Autoimmune diseases, their pharmacological treatment and the cardiovascular system

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Abstract

Cardiovascular system involvement is a frequent complication of autoimmune diseases (AD) such as systemic lupus erythematosus, scleroderma, rheumatoid arthritis, spondyloarthropaties or psoriatic arthritis. The most common forms of such involvement are pericarditis, myocarditis, accelerated atherosclerosis resulting in myocardial infarction or stroke, arrhythmias, conduction abnormalities or congestive heart failure. Some of these manifestations may be dramatic in their course and ultimately fatal. The treatment of AD may further affect the cardiovascular system and result in a lower quality of life, higher mortality and increased cost of healthcare. The aim of this review is to discuss possible cardiac complications of various AD and the related treatment of these diseases. (Cardiol J 2013; 20, 6: 569–576)

Key words: cardiovascular complications, autoimmune diseases, heart failure, adverse drug effects

Introduction

In developed countries approximately 25% of the general population suffers from some form of autoimmune disorders [1]. Autoimmune diseases (AD) are characterized by a primary dysfunction of the immune system with increased level of auto-antibodies, inflammatory and mediatory cells resulting in chronic inflammation of connective tissue [2]. The risk factors influencing the development of AD include: advancing age, gender, genetics, environmental insults, and infections [3]. Women tend to be stricken more often with rheumatoid arthritis, systemic lupus erythematosus (SLE) and scleroderma (SCL), while men tend to suffer from ankylosing spondylitis and certain types of vasculitis.

AD can be subdivided into organ specific and non-organ-specific [2]. The examples of organ specific AD include type 1 diabetes mellitus, which results from pancreatic insufficiency following the annihilation of beta cells through the invasion of T-cells, leading to insulin deficiency; Hashimoto's thyroiditis and Graves' disease affecting the thyroid gland but resulting in multi-system effect. Diffuse non-organ specific autoimmune diseases, such as SLE or SCL, tend to have a multi system involvement, including the cardiovascular (CV) system.

Autoimmune diseases and the cardiovascular system

Pericarditis is the most common CV complication of AD and is considered to be immune-mediated, although co-existing infection may play a role in some cases [1]. It is a frequent symptom in SCL (50% of patients), SLE and rheumatoid arthritis (30% each), and its extension generally reflects the activity of the systemic involvement of AD [2]. Asymptomatic pericardial effusion and/or

pericarditis may be the primary and sole manifestations of an underlying autoimmune process. Arrhythmias or conduction disorders are quite frequent in AD. They tend to be caused by an infiltration of inflammatory cells with ensuing fibrosis of the conductive system and myocardium. Inflammatory infiltrates are usually observed in SCL, systemic lupus erythematosus, rheumatoid arthritis, and seldom in polymyositis, dermatomyositis and mixed connective tissue disease. Autoimmune mediated inflammatory process may also affect coronary arteries and lead towards ischemic heart disease or acute coronary syndromes. Non-infective endocarditis with primary involvement of the left heart valves is observed in systemic lupus erythematosus. Pulmonary hypertension, developing during the course of AD is an example of an indirect effect on cardiac function. Autoimmune inflammatory processes can have disastrous effects on major vessels, causing aneurysms, arterial and venous thrombi and various forms of embolization. These can develop into emergent and potentially fatal scenarios. It would be worthy to note that each of ADs directly or indirectly affects the CV system with varying severity [2–4].

SLE is an inflammatory disease of the connective tissue, affecting approximately 0.1% of the general population, with the female-to-male ratio 6–10:1. Pericarditis manifests in just a bit over 50% of SLE patients, however they may remain asymptomatic. In certain cases pericarditis may precede clinical signs of SLE or exacerbate the underlying disease. On CV imaging, small pericardial effusions and thickening of pericardial plaques may be observed in SLE patients. Clinically urgent pericarditis occurs in 30% of patients, with substantial fluid accumulation resulting in cardiac tamponade [5, 6]. In the latest clinical evaluations, cardiac tamponade was found in 22% of patients, whose management required high-dose corticosteroids and in half these cases — a pericardial window [7]. Antiphospholipid antibodies, detected in approximately 30–50% of SLE patients, are the main risk factor for CV complications [6]. These antibodies cause complement activation and deposition of immune complexes in tissues and may affect the conductive system of the heart. Non-infective verrucous vegetations found on valves, first described in 1924 as the Libman-Sachs endocarditis, are one of the most characteristic symptoms of SLE. In 63% of cases the mitral valve is involved, however aortic valve or multivalvular involvement is relatively common. Libman-Sachs endocarditis occurs in 50% of patients with SLE [8].

