Triggers of Cardiovascular Diseases in Rheumatoid Arthritis

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Abstract: The risk of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) is higher than that in patients without RA, and it is even higher than that in patients with diabetes. Autoimmune-mediated inflammation is observed in patients with RA, resulting in endothelial dysfunction, oxidative stress and activation, and vascular migration of white blood cells. Traditionally, RA-associated CVD was assumed to be mediated by disease-related inflammation, resulting in atherosclerosis (AS). However, this concept has been challenged because treatment with anti-rheumatic drugs, such as methotrexate or proinflammatory cytokine antagonists, such as tumor necrosis factor-alpha (TNF-α) inhibitors, did not reduce the risk of CVD in patients with RA. Current cardiovascular guidelines recommend screening and treatment of CVD risk factors in patients with RA but without clear biomarkers and treatment goals. There is no scientific basis for establishing therapeutic targets for cardiovascular risk factors in RA. Numerous studies have shown that the mechanism of early cardiac dysfunction in patients

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with RA may occur prior to AS. Therefore, it is crucial to explore the related mechanisms to prevent early cardiac dysfunction in patients with RA. (Curr Probl Cardiol 2022;47:100853.)

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease. Its pathological changes primarily include chronic, progressive synovitis and vasculitis, which may be associated with damage to systems other than the joints, such as the cardiovascular (CV), respiratory, digestive, and urinary systems. The pathogenesis of RA is complex and remains unclear.[1] Although numerous treatments are available, including steroidal anti-inflammatory drugs, non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and biological agents, which effectively control joint inflammation, the mortality rate in patients with RA remains higher than that in the general population.[2] It is well-known that patients with RA may become disabled, but the main cause of death is cardiovascular disease (CVD).[3] The incidence of heart diseases in patients with RA has increased significantly and is equivalent to that in patients with type 2 diabetes.[4,5] People have now accepted RA and diabetes as independent risk factors of CVD. Numerous studies have reported 30%−60% incidence of CVD in patients with RA, primarily including heart failure (HF), ischemic heart disease (IHD), pericarditis, myocarditis, and cardiomyopathy.[6] Moreover, CV events account for 42% of total RA-related deaths and occur early in patients with RA, shortening their survival by 5 to 15 years.[7] After correcting for traditional CVD risk factors, such as age, gender, body mass index, blood pressure, smoking, diabetes, and hypercholesterolemia, the incidence of CVD events in RA was found to be 3.17%, which cannot be explained using traditional CVD factors. HLA-DRB1, the main risk gene of RA, is associated with an increased risk of MI and various other heart diseases. Pericarditis is the most commonly occurring cardiac condition, and the endocardium, myocardium, heart valve, and conduction systems of the heart are likely to be affected by RA.[8] HF is a major cause of death among patients with RA.[9] Pathogenesis of HF in RA includes IHD, inflammatory mediators, antirheumatic drug therapy, and amyloidosis.[10] The main cause of CVD that contributes to cardiac dysfunction remains unclear.[11] Thus, early diagnosis and prevention of cardiac dysfunction is of outmost importance. In this review, we describe recent observations and have combined the

knowledge to explore the causes and mechanisms of early cardiac dysfunction in patients with RA before the occurrence of AS. In addition, prevention and treatment of the disease are summarized. We discuss the specific pathological changes and pathogenesis of RA complicated by CVD and therapeutic strategies and implications for clinical treatment.

Cardiac Complications in RA

Pericarditis in RA

Pericarditis is one of the most common cardiac manifestations of RA. Many patients with early RA can be complicated with pericarditis or develop pericarditis before RA. Although clinical symptoms are observed in less than 15% of patients with RA, ECG showed that 20%−50% of patients present pericardial involvement, manifesting as pain in the chest or dyspnea. Audible pericardial friction rub with hemodynamic abnormalities due to pericardial disease are rare, occurring in less than 10% of patients with RA.[12] According to autopsy reports, 20%−40% of serum RF-positive patients present pericarditis. Therefore, strict physical examination and antibody screening are required to detect RA with pericarditis as soon as possible and the early diagnosis of pericarditis and effective treatment will significantly improve the prognosis of RA patients.[13]

