Editorial

Cardio-Rheumatology: Cardiovascular Complications in Systemic Autoimmune Rheumatic Diseases / Is Inflammation the Common Link and Target?

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Abstract: In the current Thematic Issue of Current Vascular Pharmacology (CVP), entitled “Systemic Autoimmune Rheumatic Diseases and Cardiology”, presented in two parts, Part 1 and Part 2, review articles are included from specialists in cardiology, rheumatology, immunology and related fields. These reviews discuss the cardiovascular complications of the main systemic Autoimmune Rheumatic Diseases (ARDs). For example, the underlying pathogenetic mechanisms, the role of cardiovascular imaging and recommendations for prevention and management. These articles place inflammation as the key process, linking cardiovascular complications with ARDs. From all these reviews, the conclusion is the need for collaboration between the disciplines of Rheumatology and Cardiology to establish the emerging field of Cardio-Rheumatology. This will aid to fine-tune risk stratification and optimize preventive strategies and pharmacological therapies for patients with ARDs.

Keywords: Autoimmune rheumatic disease, cardiovascular disease, cardiорheumatology, rheumatoid arthritis, systemic lupus erythematosus, Sjogren’s disease, spondyloarthropathies, systemic sclerosis, psoriasis, psoriatic arthritis, vasculitis, antirheumatic drugs, cardiovascular imaging, coronary artery disease, acute coronary syndromes, atherosclerosis, myocardial infarction, stroke.

1. INTRODUCTION

Systemic autoimmune rheumatic diseases (ARDs) have been frequently associated with increased cardiovascular morbidity and mortality mostly related to premature atherosclerosis, but also to a host of other cardiovascular diseases (CVD), e.g., vasculitis, valvulitis, myocarditis, pericarditis, cardiac arrhythmias, and thromboembolism (Fig. 1) [1-4]. The chronic inflammatory state associated with these diseases may play an important role in the pathogenesis of CVD. The current Thematic Issue of Current Vascular Pharmacology (CVP) entitled “Systemic Autoimmune Rheumatic Diseases and Cardiology” presented in two parts, Part 1 and 2, includes review articles from Cardiology, Rheumatology, Immunology and other experts that deal with the cardiovascular complications of the main systemic autoimmune ARDs and their treatment. In the context of the emerging field of Cardio-Rheumatology, experts discuss how ARDs increase cardiovascular risk, the role of cardiovascular imaging, whether control of systemic inflammation in various ARDs may result in a reduction in the risk of CVD and the associated cardiovascular morbidity and mortality rates and which preventive and therapeutic measures may be useful in these patients.

2. CARDIOVASCULAR MORBIDITY AND DEATH

The leading cause of mortality in almost all ARDs is related to cardiovascular events. A variety of cardiovascular disorders, including, albeit not limited to, hypertension, coronary artery disease, cardiac arrhythmias, pancarditis, vasculitis, and thromboembolism are encountered in ARDs (Table 1, Fig. 1). Pathophysiological mechanisms and clinical expression of cardiovascular comorbidities vary greatly between different ARDs, but atherosclerosis seems to be associated with almost all of them. As stated by Kostopoulou et al. in their review of CVDs in systemic lupus erythematosus (SLE) “this risk is driven by both general and disease-specific factors such as inflammatory mediators, autoantibodies and the deleterious effects of glucocorticoids” [5]. However, ARDs, in addition to the cardiac vasculature, can also affect the cardiac valves, myocardium, pericardium, conduction system, and peripheral vessels, leading to a plethora of cardiovascular manifestations that can remain clinically silent or lead to substantial cardiovascular morbidity and mortality, as detailed in this Thematic Issue [4, 6, 7]. Importantly, several types

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Table 1. Cardiovascular complications in systemic autoimmune rheumatic diseases (ARDs).