It is usually mild but in approximately 20% of cases have a severe progression to valvular dysfunction requiring surgical intervention [9–15]. Over the natural course of SLE, several inflammatory changes take place within the endothelium (accumulation of inflammatory cells, thickening of intima-media, formation of plaques), leading to premature and accelerated atherosclerosis, with increased risk of coronary heart disease and/or stroke. The risk of acute coronary syndromes is significantly increased, when compared to the general population, in each age group of patients with concomitant SLE and antiphospholipid syndrome, but is particularly greater in young women whose risk is increased 50-fold. In the John Hopkins SLE Cohort Study, coronary artery disease occurred in over 8% of the studied patients and was responsible for 30% of deaths in the 3-year follow-up. In the Toronto Cohort Study 11% of SLE patients developed coronary artery disease due to the vascular changes. Pulmonary arterial hypertension can occur as patients develop interstitial lung disease or intimal proliferation of pulmonary arteries [16]. Within this patient group, the CV risk is significant and associated with a worse prognosis. Neonatal lupus, a congenital form of SLE, is a passively transferred autoimmune disease. It concerns 1.6–2% of neonates born to mothers with SLE. It may be diagnosed in young infants causing complete heart block (detected by fetal echocardiography or magnetocardiography at about 20 weeks gestation). Fortunately, neonatal lupus typically resolves by the age of 6-months [2, 17].

In the 8-year follow-up multi-centre study (Atherosclerotic Vascular Events Cohort of SLE), the prevalence of atherosclerotic vascular events was found to vary between 8–13% within SLE patients, with a peak incidence 8 years after diagnosis. In the Pittsburgh Cohort, the CV risk among women with SLE was found to be approximately 7%. Prolong duration of SLE and extended use of corticosteroid were the main risk factors for the development of CV events [18].

Antiphospholipid syndrome, also known as Hughes syndrome, is an inflammatory disorder that presents with antiphospholipid antibodies causing arterial and venous thrombosis. Pulmonary hypertension is relatively common, occurring in approximately 70% of patients with antiphospholipid antibodies [19]. Antiphospholipid antibodies cause an activation of complement, followed by deposit formation of immune complexes in tissues. These patients may suffer from angina pectoris and, in some (8%) advanced cases, myocardial

infarction (MI). Additionally, there is an increased risk of re-occlusion following coronary angioplasty or coronary artery bypass grafting [20–23].

Valvular (mitral and aortic) regurgitation (12%), secondary to their thickening (30%) or destruction, is usually a mild form of valvular impairment, but in 4–6% of patients it progresses to severe valvular defects necessitating surgical intervention. Most of the valvular involvement is clinically silent, some of patients, may have severe thromboembolic events, including stroke [24–26].