Sudden Cardiac Death (SCD) in RA

Arrhythmia is another common cardiac complication in patients with RA that may occurs secondary to conduction abnormalities because of local ischemia, rheumatoid nodules, amyloidosis, or HF. In a large cohort study group of 603 cases of patients with RA followed up for 15 years, Maradit-Kremers et al. reported that SCD was two-fold more likely to occur in patients with RA than that in the control group.[14] Studies have shown that patients with RA may have a higher risk of life-threatening arrhythmias without structural heart abnormalities.[15] Abnormalities of the autonomic nervous system, such as decreased heart rate variability, and abnormalities of ventricular repolarization parameters, such as QTc interval and QT dispersion, have also been implicated Patients with rheumatoid arthritis (RA) have increased cardiovascular morbidity and mortality, including the risk of sudden cardiac death (SCD).[16] Inflammation has received increasing attention in recent years as an independent predictor of SCD.[17] It contributes to ventricular repolarization abnormalities, such as corrected QT interval prolongation, QT dispersion, and

autonomic dysfunction. Moreover, increased sympathetic activity in patients with RA can lead to an abnormal heart rate.[18] Both autonomic dysfunction and QTc prolongation have been shown to be correlated to inflammation, with the best evidence in place for CRP.[15] Early diagnosing of concealed arrhythmia and preemptively preventing SCD in this patient population is urgent.[16] Compared with routine ECG, ambulatory ECG may capture the concealed arrhythmia more accurately.

HF in RA

The increased risk of HF in RA has been well described.[19] Even after adjusting for CV risk factors and IHD, the prevalence of HF is two-fold higher in patients with RA than that in the general population and is generally higher in women than that in men, representing a major contributor to mortality.[20] Patients with RA are less likely to present typical signs and symptoms of HF, tend to respond less aggressively to the treatment, and have poor prognosis.[21] Patients with HF are also more likely to retain ejection fraction at >50% and are less likely to present clinical evidence of HF.[22] A high number of patients (66%) with RA initially present diastolic cardiac dysfunction, therefore, it may act as a precursor to overt cardiac failure.[23] With the progress of RA, left ventricular diastolic dysfunction is associated with abnormal electrocardiography (ECG), these findings suggest that patients with RA are more likely to develop HF due to diastolic dysfunction, which may be associated with systemic inflammation. Elevated levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA) and inflammatory cytokines may lead to HF progression in RA.[14] The Disease Activity Score-28, which is an RA active composite measure, is a predictor of HF in patients with RA.[24]

Cardiomyopathy (Myocarditis) in RA

Cardiomyopathy in patients with RA causes diffuse necrotizing or granulomatous myocarditis. The incidence of cardiomyopathy in patients with RA has been revealed to be 3%−30% by autopsy.[25] Myocarditis is a type of cardiomyopathy caused by necrosis and degeneration of the myocardial layer. The etiology of RA myocarditis remains difficult to evaluate. However, interleukin-1α (IL-1α) and other inflammatory mediators have been reported to be released from the degenerating myocardium along with the fragments, thereby activating inflammatory corpuscles in the adjacent cells.[26] Uncontrolled IL-1α-mediated inflammation leads to

cardiomyocyte apoptosis, contractile tissue loss and fibrosis.[27] Inflammation during active RA has a long-term effect on molecular remodeling and systolic function of the heart, which further supports the development of heart failure in patients with rheumatic disease.[28] Moreover, the toxicity of antirheumatic drugs, including corticosteroids and methotrexate (MTX), may lead to acute myocardial dysfunction.[29]

Coronary Artery Disease (CAD) in RA

As early as in 1960, RA patients with increased CAD and myocardial infarction risk have been reported, and the detection rate upon autopsy was 20%.[30] The main cause of CAD in RA may be associated with systemic inflammatory reactions that accelerate atherosclerosis (AS) progression together with abnormal lipid mass and vascular endothelial dysfunction.[31] Chronic inflammation of RA induces dyslipidemia, including decreased levels of high-density lipoprotein (HDL) cholesterol and increased levels of low-density lipoprotein (LDL) cholesterol. Vascular endothelial dysfunction is associated with the upregulation in LDL cholesterol level and the inflammatory state. Furthermore, it is widely accepted that RA and AS are auto inflammatory diseases involving multiple inflammatory cytokines and share a great deal of genetic susceptibility and environmental factors, thus RA patients are likely to be attacked by AS.[32] We have discussed cardiac involvement in RA and its significance in diagnosis and treatment of patients with RA (Fig 1). Of note, comparing with normal CAD patients without RA, symptoms of CAD is much severe in RA patients with high-risk in plaques formation, higher mean coronary calcium scores, and serious multivessel disease. AS