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<tr>
<th>ARDs</th>
<th>ARD Therapies</th>
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<tr>
<td>● Accelerated/Premature Atherosclerosis (coronary artery disease, acute coronary syndromes)</td>
<td>● Atherosclerosis</td>
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<td>● Endothelial dysfunction</td>
<td>● Conduction disturbances</td>
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<td>● Hypertension</td>
<td>● Cardiomyopathy/Heart failure</td>
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<td>● Metabolic syndrome</td>
<td>● Hypertension</td>
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<td>● Pancarditis (pericarditis, myocarditis, endocarditis/valvular heart disease)</td>
<td>● Lipid abnormalities</td>
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<td>● Cardiomyopathy</td>
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<tr>
<td>● Cardiac arrhythmias (atrial and ventricular arrhythmias, conduction disturbances, acquired and congenital heart block)</td>
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<td>● Vasculitis</td>
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<td>● Dysautonomia</td>
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<td>● Thromboembolic disease</td>
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<td>● Pulmonary arterial hypertension</td>
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of ARDs in pregnant women have been linked to congenital complete heart block, as circulating maternal anti Ro/SSA and anti La/SSB autoantibodies [8] may injure the atrioventricular node of the embryo resulting in permanent conduction block [9]. Furthermore, patients with ARDs have an increased prevalence of hypertension, ranging from 30 to 70% in rheumatoid arthritis and SLE, with clear links to immune system activation and inflammation [10, 11].

3. CVD PREVENTION

From these reviews, it becomes apparent that more aggressive primary and secondary prevention of CVD is needed in ARDs. Patients with ARDs may have a higher prevalence of traditional cardiovascular risk factors. Greater than 1.5-fold higher risk of CVD exists at most levels of traditional cardiovascular risk factors; however, this increased risk also applies to individuals with no conventional cardiovascular risk factors. ARDs can cause endothelial dysfunction, but the cardinal problem relates to the fact that active ARDs are characterized by systemic inflammation that is responsible for much of the excess risk of CVD and mortality in these groups of patients [12]. Inflammation contributes to atherosclerosis, endothelial dysfunction, plaque vulnerability, and atherothrombotic events. Inflammation may cause myocardial disease directly, leading to heart failure (HF). The risk of HF in ARDs is increased more than 2-fold and not fully explained by cardiovascular risk factors or ischaemic heart disease.

Nuclear factor kappaB (NFkB) is one of the major transcription factors that has been linked, via cell-specific effects, to both cardiovascular health and disease, including atherosclerosis, myocardial ischaemia and preconditioning, cardiac hypertrophy and HF [13]. On the other hand, NFkB plays crucial role in the regulation of inflammation and immune responses in ARDs; inappropriate NFkB activity has been linked with several ARDs, including rheumatoid arthritis [14]. Tumour necrosis factor (TNF) and interleukin 1 (IL-1) are both very potent activators of NFkB, which may thus mediate most of their pro-inflammatory activities in rheumatoid arthritis. The NFkB family controls several processes, such as immunity, inflammation, cell survival, differentiation and proliferation, and regulates cellular responses to stress, hypoxia, and ischaemia. However, the function of NFkB and its influence on disease processes varies according to the cell types in which it is activated, e.g. in atherosclerosis, NFkB activity in endothelial cells is pro-atherogenic, whereas NFkB activity in macrophages can be anti-atherogenic [13]. Keeping NFkB activation under control can be very important for the design of specific therapeutics for both CVD and ARD [13, 15]. Thus, one hopes for the future development of specific NFkB inhibitors, which will inhibit the detrimental elements of signalling while preserving the beneficial processes.