SCL is a disease which causes the fibrosis of the skin and internal organs, affecting 70,000 Americans. Female-to-male ratio is 7–10:1 [2]. CV complications in SCL patients include: pericarditis, cardiac arrhythmias, congestive heart failure (HF) and pulmonary hypertension — the main cause of death in SCL patients. In large cohort studies on SCL, the CV system involvement was responsible for up to 36% of all deaths, while cardiopulmonary deaths accounted for 70% of the mortality [27]. Symptomatic pericarditis occurs in approximately 20% of SCL patients, with evidence of pericardial involvement found in 80% of autopsy cases [28]. Inflammation and autoimmunity stimulate fibroblasts activation, myofibroblasts recruitment, and production of collagen leading to fibrosis. Progression of myocardial fibrosis in SCL results in the development of cardiomyopathy followed by diastolic and systolic HF with significantly reduced left ventricular ejection fraction [29]. Recent studies have revealed myocardial fibrosis in 37% of SCL autopsy cases. Fibrosis leads to reduced coronary blood flow resulting in myocardial ischemia and may even precipitate MI. In the absence of significant coronary narrowing, a reduction in coronary blood flow reserve is observed in 55% of asymptomatic patients. This suggests that myocardial involvement is due to the impairment of microcirculation and is associated with structural abnormalities of small coronary vessels [30]. Coronary angiography revealed tortuosity (50%), calcification (33%), stenosis (20%), ectasia and slow flow (20%), and spasm (< 10%) in SCL patients [31]. Pulmonary hypertension has a yearly incidence of 6 in 1000 SCL patients as a result of pulmonary vascular obliteration, interstitial fibrosis of pulmonary tissue or left ventricular HF, and less frequently by pulmonary embolization. Lung disease is found in 80% of SCL patients. A recent meta-analysis of more than 3.5 thousands patients showed that SCL associated pulmonary arterial hypertension (PAH) is particularly aggressive. Untreated PAH is associated with a median survival of 1 year following its diagnosis in SCL patients. PAH remains the main cause of death among SCL patients [31]. The 3-year mortality of SCL patients with PAH varies between 36% and 53% with different reports. Mortality is significantly higher (61–72%) in SCL patients with pulmonary hypertension secondary to interstitial lung disease [32, 33].

Echocardiography reveals left ventricular systolic dysfunction in about 30% of patients, and thickening of the aortic and mitral valve leaflets in 12% and 8%, respectively [2, 34, 35]. A quarter of patients with progressive SCL have developed antibodies to cardiac conducting tissue. ECG studies show that arrhythmias and conduction abnormalities are quite frequent in SCL. These are usually incomplete right bundle branch block (41%), benign supraventricular arrhythmias, transient atrial fibrillation, atrial flutter, first degree atrioventricular block, and nodal rhythms (each 10%). These ECG abnormalities are likely to be transient and result from fibrosis of the myocardium and conductive system. In 6–10% of SCL patients, sudden cardiac death secondary to ventricular arrhythmia is reported. Studies found that 75% of SCL patients have a normal resting ECG and 24-h Holter monitoring [34]. Other clinical studies revealed the presence of ventricular arrhythmia in a form of frequent single premature ventricular beats, as bigeminy, trigeminy or pairs in 67% of SCL patients. More serious ventricular arrhythmias such as non-sustained ventricular tachycardia is observed in 7–13% of SCL patients. Supraventricular arrhythmias were less frequent in SCL — atrial fibrillation/flutter or supraventricular paroxysmal tachycardia were found in 20–30% of patients. Conduction disturbances were diagnosed in 25–75% of SCL patients. Sudden cardiac deaths were reported in 5–21% of individuals, usually in patients with skeletal muscle involvement. One effective treatment is cardiac ablation for drug-intolerant and drug-resistant arrhythmias; it, however, should be considered as an alternative treatment. Life-threatening ventricular arrhythmias require an implantable cardioverter defibrillator, whereas advanced conduction disorders need to be managed with a pacemaker implantation [27]. The question must be asked whether it would be warranted to implant a cardioverter-defibrillator device in SCL patients, as a primary prevention.

Rheumatoid arthritis (RA) is an inflammatory disease with distinctive joint malformations affecting about 1–2% of the general population. Peak incidence occurs in the fourth and fifth decade of

life, 3 times more often in women. Patients with RA have a significantly increased risk of developing HF (34%) compared to the general population. In particular, this trend is strongly marked in women, and is constantly higher in the long-term follow-up suggesting that prolonged exposure to inflammatory agents has no impact on the development of HF [36–38]. Similarly, there is a high prevalence of coronary heart disease, with 43% higher risk for patients with positive rheumatoid factor and as much as 2.5-fold increased risk for patients without the presence of rheumatoid factor. Effects of chronic inflammation, such as endothelial dysfunction and dyslipidemia, increase risk of CV mortality. Silent course of angina pectoris with frequent complication of sudden cardiac death is characteristic for RA. Inflammatory changes, especially in the left anterior descending and left circumflex arteries, are found at autopsies [39–43]. Pericarditis is a common symptom of heart involvement in RA and it is present in 75% of patients [2]. Constrictive pericarditis may occur in few percent. Pulmonary hypertension is rare and usually secondary to intestinal lung disease. Pathologic examinations revealed inflammatory pulmonary vasculitis, plexiform vasculopathy with intimal hyperplasia and smooth muscle hypertrophy [44]. Pulmonary hypertension may also originate from chronic venous thromboembolic disease, especially in patients with coexisting SCL. Some clinical studies reported an increase in the carotid artery intima-media thickness in RA patients compared to the general population [3]. Certain RA patients may develop valvular dysfunction [45]. CV complications affect 53% of RA patients [46, 47].