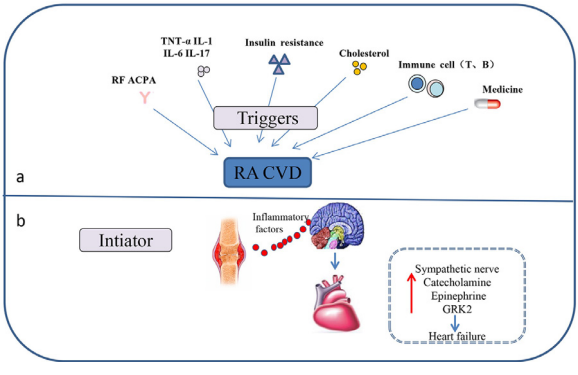

FIG 1. Triggers of cardiovascular Disease (CVD) in Rheumatoid Arthritis (RA). (A) Traditional triggers of RA CV complications. (B) Sympathetic drive and the expression of GRK2 in CVD.

plaques in patients with RA exhibit different forms and greater instability. Therefore, strategies to reduce CVD implied in the general population should be widely used in patients with RA.

Triggers of CVD Complications in RA

Other than the traditional epidemic factors of CVD, the specific pathologic changes of RA independently triggers the morbidity of CVD, among them the initial factor is worth to be revealed thus contributes to both early diagnosis and treatment. Although most studies have focused on AS in patients with RA, other factors also play a crucial role in early cardiac dysfunction in patients with RA. When patients with RA are diagnosed with abnormal cardiac function, diastolic function is found to be abnormal before early diagnosis, whereas AS is not detected. Patients with RA are twice as likely to suffer from SCD compared to patients with diabetes.[33] Therefore, we hypothesize that heart dysfunction occurs in patients with RA prior to AS, but the pathological mechanism of early cardiac dysfunction remains unclear. It is well-known that blood lipids have a strong predictive effect on AS, but the level of blood lipids in patients with RA is negatively correlated with inflammation. Recent human studies in active RA have shown that the rate of catabolism of lipids is higher than the expected rate of the general population.[34] It is clear that the traditional risk factors for AS are different in RA, and their presence does not explain the acceleration of AS in these patients.[35] Further, chronic inflammation is the main characteristic of AS and plays an important role in the acceleration of AS.[36] The imbalance in the autonomic nervous system (ANS) may be because of chronic inflammation, but, in turn, changes in ANS may affect inflammation, disease development, and severity.[37] Therefore, ANS dysfunction may be a significant and initial factor in RA CVD.

Sympathetic Drive in CVD

In patients with RA, sympathetic nerves excite and produce a high amount of catecholamines, which regulate cardiac contractions in the physiological state. The chronic inflammatory immune response of RA is accompanied with a decrease in the parasympathetic function and an increase in the excitability of the sympathetic nervous system.[38] In the early stage of CIA, the sympathetic nervous system is over-activated by inflammation, but the autonomic nervous dysfunction in the heart does not deteriorate after acute arthritis subsided.[39] Therefore, the increase in

sympathetic nerve activity in RA may cause the occurrence of CVD in addition to AS. RA is associated with decreased parasympathetic tension and increased sympathetic tension.[40] A recent systematic review showed that 60% of patients with RA present autonomic nervous dysfunction.[11] Maintaining the dynamic balance in the body requires synergistic action of the neuroendocrine and autonomic nervous systems. By controlling these two major information processing systems, specific neural networks within the central nervous system produce adaptive neurohumoral responses, which are necessary for proper regulation of the cardiovascular, fluid, and energy balance systems.[41] Balance can be re-established initially, but as HF progresses, the central neural network changes, and, usually, resting autonomic nerve reflexes are discovered. Chronic GRK2 hyperactivity has been reported for the first time to cause cardiac dysfunction and remodeling, which may be due to the desensitization of GRK2 in some tissues.[42] It has been found that long-term administration of high concentration of epinephrine can induce G protein-coupled receptor kinase 2 (GRK2) phosphorylated β1AR in cardiomyocytes, induce receptor desensitization and endocytosis, and inhibit the contractile function of cardiomyocytes.[43] Thus, we propose that GRK2 inhibitors can relieve arthritis, reduce inflammatory cell infiltration, restore β1AR sensitivity, and play an important role in the prevention of cardiac dysfunction, which is hoped to become a target of cardiac therapy in the future.[44]