4. DUAL THERAPEUTIC TARGET

There should be a dual target in the management of patients with ARDs that should include both cardiovascular risk factor/CVD control and control of ARD activity [6, 7]. Aggressive management and control of cardiovascular risk factors (e.g.
smoking cessation, antihypertensive and lipid-lowering medications) are needed, at earlier stages. ARD activity is emerging as a key predictor and target for the prevention of CVD risk. ARD treatment seeks to reduce disease activity, as assessed using various scores. Reducing disease activity and inflammation may be essential for reducing myocardial disease and fibrosis of the heart, lung, and kidney. Aggressive management of inflammation may lead to a significant improvement in the clinical cardiovascular outcome of patients with ARDs. Reduction of CVD risk has been reported using several anti-inflammatory disease-modifying antirheumatic drugs (DMARDs), either the classical non-biologic or the newer biologic DMARDs, as detailed in the reviews by Mourouzis et al. and Drakopoulou et al., respectively [16, 17]. However, as pointed out in the review by Papagoras et al., more data will be needed to verify the impact of these anti-rheumatic treatments on cardiovascular risk and whether there are differences among them in this regard [6].

5. CV IMAGING

Evaluating patients with ARDs for subclinical atherosclerosis with imaging techniques (e.g. measuring carotid intima-media thickness or flow-mediated dilation of the brachial artery by ultrasound techniques) and/or use of biomarkers (e.g. natriuretic peptides, cardiac troponin) is emphasized in the review by Atzeni et al. [12]. Imaging with the use of cardiac magnetic resonance (CMR) is apparently crucial in patients with systemic vasculitides, as highlighted by Soulaidopoulos et al. [18]. Compared with other non-invasive imaging techniques, CMR has greater versatility and higher spatial resolution allowing for the early detection of cardiovascular involvement incurred by vasculitides (e.g. before any vascular aneurysm/stenosis or myocardial dysfunction occur).

6. DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

Disease modifying antirheumatic drugs (DMARDs) comprise both non-biological and biological agents [16, 17]. As detailed by Mourouzis et al., synthetic, non-biologic DMARDs such as methotrexate, sulfasalazine, chloroquine/hydroxychloroquine, leflunomide and tofacitinib show decreased CVD morbidity and mortality [16]. However, the strongest data favouring non-biologic DMARD use in rheumatoid patients are shown for methotrexate which has been the focus of the majority of studies and for hydroxychloroquine for which adequate proof for a favourable effect also exists. There have been reports of conduction disturbances (atrioventricular block, bundle-branch block) and restrictive cardiomyopathy during prolonged use of chloroquine, where symptoms were resolved with rapid tapering of the drug [2]. However, other studies have reported a protective role of chloroquine in the unexpectedly high rate of cardiac arrhythmias and conduction disturbances observed in SLE [19].

Biologic agents by reducing overall inflammation appear to improve ARDs [17], and since atherosclerosis is actually an athero-thrombo-inflammatory disease [20], they are also expected to lead to a reduction in the incidence of CVD, which is elevated in patients with ARDs, and thus may confer cardioprotection [21]. Such cardioprotective effect has been demonstrated for certain biologic agents, like the TNF inhibitors (Fig. 1), especially in patients responding to such treatment. However, this does not apply to all biologic agents, e.g. some IL inhibitors, as detailed by Drakopoulou et al. and Kapniari et al. [17, 22]. Furthermore, even for the TNF inhibitors, there is a concern for patients with New York Heart Association (NYHA) class III or IV HF or those with left ventricular ejection fraction <50%, where these agents may exacerbate congestive symptoms and thus are contraindicated.

Beyond the potentially beneficial effects that certain DMARDs may have on the cardiovascular risk of patients with ARDs, there is also a real proatherogenic risk involved with some anti-rheumatic therapies, such as the well-established proatherogenic effects of steroid therapy (Fig. 1), as described by Kostopoulou et al., where the pathogenesis of accelerated atherosclerosis is discussed in patients with SLE [5]. These authors also point out the promotion of comorbidities including hypertension, dyslipidaemia, glucose intolerance and central obesity conferred by glucocorticoids.