In a retrospective population-based cohort from the Rochester Epidemiology Project, the 10-year CV risk in RA patients was found to be comparable to that of healthy individuals who were on the average 10 years older [48].

Patients suffering from polymyositis and dermatomyositis, diseases involving the skin and muscles which have co-existing CV disease, are deemed to have a poor prognosis. It is estimated that up to 20% of patients with polymyositis die from cardiac disease. The average risk of post MI mortality in polymyositis and dermatomyositis is 16-fold increased; men 9-fold, women up to 32-fold. Congestive HF (up to 45%), angina pectoris (44%), MI, Prinzmetal angina and pericarditis (10% respectively) are the most common manifestation of cardiac involvement in these patients. The frequency of these CV complications varies depending on the population selected and diagnostic methods used. Another reported CV complications are arrhythmias and conductive abnormalities, which include supraventricular or ventricular tachycardia, atrioventricular blocks, bundle branch blocks, nonspecific ST-T changes and abnormal Q waves occurring in 32% of patients [49]. Lymphocyte infiltration throughout the sinoatrial node is rare, however when it occurs, it results in a complete heart block requiring a pacemaker implantation. Extensive deposits of inflammatory cells (primarily T lymphocytes and macrophages) followed by degeneration of cardiac myocytes and secondary restrictive cardiomyopathy. As a result, severe congestive HF with significantly reduced left ventricular ejection fraction is observed. Interstitial lung disease is also found in 5–30% of patients and leads to right ventricular HF [49].

The Quebec cohort study recruited 607 patients with dermatomyositis and polymyositis showed the risk of MI equal to 5.3/1000 person-years. Higher incidence of MI in patients with dermatomyositis and polymyositis comparing to the general population was observed in all demographic groups except men younger than 65 years. In this cohort, the rate of stroke was 5.1/1000 person-years, twice as high as in healthy subjects (3.1/1000 person-years) and similar to recorded in RA patients.

In the case-control study of the Healthcare Cost and Utilization Project, data from over 50,000 hospitalizations of patients with dermatomyositis (20% of US hospitals) were analyzed. For dermatomyositis patients, the rate of death and CV diseases was 2-fold higher than in age- and gender-matched patients without dermatomyositis. Congestive HF was one of the most frequent causes of death in these patients. This study also found that the prevalence of hypertension and diabetes mellitus among dermatomyositis patients was significantly higher than in the general population (62% and 29% compared with 9% and 4%, respectively). Similar findings were observed in patients with dermatomyositis or polymyositis regarding any cerebrovascular accident [50].

Spondyloarthropaties are inflammatory diseases of the vertebral column. The most common of these — ankylosing spondylitis (AS) is diagnosed in approximately 1.5% of the population, with 2–3:1 male-to-female ratio, affecting younger male population. The most common CV complications found in patients with AS are: aortic regurgitation (up to 50%), inflammation of the ascending aorta, atrio-ventricular blocks, bundle branch blocks and pericarditis. Presence of the HLA-B27 gene

predisposes individuals to proximal aortitis, diastolic dysfunction and conduction abnormalities [51]. Aortic root disease is reported in 100% of autopsies and in over 80% of transoesophageal echocardiographies. Twenty percent of patients with ascending aorta disease may have either congestive HF, experienced stroke or undergone valve replacement surgery [52].

Psoriatic arthritis affects about 0.5% of the general population. The inflammation of the ascending aorta with secondary aortic valve involvement may develop as a result of psoriatic arthritis. This is, however, an extremely rare complication. CV symptoms are significantly more frequent in patients with reactive arthritis. Pericarditis, myocarditis, inflammation of initial segment of the ascending aorta with secondary aortic valve regurgitation, and nonspecific ST-T changes or conduction abnormalities are diagnosed [53].