Autoantibodies

Elevated levels of pro-inflammatory cytokines, circulating autoantibodies, and specific T cell subsets are thought to drive these findings by promoting atherosclerotic plaque formation and heart remodeling.[45] RA is a systemic autoimmune disease characterized by the presence of autoantibodies.[46] Except for RF, numerous patients with RA have been shown to produce antibodies that recognize certain peptides containing arginine residues, such as ACPA. The presence of ACPA has also been demonstrated in many studies on early arthritis to predict later development of RA.[47] RF can induce proinflammatory cytokines, such as tumor necrosis factor (TNF), IL-1, and IL-6, by combining with ACPAs. RA patients with higher level of RF expression had higher HF risk. Compared with RF negative RA participants, the HF risk in RF positive RA patients is doubled. Autoantibodies affect cardiac function through negative chronotropic effects or negative inotropic effects, which induce cardiomyocyte apoptosis and activate the complement pathway.[48,49] In addition, studies have shown that autoantibodies may impair inotropic cardiac function of

human and rat by binding to Fcγ receptor on myocytes in dilated cardiomyopathy, however, whether this mechanism is also applied in the blunted heart function of RA is unclear.[50] Currently, more attention is paid to disclose the pathological role of antibodies and autoimmunity in the pathogenesis of RA induced cardiomyopathy, and subsequent HF.

Pro-Inflammatory Cytokines

Epidemiological studies have shown that the release of pro-inflammatory cytokines, such as TNF-α and IL-6, from the synovial tissue and circulating immune cells in RA directly affects the onset of systemic inflammation and CVD. Extensive studies have suggested that inflammation participates in the onset and pathogenesis of AS and CVD even in the general population.[51] Researches have demonstrated that CRP level $>$ 3 mg/L is associated with an increased risk of CVD in the general population. More than half of the patients with RA were reported to have CRP of over 3 mg/L and a significant positive correlation between CRP and CVD has been approved.[52,53]

Increased plasma IL-1 level in patients with RA is related to several indicators of disease activity, including the Ritchie joint index, duration of morning stiffness, and pain score.[54] IL-1 plays an important role in most cell types involved in heart injury and repair and exerts multi-directional effects on the infarcted myocardium. Various studies have shown that IL-1 promotes apoptosis and hypertrophy of myocardial cells while inhibiting the contractility of the myocardium.[55] Additionally, IL-1β is able to induce cardiomyocyte hypertrophy, upregulate atrial natriuretic peptide, and inhibit the expression of calcium regulatory genes.[54]

IL-6 mediated signaling pathway in cardiomyocytes exhibits myocardial protective effects during acute reactions; however, over the long term, increased IL-6 level may lead to poor adaptability to hypertrophy and decreased systolic functions.[56] In response to inflammation, cardiomyocytes are able to produce IL-6, and subsequently, the increased IL-6 in myocardium contributes to a decrease in cardiac function.[57] In addition, elevated IL-6 stimulates CRP production by hepatocytes, and further affects cardiac function by promoting the incidence of CVD.[58]

Recently, it has been found that IL-17, an important pro-inflammatory cytokine family accelerates myocardial fibrosis and AS in non-RA animal models.[45,46] Moreover, elevated IL-17 levels have been detected in patients with acute coronary syndrome.[59] In patients with RA, IL-17 affects microvascular function and arterial compliance, thus playing an important role in the development of endothelial dysfunction and CVD.[60]

