>5</sup> Additional contributing factors include prothrombotic state, hyperhomocysteinemia, insulin resistance, and immune system dysregulation with activation of T-cells. All of the above factors may lead to endothelial dysfunction (with both macro- and microvascular dysfunction) and increased arterial stiffness, which finally accounts for accelerated atherosclerosis (Figure 1).<sup>4</sup>

From an historical perspective, the treatment options for RA over time have included initially aspirin, or non-steroidal anti-inflammatory drugs (NSAIDs), and later corticosteroids. In the mid 1970s the non-biologic (or conventional) disease-modifying antirheumatic drugs (DMARDs) (with methotrexate and hydroxychloroquine being the most widely used agents today), which have the ability

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**Figure 1.** Pathogenesis of atherosclerosis and heart failure in patients with rheumatoid arthritis. bDMARDs – biological disease-modifying antirheumatic drugs; IL – interleukin; TNF- $\alpha$  – tumor necrosis factor- $\alpha$ ; CRP – C-reactive protein; FFA – free fatty acids.

to interfere with the entire disease process, have been introduced in the treatment of RA.<sup>7</sup> Finally, the latest development in its treatment consists of the introduction into clinical practice by the end of the 20th century of the biological DMARDs (bDMARDs). The latter group of drugs includes 5 subgroups: namely, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) inhibitors, anti-B-cell agents, T-cell costimulation inhibitors, interleukin (IL)-6 inhibitors and IL-1 inhibitors (Figure 1).<sup>7</sup> Treatment with bDMARDs should be reserved for patients who fail to reach the treatment target within 6 months of treatment, or when no improvement is achieved after 3 months of therapy with a combination of a conventional DMARD with glucocorticoids.<sup>7</sup>

Concerning the important issue of safety, and with particular emphasis on cardiovascular outcomes, treatment strategies have a variable effect. Thus NSAIDs, through water retention, may elevate blood pressure and precipitate or exacerbate heart failure through volume overload or renal function impairment (reno-cardiac syndrome). Corticosteroids are responsible for exacerbating dyslipidemia, increasing

blood pressure and adversely affecting glucose metabolism. Nevertheless, the latter effects are counterbalanced (at least in part) by their favorable effect on inflammation, with the net final effect on cardiovascular risk being variable.<sup>4</sup> Regarding conventional DMARDs, methotrexate appears to lower myocardial infarction risk by approximately 70%.<sup>4</sup> In the case of bDMARDs, concerns have been raised with respect to anti-TNF- $\alpha$  agents in heart failure. TNF- $\alpha$ , along with other cytokines, is overexpressed in heart failure patients and exerts a detrimental effect on cardiac cell contractility.<sup>8</sup> Based on the above observation, anti-TNF- $\alpha$  agents appeared as an attractive therapeutic option in patients with heart failure (either with or without RA). However, clinical trials and post-marketing registries showed no benefit of anti-TNF- $\alpha$  therapy on heart failure treatment or mortality. Most importantly, in advanced heart failure the latter therapy was held responsible for higher rates of hospitalization and increased mortality. Based on these findings, the use of biological anti-TNF- $\alpha$  agents is discouraged by the 2012 guidelines of the American College of Rheumatology in patients

with advanced heart failure (New York Heart Association classes III and IV) and an ejection fraction <50%.<sup>4,6,9</sup> On the other hand TNF- $\alpha$  antagonists may improve cardiovascular risk through their beneficial effects on endothelial dysfunction and arterial stiffness.<sup>4</sup> Recently, TNF- $\alpha$  antagonists were compared with conventional DMARDs in more than 10,000 patients with RA in the CORRONA registry. TNF- $\alpha$  antagonism resulted in a reduction of the composite cardiovascular endpoint (non-fatal myocardial infarction, transient ischemic attack/stroke and cardiovascular-related death) by 61% compared with conventional DMARDs. Such an effect was not observed with methotrexate therapy.<sup>10</sup> Thus, according to the current data, coronary artery disease does not constitute a contraindication to anti-TNF- $\alpha$  agents.

Fifteen years after the introduction of bDMARDs into clinical practice, since safety concerns on cardiovascular complications have been adequately addressed, it is time for a step forward. Such a step includes the potential use of these agents in the therapeutic armamentarium of heart diseases. The rationale behind this strategy is the presence of a common link between atherosclerosis and RA: namely, inflammation.<sup>11</sup> Thus, it is of paramount importance to recognize which patient and which cardiovascular disorder may benefit from bDMARDs treatment. Towards this goal, an understanding of the effects of the latter treatment on heart and vessels can be expected to be helpful. In this issue of the HJC, Ayyildiz et al assessed the impact of infliximab, a monoclonal antibody against TNF- $\alpha$ , in 20 patients with RA.<sup>12</sup> The study additionally included 18 patients receiving corticosteroids and 30 healthy controls. The authors found that long-term TNF- $\alpha$  inhibition improved left ventricular longitudinal and radial systolic deformation, while decreasing left ventricular torsion. Apart from anti-TNF- $\alpha$  agents, other bDMARDs, such as the IL-1 inhibitor anakinra, have been shown to improve left ventricular and vascular function.<sup>13</sup> Interestingly, in a relevant study, the effects of anakinra on coronary flow reserve, endothelial and aortic function, as well as left ventricular mechanics, were more pronounced in RA patients with coronary artery disease than in those without.<sup>14</sup> Anakinra has also shown favorable results in the treatment of another autoimmune-autoinflammatory condition, refractory recurrent idiopathic pericarditis.<sup>15-18</sup>

In conclusion, the era of bDMARDs in the treatment of cardiovascular disorders has begun. Results from recent studies with bDMARDs that assessed

surrogate endpoints, such as the one published in this issue of the Journal, are rather encouraging. Along similar lines, several randomized trials are currently being conducted with bDMARDs to assess not only surrogate endpoints but also clinical targets, including prevention of cardiovascular events in patients with acute coronary syndromes, effects on carotid plaque burden, prevention of recurrences of atrial fibrillation after electrical cardioversion, etc. Finally, we wish to emphasize that collaboration among cardiologists and rheumatologists who are more familiar with biological agents is essential.

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