Summary of the CV complications in autoimmune diseases is shown in Table 1.

Treatment of autoimmune diseases and cardiovascular system

In spite of the unfavorable influence of autoimmune diseases, AD treatment has also a significant impact on the CV system. The pharmaceutical treatment of autoimmune inflammatory diseases takes a toll on the CV system, creating a broad array of side effects. The most common drugs used in AD pharmacotherapy are non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and so-called disease-modifying antirheumatic drugs (DMARDs) like methotrexate, sulfasalazine or chloroquine. Cyclophosphamide, cyclosporine, and biological treatment are also used.

Glucocorticoids are associated with hypertension (62%), diabetes (18%), dyslipidemia (66%) or thromboembolic complications. They alter kidney function inducing fluid and electrolyte disorders, resulting in congestive HF and hypertension [54, 55]. Glucocorticoids are generally considered to increase the CV risk. Although, the case-control nationwide study has not confirmed this finding [50]. Contrary, results from the QUEST-RA study showed that glucocorticoids use is accompanied by a small decrease in risk of all CV events [56]. Recent studies in SLE and RA have suggested that corticosteroids have a potential to reduce CV risk probably by lowering the autoimmune activity and the severity of inflammation [57].

NSAIDs therapy increases the risk of MI, cerebrovascular accident, congestive HF and systemic hypertension [58]. NSAIDs are especially

Table 1. The impact of autoimmune diseases in the cardiovascular system.

	Pericarditis	Heart failure	Arrhythmias	Angina pectoris/ myocardial infarction	Ascending aorta inflammation	Endocarditis	Myocarditis	Accelerated atherosclerosis	Pulmonary hypertension
Systemic lupus erythematosus	✓	✓		✓		✓	✓	✓	
Antiphospholipid syndrome				✓		✓			
Systemic sclerosis	✓	✓	✓						✓
Rheumatoid arthritis	✓	✓		✓				✓	
Polymyositis	✓	✓	✓	✓					
Dermatomyositis	✓	✓	✓	✓					
Spondyloarthropaties	✓		✓		✓				
Psoriatic arthritis					✓		✓		
Reactive arthritis	✓		✓		✓				

dangerous in the elderly, as they may exacerbate pre-existing HF due to renal dysfunction [59, 60]. The cyclooxygenase-2 (COX-2) inhibitors may create a pro-thrombotic/coagulation imbalance on the endothelial surface, with thrombus formation and potentially fatal embolization. Two large meta-analyses based on over 90 clinical trials showed that NSAIDs increase blood pressure, with higher elevations in hypertensive patients. This drug-induced elevation of blood pressure is associated with a reduction in blood concentrations of prostaglandins and renin. Among the NSAIDs reviewed, piroxicam induces the highest increase in blood pressure, whereas aspirin and flurbiprofen evoke a lower increase in overall blood pressure. NSAIDs interfere with the anti-hypertensive effects of several classes of CV drugs, including: diuretics, angiotensin-converting enzyme inhibitors and beta-blockers. Sustained use of non-selective NSAIDs and selective COX-2 inhibitors results in an extremely increased hazard ratio for ischemic stroke, 1.7 and 4.5, respectively. Furthermore, NSAIDs therapy is associated with sodium and water retention, with double the hospitalizations due to congestive HF [58–60].

Patients being treated with sulfasalazine and leflunomid may develop pericarditis and hypertension, respectively. Chloroquine an antimalarial drug, which has shown a great benefit in the management of ADs has been associated with widening of the QRS complex, QT interval prolongation, T wave changes and in rare cases complete heart block, necessitating pacemaker implantation [61–63]. Cardiomyopathy and ensuing congestive HF resulting from long-term chloroquine therapy have also been reported, albeit rarely [64–66]. In the case-control study, DMARDs (especially azathioprine) correlate inversely with the CV events in dermatomyositis and polymyositis. Hydroxychloroquine improved lipid profiles in SLE patients, however this study failed to prove its beneficial effect on the clinical events form the CV system [50]. A huge QUEST-RA study (2005–2006) recruiting over 4000 patients from 15 countries proved that one year treatment with methotrexate was associated with 15%, 18%, and 11% decreases of risk for all CV events, MI, and stroke, respectively [56]. Methotrexate may cause pericarditis or pericardial effusions, and lead to pulmonary fibrosis and congestive HF. Methotrexate may increase the risk of hypotension, diabetes and thromboembolic events (arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, pulmonary embolization). However, methotrexate

has been of some benefit to the CV system as it has been reported to reduce atherosclerotic lesions in coronary arteries [67]. It also can be used as adjunctive therapy for asthma to reduce inflammation.