The role of TNF-α in the development of AS has been fully demonstrated and may include induction of endothelial dysfunction and vascular instability, the absorption of inflammatory cells at the injured site or promotion of reverse remodeling of vascular smooth muscle cells. TNF-α plays an important role in the pathogenesis of CHF, and leads to cardiac remodeling and peripheral vascular disorder. Moreover, TNF regulates both cardiac contractility and peripheral resistance, which are the most important hemodynamic determinants of cardiac function. Moreover, elevated levels of TNF and its soluble receptors are related to the progression of ischemia−reperfusion injury, myocarditis, allograft heart transplantation, and CHF in RA.[61]

Overactive Immune Cells

Besides the action of secreted cytokines or antibodies, the over activated immune cells directly affect cardiovascular system. Emerging evidence suggests that T lymphocytes play a critical role in RA and heart diseases.[62] In people suffering from RA, CD4 positive T cells exhibit loss of the co-stimulatory molecule CD28, which typically provides the "second signal" required for T cell activation primarily due to the mutation of HLA-DRB1.[63] RA patients with a higher level of circulating $CD4^{+}CD28^{null}$ T cells show an increased risk of CV events. $CD4^{+}CD28^{null}$ T cell present in AS plaques and recruits other subtypes of T cell and macrophage by producing IFN-γ.[64] Regulatory T (Treg) cells exert anti-inflammatory effects and are reduced in RA, the imbalance of $CD4^{+}CD28^{null}$ against Treg not only aggravates RA but also reduces the thickness of fibrous cap and predisposes the rupture of AS plaque.[65] Depletion of B cells ameliorates the cardiac fibrosis in a murine acute cardiomyopathy model.[66] B cells are expanded in RA with the differentiation into plasma cells and memory B cells and abundant autoantibodies produced. Except for the pathological role of antibodies in the development of heart dysfunction, B cells may influence the cardiovascular system through multiple mechanisms. High level of B cell activating factor (BAFF) and CCL7 synthesized by mature B lymphocytes in RA and these mediators may drive monocytes to myocardium leading to heart injury.[67] In addition, the activated B cells in the process of RA express a great deal of metalloproteinase-9 which degradates the extracellular matrix both in joints and heart, contributes to joint deformity and cardiac remodeling .

Metabolic Disorder

Similar to other chronic inflammatory diseases, patients with RA exhibit metabolic alterations that may lead to the significant increase in

CVD risk. The main features of metabolic syndrome of RA patients include insulin resistance, central obesity, dyslipidemia, and hypertension. Although, a study found that total cholesterol, LDL cholesterol, and HDL cholesterol levels are decrease in patients with RA, however, HDL cholesterol is decreased most significantly, increasing the AS index (total cholesterol and/or HDL cholesterol),[68] therefore, the CV risk is enhanced. The cause of dyslipidemia in RA remains unclear, evidences have shown that some polymorphisms in genes may be involved. Many studies have confirmed the link between RA and insulin resistance.[69]

Insulin resistance in RA is assumed to be associated with seropositivity,[70,71] pro-inflammatory cytokines, such as IL-6 and TNF-α; disease activity, and glucocorticoid usage.[72,73] Serum retinol binding protein 4 (RBP4), a protein secreted by adipocytes, is elevated in patients with impaired glucose tolerance and type 2 diabetes.[74] It has been reported that the level of RBP4 in patients with RA is higher than that in the control group and is positively correlated with the severity of RA.[74] Insulin resistance is important in the development and progression of atherosclerotic CVD and is considered as a characteristic pathogenesis for CVD.[75,76] Conversely, RA induced insulin resistance leads to aggravated inflammatory signaling pathways and results in increased systemic inflammatory response. As recently reviewed, increased blood pressure, which is a major CVD risk factor prevalently occur in patients with RA due to genetic polymorphisms, and the use of anti-rheumatic drugs. Systemic inflammation evokes oxidative stress and endothelial cell dysfunction, leading to increased peripheral vascular resistance.

Anti-Rheumatic Treatments

Drugs used to treat RA may have contradictory effects on cardiovascular system, despite reducing the activity of disease and undesirable CVD outcomes. However, the use of certain drugs increases the risk of CVD.

