Biologics and the Cardiovascular System: A Double-Edged Sword

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Abstract: Patients with chronic inflammatory diseases such as rheumatoid arthritis have a higher risk of cardiovascular diseases and related mortality compared to the general population. This risk is first due to classical cardiovascular risk factors but also due to systemic inflammation which is independently involved, causing accelerated atherosclerosis, myocardial infarction, cerebrovascular disease and heart failure (HF). Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-1 and IL-6 could be major actors on this pathophysiology. Biologics are effective specific treatments in the management of inflammatory rheumatic and systemic diseases. In this review, beneficial and deleterious effects on the heart and vessels of the biologics used in the management of inflammatory arthritis and vasculitides will be discussed, focusing on TNF-alpha, IL-6 and IL-1 blockades, and anti-CD20. Non-inflammatory cardiac conditions, such as heart failure, myocardial infarction, and cardiovascular conditions such as atherosclerosis, as well as inflammatory diseases including vasculitides will be discussed.

Keywords: Cardiovascular disease, inflammation, biologics, TNF-alpha, IL-1, IL-6, cytokines, atherosclerosis, heart failure.

1. INTRODUCTION

It is well established, but often underestimated, that patients with chronic inflammatory diseases such as rheumatoid arthritis (RA) have a higher risk of cardiovascular diseases and related mortality compared to the general population [1, 2] (see also Editorial by Roubille and Tardif). This risk is mainly due to classic cardiovascular risk factors such as hypertension, diabetes mellitus, smoking, overweight, dyslipidemia and sedentary lifestyle. However, systemic inflammation may be independently involved in this increased risk of cardiovascular (CV) diseases (CVD) [3], causing accelerated atherosclerosis, myocardial infarction [1], cerebrovascular disease [4] and heart failure (HF) [2, 5]. Indeed, inflammatory markers such as hypersensitive C-reactive protein have been shown to be independent predictors of cardiovascular events in the general population [6, 7]. The control of inflammation and the lowering of biological markers of inflammation through various interventions could help to reduce CV events [8]. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin (IL)-1 and IL-6 as well as B cells contribute to the pathogenesis of both atherosclerosis and chronic inflammatory diseases, such as RA [9]. At present, TNF-alpha is suggested to participate in endothelial dysfunction, vascular instability and atherosclerosis progression and may contribute to the progression of heart failure. This cytokine also plays a role in the inflammation leading to plaque rupture [10] and in thrombophilia by promoting thrombotic events. Therefore, reducing the inflammatory burden in RA by lowering inflammatory cytokine levels, including TNF-alpha and IL-6, may reduce the cardiovascular risk. It would also be logical to consider TNF-alpha inhibitors and other biologics in primary cardiovascular diseases. A EULAR working group has published ten recommendations for the screening, prevention and therapy of cardiovascular diseases in RA, ankylosing spondylitis and psoriatic arthritis [11]. Taken together, these recommendations combined with the involvement of pro-inflammatory cytokines in the pathogenesis of atherosclerosis and CVD in arthritis could underline the interest of biologics.

Biologic agents are specific drugs targeting inflammatory cytokines. The best known are for TNF-alpha, monoclonal antibodies such as infliximab, adalimumab and golimumab, etanercept, a TNF-alpha receptor fusion protein, and certolizumab a pegylated humanized antibody Fab fragment, for IL-1 anakinra, an IL-1 receptor antagonist, for IL-6 tocilizumab, a monoclonal antibody directed against the IL-6 receptor, and for the B cells, rituximab a chimeric anti-CD20 monoclonal antibody. These biologics may be used for the treatment of moderate-to-severe RA as well as other rheumatic diseases such as ankylosing spondylitis, psoriatic arthritis, systemic vasculitides and systemic lupus.

Identifying any effect or risk of CVD that may be associated with biologics is hampered by the increased risk conferred by inflammatory diseases themselves, such as RA.