Infliximab increases the frequency of arrhythmias, hypertension and HF, and in rare cases may cause episodes of hypotension. However, the large population QUEST-RA study revealed lowered risk for all CV events in patients with a long history of TNF-alpha blockers treatment [56].

Etanercept, an immunosuppressive agent with an extremely long half-life of 102 ± 30 h, is used to treat rheumatoid arthritis. Etanercept has many side effects from increased risk of coronary artery disease, MI, chronic HF, deep vein thrombosis and hypertension. Fortunately, these side effects are relatively rare and observed in only 1.5% of patients receiving this treatment [68].

Cyclosporine inhibits the cellular and humoral immune response by modifying inflammatory reactions by its influence over the T_H cell activation, indirectly inhibiting the production of antibodies and macrophage activation. Patients treated with cyclosporine may experience hypertension, hyperlipidemia, chest pain or cardiac arrhythmias. The most severe complication of cyclosporine therapy is renal failure resulting in hypertension, fluid and electrolytes imbalance (hyperkalemia, hypomagnesemia) and imminent congestive HF [69, 70].

Anakinra, a human interleukin-1 receptor antagonist, was first used in to treat autoimmune disease in 2001. According to more recent reports, it also helps reduce myocardial ischemia in acute coronary syndromes. The exact mechanism of action is not fully known and requires further evaluation [71].

Summary of the CV side effects of the drugs used in AD therapy is shown in Table 2.

Implantable cardioverter-defibrillators have proven themselves in preventing sudden cardiac death, in cardiac patients, however there is lacking data on their use in patients who manifest life threatening arrhythmias as a result of autoimmune disease and therefore a further investigation is required.

Conclusions

Multisystem involvement is the hallmark of AD, and the CV system is a frequent target of the most common systemic autoimmune diseases. In the last several decades, the increased prevalence of CV complications in patients with AD has been observed. CV manifestations range from mild

Table 2. Side effect of drugs used in autoimmune diseases of the cardiovascular system.

Drug	Side effects from the cardiovascular system
Glicocorticosteroids	Arterial hypertension, diabetes, thromboembolic complications, renal impairment, heart failure
Nonsteroidal anti-inflammatory drugs	Edema, arterial hypertension, worsening heart failure, acute coronary events
Sulfasalazine	Pericarditis
Leflunomid	Arterial hypertension
Chloroquine	Arterial hypotension, changes in the ECG: QRS prolongation, QT prolongation, T wave changes, cardiomyopathy, III degree atrioventricular block, heart failure, ventricular arrhythmias
Infliximab	Arrhythmias, arterial hypertension, heart failure aggravation, arterial hypotension
Etanercept	Coronary artery disease, myocardial infarction, heart failure, thrombosis, arterial hypertension
Cyclosporine	Chest pain, irregular heartbeat, kidney failure, arterial hypertension, heart failure
Metotrexate	Pericardial effusion, pulmonary fibrosis, asthma, pulmonary hypertension, heart failure, diabetes
	Beneficial effect of reducing atherosclerotic lesions in coronary arteries
Anakinra	Beneficial effect of reducing the area of ischemia in acute coronary syndromes

to severe, even being the initial presentation of AD. Cardiologists should remain vigilant to for underlying diseases. Since silent CV involvement is common, it is rarely recognized.

Both autoimmune diseases and their management have a significant impact on the CV system, which results in decreased quality of life, higher mortality and increased cost of healthcare. Improving the quality of life, preventing CV adverse events, decreasing hospitalizations and mortality, all-the-while minimizing pharmacological side effects is the present goal of this multidisciplinary management of autoimmune disease.

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