Increasing evidence suggests the potential cardiovascular risk of long-term use of NSAIDs, which exert therapeutic effects by inhibiting cyclooxygenase (COX) isoforms. NSAIDs account for 46% of all CV deaths in 312 accumulated events from 26 trials. A network meta-analysis of seven NSAIDs showed that naproxen is associated with the lowest risk for CV, whereas the remaining six NSAIDs exhibit a similar risk of CVD.[20] In recent years, a new COX theory states that inflammation primarily affects inducible COX-2 and a variety of COX-2 inhibitors become the most commonly prescribed NSAIDs. COX-2 inhibitors can significantly reduce the gastrointestinal reaction of traditional NSAIDs,

which are classified as COX-2 inhibitors, such as meloxicam or celecoxib. However, NSAID treatment is associated with a significantly increased risk of death at the beginning of the treatment, which persists throughout the course of treatment.[20] Inhibition of COX-2 reduces vascular and antiplatelet effects of prostacyclin, inhibits its production, therefore, increases blood pressure and accelerates atherosclerotic plaque rupture and thrombosis.[77] Many other factors may contribute to the increased risk of CV associated with COX-2 inhibitors, but the mechanism remains unclear. The diversities of NSAIDs and the imbalance in COX-1/2 inhibition as well as the degree of inhibition, dose, and time for treating patients with CV and gastrointestinal risk factors should be considered owing to the potential negative impact of NSAIDs on CV outcomes. Elderly patients are high-risk groups for NSAIDs and show a high incidence of CVD. The use of NSAIDs should be case-specific, and the lowest effective dose should be used for the shortest time.

Glucocorticoids are frequently used to treat RA primarily for the short-term control of disease activity. However, glucocorticoids can aggravate hypertension or cause abnormal blood lipid levels, abnormal glucose tolerance, insulin resistance, and abdominal obesity, promoting the occurrence and development of CVD.[78,79] Current recommendations for glucocorticoids in the treatment of rheumatoid arthritis are not ideal. More rigorous assessment of dose, duration, and duration of use is needed, and all guidelines agree that glucocorticoids, especially if given in small doses and over short periods, are an appropriate treatment option for RA. However, in the absence of reliable and detailed evidence, many of the recommendations remain vague. Regular monitoring of blood pressure and blood glucose levels should be conducted before and during the treatment. Additionally, patients with RA should be treated early and combined with of drugs. Therefore, glucocorticoids are considered a risk factor for HF.[78,79] RA is known to be associated with an increased risk of cardiovascular disease (CVD) compared with the general population. This seems to be due not only to the increased incidence of classic CVD risk factors and comorbidities such as smoking, obesity, hypertension, diabetes, metabolic syndrome, etc., in RA, but also to the inflammatory burden borne by RA itself.[80]

TNF-α is a cytokine that is a central inflammatory cascade that modulates the immune response to many aspects of cellular and humoral immunity.[81] Increased levels of TNF-α in synovial fluid and synovial membrane in RA patients.[82] Due to its effect on various cells in the synovial membrane TNF-induces local inflammation and vascular PAN formation, leading to cartilage erosion and bone destruction.[83] Therefore it's

important to study TNF inhibitors. TNF inhibitors have been widely used in patients with RA who cannot be effectively controlled by general treatment. In particular, in patients with RA, hormone, homocysteine hematic disease, pulmonary interstitial lesions, secondary pulmonary hypertension, and high blood coagulation can be treated. But, these inhibitors can increase CV risk factors, such as insulin resistance, HDL cholesterol, and endothelial function. TNF-α has been shown to induce insulin resistance in animal models.[68] However, these findings have not been observed clinically. The study found that decreasing TNF inhibitors were not superior to decreasing DMARDs.[84]

Blocking TNF-α activity also improves metabolic index and cholesterol levels in RA patients. Meta-analyses have generally reported that increases in total, LDL, and HDL cholesterol and triglycerides occur with TNF-α antagonism.[85,86] Anti-TNF-α therapy has been associated with a reduced risk of all CV events in patients with RA. However, in patients with HF, blocking TNF-α with infliximab has a negative effect on prognosis.[87] Recently, the mortality of RA patients treated with anti-TNF-α drugs is lower than that of patients treated with traditional anti-rheumatic drugs. However, the study did not specifically assess whether the reduction in mortality was due to a reduction in CVD.[88]