In this review, beneficial and deleterious effects on the heart and vessels of the biologics licensed for the management of...
inflammatory arthritis and/or vasculitides, will be discussed, focusing on TNF-alpha, IL-6 and IL-1 blockades, and anti-CD20. Non-inflammatory cardiac conditions, such as heart failure, myocardial infarction, and CV conditions such as atherosclerosis, as well as inflammatory diseases including vasculitides will be discussed. Taking into account the wide spectrum of the field, this review is aimed at a comprehensive synthesis rather than an exhaustive listing.

2. TNF-ALPHA BLOCKADE AND THE CARDIO-VASCULAR SYSTEM

2.1. Anti-TNF-alpha Reduces Cardiovascular Events in RA Patients

Inhibition of TNF-alpha has revolutionized the management of many chronic inflammatory diseases like RA, reducing the disease symptoms, improving function and preventing joint damage. Patients suffering from RA, especially those with high disease activity, have an increased risk of HF [12]. Consistently, patients with RA treated with anti-TNF-alpha therapy seem to have lower CV risk compared to anti-TNF-alpha therapy-naïve patients [13, 14]. TNF-alpha inhibitors may improve the CV outcomes including HF. Wolfe et al. found that heart failure was less common in anti-TNF-alpha treated patients (3.1%) than in the remaining patients (3.8%) (p<0.05) [15]. TNF-alpha inhibitors when compared to traditional disease-modifying anti-rheumatic drugs (DMARDs) in RA do not seem to worsen pre-existent heart failure [12] or to increase all-cause mortality [16]. The British Society for Rheumatology Biologics Register (BSRBR) demonstrated a reduction in the incidence of myocardial infarction in patients with RA responding to TNF-alpha-blocking therapy within the first 6 months compared with patients receiving traditional DMARDs [16]. Therefore, anti-TNF-alpha inhibitors may be more beneficial than harmful regarding the risk of HF by controlling the inflammatory activity of RA, especially if they are not combined with steroids or cyclooxygenase (COX)-2 inhibitors which have their own cardiovascular risk [12].

Moreover, RA has been associated with accelerated and generalized atherosclerosis, preceded by endothelial dysfunction and arterial stiffness. Vascular diseases occur in patients with more severe RA, who are ACPA (anti-citrullinated peptide antibodies) positive and often suffering from extra-articular involvement (for instance pulmonary involvement or vasculitis) [17]. Early endothelial dysfunction has been reported in patients with early RA [18]. TNF-alpha may be involved in this accelerated atherosclerosis as it may regulate the expression of platelet derived growth factor (PDGF), vascular endothelial cell growth factor (VEGF), fibroblast growth factor (FGF), adhesion molecules, cytokines, and matrix degrading metalloproteinases (MMPs) [19]. To assess atherosclerosis and endothelial dysfunction in RA, all the following techniques could be useful: common carotid intima-media thickness (ccIMT), brachial artery flow-mediated vasodilatation (FMD), and nitroglycerine-mediated vasodilatation (NMD). RA is characterized by increased ccIMT possibly related to generalized atherosclerosis, impaired FMD indicating preclinical endothelial dysfunction, and increased arterial stiffness, which may be associated with increased TNF-alpha levels [18]. Given this implication of TNF-alpha, the capacity of anti-TNF-alpha therapy to inhibit atherosclerosis has been evaluated in RA patients. TNF-alpha inhibitors were shown to improve endothelial function, and decrease ccIMT [20], as well as arterial stiffness in RA patients [21-23] including aortic stiffness [24].

In regard to the impact of anti-TNF-alpha on lipid profile in RA patients, several conflicting studies exist but they provide no conclusive answers (see review in [25]). Lipid profiles after infliximab treatment in RA patients have revealed short-term anti-atherogenic effects but also long-term pro-atherogenic effects [25]. However, many of these studies are limited by confounding factors such as concomitant treatment with methotrexate and prednisone. Data from studies on lipid profiles of etanercept and adalimumab seem also inconclusive or conflicting. Consequently, the possible favorable effect of anti-TNF-alpha on atherosclerosis in RA patients may not be related to their effects on lipid profiles. Large controlled long-term studies are necessary to clarify the role of lipid changes induced by TNF-alpha blockade on cardiovascular morbidity in RA.