7. ANTIPHOSPHOLIPID SYNDROME (APS)

With regards to APS, a systemic autoimmune, albeit multifactorial, thrombophilic disease, it is characterized by venous, arterial or microvascular thrombosis, that commonly occurs without any underlying cause (primary APS). APS is also often associated with SLE, rheumatoid arthritis or other autoimmune diseases (secondary APS), as detailed by Polytaichou et al. [23]. Cardiovascular complications in APS comprise accelerated atherosclerosis, acute coronary syndrome, Libman-Sacks endocarditis, cardiomyopathy or intracardiac thrombi. Although anticoagulation therapy is of paramount importance in preventing thromboembolic complications, data regarding treatment of the primary initiating pathophysiological mechanism of the syndrome remain scarce.

8. JUVENILE IDIOPATHIC ARTHRITIS

Juvenile idiopathic arthritis (JIA) needs special mention as it is the most common ARD in children and, similarly to adult ARDs, it may predispose to CVD, as detailed by Arsenaki et al. in part 2 of this thematic issue [24]. Again, the increased inflammatory burden, along with an adverse cardiovascular risk factor profile and cardiovascular side effects from anti-inflammatory drugs may contribute to CVD development in these young patients. Interestingly, the data in this subset of ARDs are limited, mainly derived from observational studies. Importantly, JIA, especially in its systemic and polyarticular form, can
affect all cardiac structures; cardiovascular complications account for a significant percentage of morbidity and mortality conferred by the disease, with pericardial disease reported in up to 30% of JIA patients. As advised by the authors, individualized screening, improved risk stratification and intensification of primary prevention measures for CVD are likely to be of benefit in this young patient population.

Importantly, adults with a history of JIA have a significantly increased risk of metabolic syndrome compared with those without arthritis [25]. Furthermore, adults with long-lasting active JIA have altered arterial properties compared with controls, attributable to long-term treatment with corticosteroids and its associated insulin resistance [26]. In general, the vascular function has been shown to be impaired in patients with systemic onset JIA at a very young age, partly attributed to the effects of disease-related characteristics, such as inflammation, disease activity, and medications [27]. Finally, subclinical atherosclerosis has been suggested to be associated with JIA, possibly related to alterations in high-density lipoprotein (HDL) particle distribution, cholesterol efflux and non-lipid transporting activities [28]. However, other studies have refuted such claims by assessing carotid intima-media thickness (IMT) and carotid stenosis as surrogate measures for CVD in adults with long-term active JIA and healthy age- and sex-matched controls, and finding no differences in these two groups [29]. This is in keeping with reports of long-term follow-up of patients with JIA exhibiting no increase in CVD events when compared with the general population [30]. Interestingly, in this latter report, the presence of CVD risk factors was found to be increased in the JIA group compared with the controls in 3 categories, those with family history of CVD, hypertension, and ever smokers. Further studies will be needed to more definitively clarify the relationship between CVD, cardiovascular risk factor development, and JIA. For now, controlling the chronic inflammatory state of JIA by current therapies and managing comorbidities seems reasonable as it may confer significant long-term benefits [31, 32].

9. CARDIO-RHEUMATOLOGY

From all the reviews included in this Thematic Issue of Current Vascular Pharmacology, it becomes abundantly clear that collaboration between the 2 disciplines of Rheumatology and Cardiology is desirable to fine-tune risk stratification and optimize pharmacological therapies in patients with ARDs. This may best be accomplished by establishing the role of the emerging field of Cardio-Rheumatology or Rheumato-Cardiology [33].

LIST OF ABBREVIATIONS

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<tr>
<td>APS</td>
<td>Antiphospholipid Syndrome</td>
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<td>ARDs</td>
<td>Autoimmune Rheumatic Diseases</td>
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<td>CMR</td>
<td>Cardiac Magnetic Resonance</td>
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CV = Cardiovascular
CVD = Cardiovascular Disease
DMARDs = Disease-Modifying Antirheumatic Drugs
HF = Heart Failure
JIA = Juvenile Idiopathic Arthritis
SLE = Systemic Lupus Erythematosus
TNF = Tumour Necrosis Factor

REFERENCES