IL-6 is a cytokine derived from T lymphocytes, macrophages, and adipocytes. This molecule stimulates the synthesis of CRP and fibrinogen in the liver, causes RA, and accelerates AS by binding to its membrane receptor or soluble receptor. Studies have shown that IL-6R signals play a causal role in the development of CAD.[73] IL-6 in RA is targeted by tocilizumab, a monoclonal antibody against IL-6 receptor, which shows good tolerance in patients. Although tocilizumab can effectively reduce the severity of the disease, it can also seriously interfere with the homeostasis of lipids and cholesterol, such as by increasing LDL and total cholesterol, resulting in uncertain CV outcomes.[85,89]

The emergence of DMARDs has decreased the incidence and mortality due to CVD.[90] However, no biological protection with DMARDs has been observed. This result is consistent with other studies reporting that the use of biological DMARDs is not associated with the risk of MI.[91] The limitation is that we cannot assess the risk of CVD based on specific biological DMARDs because most patients are treated with TNF inhibitors and according to reimbursement guidelines.[92] MTX is the most commonly prescribed DMARD and is associated with a lower CV risk. A recent meta-analysis found that MTX reduces CV events by 21%.[90] Moreover, MTX reduces the risk of heart disease in patients with RA, and it is an analogue of folic acid that exerts significant

immunosuppressive and anti-inflammatory effects in RA and other autoimmune diseases. MTX inhibits the activities of key enzymes, such as dihydrofolate reductase, thymidine synthase, and aminoazolamide ribonucleotide converting enzyme, which inhibits cell proliferation and turnover.[93] The resulting reduction in purine, pyrimidine, and DNA synthesis provides therapeutic outcomes in disease state. Another important mechanism of MTX is the accumulation of adenosine by inhibiting angiotensin. Thus, the major immunomodulation and anti-inflammatory effects of MTX in RA are mediated by reduction in the synthesis of purine and pyrimidine and accumulation of adenosine.[93] Another study determined whether low doses of MTX reduced the risk of heart disease in patients with metabolic syndrome or diabetes.[94] Over the past decade, it has been suggested that MTX could be a major drug in the treatment of RA and other autoimmune diseases and may be reused for CV risk management.

B cell-activating factor (BAFF) plays an important role in the survival, activation, and differentiation of B cells through maturation, transmembrane activator, and calcium regulatory ligands. B1 and B2 cells are the two main subgroups of B cells. B lymphocytes modulate the development of atherosclerosis. B1 lymphocytes can protect atherosclerosis, while B2 lymphocytes can promote the formation of atherosclerosis.[95] B2 cells are divided into MZ-B cells and Fol-B cells, which secrete immunoglobulins, stimulate inflammatory T cells, and aggravate AS. The BAFF receptor pathway is a key driver of CAD and a key pathway in B2 cell survival. Anti-BAFF antibody therapy aggravates AS in mice, although mature B2 cells are effectively depleted, suggesting a unique mechanism of action.[96] Kyaw et al. demonstrated that depletion of B cells using anti CD20 monoclonal antibody inhibited the development of AS in ApoE−/− mice maintained on a high-fat diet.[97] Biological products targeting B cells have entered the clinical field for treatment of autoimmune diseases such as RA (Fig 2).[98,99]

Interestingly, the risk of CVD in patients with RA increases, but the effects of these treatments on CVD risk in humans are unclear.[34,100] Because of the high incidence of CVD in patients with RA, these patients should be carefully evaluated. These findings underscore the important role played by RA disease-related inflammation in determining the risk of CVD and suggest a possible mechanism for effective RA treatment to reduce the deleterious effects of inflammation on CVD risk. It has been clearly demonstrated that inflammatory rheumatic disease worsens atherosclerotic CVD and increases mortality due to CVDs. The mechanism of early cardiac dysfunction under massive activation of inflammatory factors caused by RA has been examined previously. In the physiological

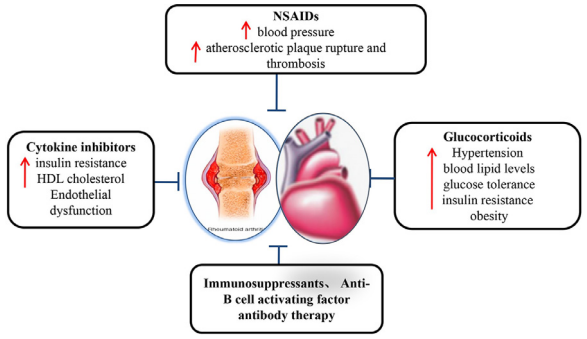

FIG 2. Medicine-induced early cardiac dysfunction in RA.

state, catecholamines regulate cardiac contraction, and adrenaline acts on G protein-coupled receptors (GPCR), which play a direct and critical role in regulating CV function.[101] Therefore, the cause of early cardiac dysfunction in RA remains unclear.