2.2. TNF-alpha Levels are Increased in Heart Failure: Beneficial or Harmful?

Excessive production of pro-inflammatory cytokines may contribute to HF [26]. Cachexia is frequent in severe evolved HF [27] and is strongly correlated with the level of TNF-alpha, also known as cachectin, in patients with severe congestive HF [27, 28], and with the level of TNF-alpha receptors type I and II (TNFR1 and TNFR2) [28]. As TNF-alpha levels are associated with the severity of clinical signs and symptoms in HF [28], this cytokine was suggested to play a role in HF pathophysiology. TNF-alpha bioactivity may be cytoprotective or detrimental for the myocardium, depending on concentrations, type of activated receptor, and kinetics of production.

2.2.1. TNF-alpha may Promote HF

In experimental models, TNF-alpha seems to contribute to the pathogenesis of HF. Exogenous administration and experimental overexpression of TNF-alpha promote left ventricular remodelling [29], acute reversible contractile dysfunction [29, 30], cardiomyocyte apoptosis and reduced survival. TNF-alpha may contribute to myocardial dysfunction in ischemia/reperfusion or HF.

2.2.2. TNF-alpha may also be Cardioprotective

In myocardial infarction (MI), TNF-alpha increases as in HF, as do its receptors after reperfusion. Physiological levels of TNF-alpha may have beneficial effects in acute heart ischemia. In experimental models of MI, TNF-alpha protects cardiomyocytes from hypoxic injury [31], and mice lacking both TNFR1 and TNFR2 were more susceptible to MI than the controls [32]. TNF-alpha when administered before a cardiac ischemia mimics ischemic preconditioning-like tolerance against infarction and contractile dysfunction similar to brief non-lethal ischemia [33]. Under this condition, in MI TNF-alpha is cardioprotective against ischemia-reperfusion in a dose- and time-dependent manner [33]. Small doses of exogenous TNF-alpha (0.5 ng/ml in vitro) given prior to ischemia-reperfusion enhance cell survival while higher concentrations (10-20 ng/ml in vitro) are
cytotoxic and increase infarct size [34, 35]. TNF-alpha may have ischemic preconditioning effects in the isolated perfused mouse heart and TNF-alpha knockout mice lose ischemic preconditioning [36]. Moreover, when the heart is pre-treated with TNF-alpha inhibitors prior to preconditioning ischemia, no protection against infarction is shown [35]. It seems that deficiency of TNFR1 and activation of TNFR2 protect the myocardium [32].

How may TNF-alpha and TNFR2 activation be cardioprotective? A few hypotheses are suggested. One of them is that TNF-alpha may activate an intrinsic cell survival pathway, which is protective against reperfusion injuries. This pathway, evidenced in MI, is called the survivor activating factor enhancement (SAFE) pathway [37] and involves the phosphorylation of the signal transducer and activator of transcription 3 (STAT3) via Janus kinase (JAK). Activation of the SAFE pathway by TNF-alpha implicates only TNFR2. Moderate activation of the SAFE pathway seems to be necessary for the cardioprotective effect of TNF-alpha in ischemic pre- and post-conditioning [38]. For example, in pre-conditioning, STAT3 increases Bcl-2, an anti-apoptotic gene, reduces bax, a pro-apoptotic gene [39], and is translocated to mitochondria and modulates the opening of the mitochondrial permeability transition pore [40], one of the main putative actors of cardioprotection in ischemia-reperfusion injury. On the other hand, excessive stimulation of the SAFE pathway in MI by TNF-alpha seems to be harmful. All together, these findings illustrate that TNF-alpha could be involved in inflammatory pathways and cardiovascular pathophysiology through a certain imbalance.

