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EDITORIAL

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Cardiovascular risk in rheumatoid arthritis: An update for general practitioners

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Rheumatoid arthritis (RA) is a chronic immune related inflammatory disease which affects almost 1% of the general population and which is ranked among the top 15% of diseases causing major disability worldwide [1]. RA shares some pathologic features, genetic predisposition and risk factors with ather¬osclerosis. Inflammation plays a central pathophysiologic role in both diseases. RA is associated with an increased risk of cardiovascular mortality [1-3]. Coronary CT angiography [4] and post mortem data [5] detect a higher prevalence of vulnerable coronary plaques in patients with RA compared with controls. Furthermore, it has been shown that in most RA-patients with an early stage of disease an asymptomatic cardiac pathology can be detected [5].

The article by Cocco et al. [1] adds an important piece to the puzzle. An analysis of a Swedish cohort study using national registries [7] found that, in patients with active RA compared with matched con-trols, the severity of disease at presentation with an incident acute coronary syndrome (ACS) is in-creased and short-term all-cause mortality is worse. Interestingly, worse outcome in patients with RA compared with matched controls severity of the pathology is increased and this situation persists after adjustment for clinical covariates, including the type of ACS. Moreover, among deaths, the majority of cases had a cardiac cause (89.9% vs. 90.8%). Of note, all-cause mortality during the first 30 days after an ACS was quite high in patients with RA (15.7%) compared with matched controls (10.7%).

Altogether, as compared with the general population, in RA the prevalence of cardiovascular events is increased to an extent comparable to that of type 2 diabetes mellitus [1,3]. RA-patients have a higher incidence of myocardial ischemia and infarction, cardiac failure, valvular heart disease, pericarditis, myocarditis and, to a lesser extent, venous complications. The occurrence of sudden cardiac death is two-fold increased and that of major adverse cardiovascular events is augmented to almost 50%. Car¬diovascular deaths increase seven years following symptoms onset. These findings support the notion of an aggravated course of coronary atherosclerosis and ACS in patients with RA.

RA and atherosclerosis as the underlying cause of coronary artery disease share several features in pathophysiology, genetic predisposition and risk factors, assigning a central role to inflammation [1,8]. Indeed, like RA, atherosclerosis is a chronic inflammatory disease, specifically of the arterial wall. The dynamic nature of atherosclerosis is characterized by its evolution, culminating in plaque rupture or erosion with ensuing atherothrombosis and vascular occlusion as the pathophysiological culprit of an ACS [9]. Endothelial activation promotes pro-inflammatory stimuli and the occurrence of cell adhesion molecules in arteries exposed to impaired blood flow [10]. In these areas lipoprotein accumulation and lipoprotein accumulation increase cell adhesion molecules and synthesis of mediators and pro-inflammatory cytokines by endothelial cells which, in turn, result in the recruitment and activation of various types of circulating leucocytes comprising neutrophils, monocytes and T cells (predominantly the T helper 1 subset). In the arterial intima, monocytes differentiate into macrophages and take up oxidized lipoproteins, converting them into foam cells. T cells can recognize specific antigens derived from these modified lipoproteins and orchestrate the immune response. Atherosclerotic lesion pro¬gression involves migration and proliferation of vascular smooth muscle cells in the intima and incre¬ased turnover of components of the extracellular matrix (i.e. collagen, elastin and proteoglycans) by matrix-degrading enzymes. Advanced stages of atherosclerotic plaques are characterized by a lipid core, an accumulation of extracellular lipids with cholesterol crystals derived from dead cells (i.e. foam cells and vascular smooth muscle cells), sealed on the luminal side by a fibrous cap separating it from circulating blood. These dynamic changes in plaque composition culminate in plaque rupture or ero¬sion, followed by thrombus formation [10].

In RA, the inflammatory process in the synovial joint is characterized by endothelial activation with increased expression of adhesion molecules and infiltration of immune cells comprising T cells of the T helper 1 subset and monocytes. Cartilage degradation in the synovial joint constitutes the hallmark of RA, mediated by persistently activated fibroblast-like synoviocytes (FLS) that express matrix-degra¬ding enzymes. The combination of degradation products from the extracellular matrix exposing anti¬gens that can be recognized by T cells and inflammatory signals from adjacent cells lead to perpetua¬tion of the inflammatory process, including neovascularization []8,11]. As described in patients with RA [12] increased numbers of a distinct T cell subset-CD4+CD28null T cells were detected in blood from patients with an ACS [13]. CD4+CD28null T cells are characterized by clonal restriction indicative of a reduced repertoire of antigens recognized by the T cell receptor complex in both patients with RA [12] and patients with an ACS [14] when compared with controls. In line with this, T cells in coronary thrombi aspirated from the culprit lesion in the

epicardial vessel in patients with an ACS are profoundly clonally restricted compared with circulating T cells [15]. Moreover, circulating T cells from patients with an ACS [15] and patients with RA [16] showed clonal restriction when compared with controls. These findings indicate similar autoimmune responses against specific antigens in RA and ACS alike.

Anti-inflammatory drugs have been used for a long time in patients with RA and the antimetabolite methotrexate was associated with a reduction in cardiovascular events [1,3,17].

On other hand the use of non-steroid antirheumatic drugs, especially ibuprofen, is associated with an increased risk for adverse cardiovascular events, mostly be reducing the renal function [19].

Control of the joint pathology remains the principal therapeutic aim in RA, but the impact of cardiovas¬cular complications should not be forgotten. Patients with RA who are at high cardiovascular risk should be given the best available therapies to reduce the cardiovascular complications. Among the novel anti-inflammatory biologic agents used in patients with RA, it will be interesting to learn about the effects on cardiovascular outcomes during long-term follow-up of therapeutic inhibition of tumor necro¬sis factor-α, inhibition of interleukin-1β or antagonism of the interleukin-6 receptor, respectively. In turn, in patients with coronary artery disease, ongoing trials are evaluating the effects on cardiovascu¬lar events of methotrexate and inhibition of interleukin-1β [3,9,18].It will be of great interest whether these trials confirm or refute the inflammatory hypothesis presented.

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