In summary, the direct cause of HF has been shown to be inflammation.[102] Previous studies showed that in patients with RA, the incidence of HF increases; however, it is unclear whether further hypertension and ischemic heart disease result from increased RA or whether the immune disorder leads to myocardial dysfunction.[102] Interactions of cytokines, chemokines, cell adhesion molecules, and pro-inflammatory cell surface receptors play a role in the initiation and perpetuation of inflammatory responses. Inflammation is both cell mediated and cytokine mediated. The progression of cytokines associated with HF can be attributed to continued proinflammatory cytokine signaling. Proinflammatory signal is mediated by a variety of cytokines, which can induce myocardial hypertrophy, apoptosis, fibrosis, and ultimately lead to poor myocardial remodeling. In the case of cardiac injury, these inflammatory signaling molecules can induce compensatory cardiac hypertrophy and fibrosis. TNF-α has been shown to cause cardiomyocyte dysfunction, cardiomyocyte hypertrophy, fibrosis, which subsequently lead to cardiomyopathy. Elevated levels of TNF-α are associated with cardiac fibrosis, ventricular dilation, and mortality.

Anti-inflammatory cytokine signaling can alleviate hypertrophic heart remodeling. These anti-inflammatory mediators also stimulate T lymphocyte proliferation to Th2 cells.[95] Thus, what is the role of inflammation in HF? Is it a direct causal relationship or is inflammation one of the many factors affecting HF? Nearly all inflammatory mechanisms in the body involved in protection and regeneration use common signal mediators. In fact, although traditional CV risk factors are more prevalent in patients

with RA than those in the general population, they do not adequately account for increased CV morbidity and mortality observed in these patients. The same degree of inflammation does not explain these clinical differences, and, thus, inflammation is the last common mechanism rather than the main trigger.[33,103] Nonsteroidal anti-inflammatory drugs (NSAIDs), anti-rheumatoid drugs and corticosteroids are commercially available to reduce pain, swelling and suppress a variety of disease factors. Arthroscopy can be useful when joint tissue is severely degenerated. Gene therapy is a major advance in RA. Inflammatory mediator suppressor gene loci and matrix degrading enzymes are inserted into the site to reduce disease progression.[104]

Many inflammatory pathways in the pathobiology of RA have also been suggested to be responsible for atherosclerosis. Immune regulation is the main means of RA treatment, and a variety of biological and abiotic drug therapies can be used alone or in combination to control joint and systemic inflammation and prevent joint destruction.[105]

Conclusions

CVD is very common in patients with RA, affecting more than one-third of the people aged ≥40 years. CVD is the most common cause of early death in patients with RA. Therefore, improving the understanding of inflammation-induced RA is useful for establishing future therapeutic goals to reduce the risk of CVD in patients with RA. In fact, a recent national study showed that newly diagnosed patients with RA administered with continuous RA drug therapy showed no increased risk of CV mortality compared to the general population, as observed in early cases of the disease.[106] In patients with RA, sympathetic nerves excite and produce a high amount of catecholamines, which regulate cardiac contraction in the physiological state. GRK2 mediates desensitization of myocardial receptors; thus, treatment with its inhibitors is anti-arthritic and prevents cardiac dysfunction. Therefore, early prevention is necessary to reduce the incidence of the disease and prolonging life. By regulating the functions of immune cells, the nervous system plays an active role in the inflammatory immune process. The chronic inflammatory immune response of RA is accompanied by decreased sympathetic function and enhanced excitability of the sympathetic nervous system. The sympathetic nervous system provides energy to sustain long-term activation of the immune system.[107] Clinical studies have shown that the level of catecholamines, which inhibit the function of beta receptors, secreted by the sympathetic nerves in the plasma of patients with RA is

significantly higher than that in healthy people and may be the priming factor of CVD in patients with RA.[108]

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