In HF, the activation of the SAFE pathway by TNF-alpha may also be cardioprotective. Left ventricular STAT3 is deficient as well as phosphorylation of JAK in patients with dilated cardiomyopathy [41]. The same changes in STAT3 levels have been found in women with post-partum cardiomyopathy [42]. In experimental models, mice lacking cardiomyocyte STAT3 develop severe cardiac fibrosis while aging [43]. Nevertheless, as in MI, in experimental ischemic HF, TNFR1 and TNFR2 have opposite effects. TNFR1 activation promotes remodeling, apoptosis, hypertrophy and inflammation while TNFR2 protects from these effects [34, 44]. As mentioned above, the SAFE pathway is activated by TNFR2 only, but overstimulation of this pathway could be harmful.

Thus, in HF, there could be an imbalance between cardioprotective effects of TNF-alpha involving the activation of the SAFE pathway via TNFR2. Detrimental effects of TNF-alpha include activation of TNFR1 and/or overstimulation of the SAFE pathway [38]. Nevertheless, it is not yet known whether data on ischemic HF could be translated to non-ischemic HF.

2.3. Anti-TNF-alpha in Heart Failure

Data from experimental HF models [45] and preliminary clinical studies supported the hypothesis that inhibition of circulating TNF-alpha may improve ventricular dysfunction. Results of TNF-alpha blockade in RA patients supported this concept. Indeed, a Phase 1 study showed that a single intravenous infusion of etanercept was safe and improved the functional status of HF patients (quality of life scores and ejection fraction) [46]. Moreover, bi-weekly injections of etanercept for three months in patients with advanced HF resulted in a significant improvement in left ventricular ejection fraction (LVEF) and structure [47].

However, despite the encouraging results of preclinical data, clinical trials with TNF-alpha blockade in patients suffering from HF without inflammatory disease have shown no benefit and that it could even be harmful. Hence, etanercept was shown to have no effect on HF and high-dose infliximab had detrimental effects on patients with moderate to severe HF.

With regard to HF, results of two large clinical trials assessing etanercept in the treatment of congestive HF, RENAISSANCE (Randomised Etanercept North American Strategy to Study Antagonism of CytokinEs), and RECOVER (Research into Etanercept CytOkine Antagonism in Ventricular dysfunction) were combined and given the name RENEWAL (Randomized EtaNercept Worldwide Evaluation) [48]. These two trials differed only in the doses of etanercept used. In RECOVER, the patients were randomized to placebo (n=300) or etanercept 25 mg subcutaneous (SC) once weekly (n=300) or twice weekly (n=300). In RENAISSANCE, patients were randomized to placebo (n=300) or etanercept 25 mg SC twice weekly (n=300) or three times weekly (n=300). RENEWAL analyzed results of 1,500 patients from RECOVER and RENAISSANCE treated with placebo (n=600) or etanercept 25 mg SC twice (n=600) or three times weekly (n=300). The aim of RECOVER and RENAISSANCE was to evaluate etanercept (25 mg once, twice or three times a week) versus placebo in patients with New York Heart Association (NYHA) class II to IV chronic HF and a LVEF ≤ 0.30. The primary endpoint of both studies was a change in clinical status from baseline to 24 weeks, based on a composite score (death, HF hospitalization, NYHA class and patient global assessment). Analysis of the effect of etanercept on longer-term morbidity and mortality was referred to RENEWAL. The primary endpoint of RENEWAL was the composite of deaths by all causes or hospitalizations for or with HF. Secondary endpoints included all causes of mortality, the total number of hospitalizations for or with HF, change in NYHA class at 24 weeks, patient global assessment and quality of life. Both RECOVER and RENAISSANCE trials were terminated prematurely due to lack of benefit. There was no significant difference between placebo and etanercept in the change in composite score from baseline to 24 weeks in either RECOVER (p=0.34 overall) or RENAISSANCE (p=0.17 overall). In RENEWAL, estimated etanercept-to-placebo relative risk was 1.1 (p=0.33) for outcome of death or HF hospitalization, and 1.13 (p=0.39) for the secondary outcomes. Etanercept had no effect on clinical status or on death or chronic HF hospitalizations [48]. These results did not demonstrate a benefit of etanercept in patients with HF despite positive preclinical and preliminary data.

In another trial named ATTACK (Anti-TNF-alpha Therapy Against Congestive Heart Failure), 150 patients with NYHA class III to IV HF and a LVEF ≤ 0.35 were recruited to evaluate infliximab in congestive HF (49 patients received placebo, 50 infliximab 5 mg/kg and 51 infliximab 10 mg/kg) [49]. The primary endpoint was a change in clinical status from baseline to 14 weeks, based on a composite score. Secondary
endpoints included change in inflammatory markers during the 28-week trial period, change in LVEF at 14 and 28 weeks, the combined risk of death or hospitalization for worsening HF at 28 weeks and the change in quality of life. No difference in LVEF was evidenced and a significant increase in death and HF hospitalization at 28 weeks was demonstrated in patients who received the higher dose of infliximab. Infliximab was found to worsen HF, which remained worsened for up to five months after the discontinuation of the therapy [49]. Consequently, the presence of severe HF contraindicates anti-TNF-alpha treatment in RA patients.

How can these results be explained? Firstly, given the ambivalent role of TNF-alpha, the dosage of anti-TNF-alpha therapy chosen in RCTs may suppress preconditioning cardioprotective concentrations of TNF-alpha [50], based on the hypothesis that physiological levels of TNF-alpha may be necessary for cardiovascular homeostasis. However, there are no data available about minimal doses of anti-TNF-alpha without any effect on the cardioprotective preconditioning promoted by TNF-alpha. On the contrary, the dosage of TNF-alpha therapy may not be sufficient to antagonize circulating and myocardial levels of TNF-alpha. This seems less likely regarding the high dosage of infliximab in the ATTACH trial, which is not common in RA daily management where doses up to 3 to 5 mg/kg are more frequently used. Furthermore, no monitoring of TNF-alpha levels was reported in RENEWAL. Moreover, TNF-alpha blockade may not be sufficient to neutralize the pro-inflammatory cytokine network leading to HF, which involves many mediators other than TNF-alpha, such as IL-1 and IL-6 [48]. Other explanations are considered, and include the “TNF-alpha rebound” and complement fixation, especially with infliximab [49]. All these suggestions are speculative and data from these trials point toward an alert about the safety of TNF-alpha blockade in patients with HF and contribute to contraindicate these treatments in RA patients suffering from HF.

Recent clinical trials suggest that adalimumab reduces vascular disease in patients with autoimmune disease. Indeed, in a registered trial (NCT00940862), Tardif et al. studied the effect in 30 patients treated for psoriasis (results to be published).

Finally, recent new data from a classic myocardial infarction model in mice suggest that TNF-alpha could be involved in vasoconstriction, even in the early stages of HF, leading to cognitive dysfunction [51]. Interestingly, some of the effects could be fully reversed in vitro by etanercept. TNF-alpha mediates its effect via a sphingosine-1-phosphate (S1P)-dependent mechanism, requiring sphingosine kinase 1 and the S1P2 receptor. In vivo, sphingosine kinase 1 deletion prevents and etanercept (2-week treatment initiated 6 weeks after myocardial infarction) reverses the reduction in cerebral blood flow, without improving cardiac function, suggesting a potential therapeutic target to improve cognitive function in heart failure.

2.4. Anti-TNF-alpha in Vasculitides

2.4.1. Behcet’s Disease

Behcet’s disease (BD) is a multisystem inflammatory chronic-relapsing disorder classified among the vasculitides, responsible for uveitis and retinal vasculitis, oral and genital ulcerations, and vascular, intestinal, and central nervous system inflammation. Among anti-TNF-alpha therapy, infliximab seems especially effective at treating ocular lesions due to BD, especially in patients who are refractory to conventional treatments such as interferon-alpha, azathioprine, methotrexate and cyclosporine A. Nevertheless, published evidence is mainly derived from case series and reports on the open use of infliximab as an add-on therapy, but not from randomized controlled trials. There is only one randomized trial versus placebo, which reported the effectiveness of 4-week administration of etanercept 25 mg twice a week at managing mucocutaneous manifestations [52] in 40 patients but which did not affect the pathergy reaction (primary endpoint). These uncontrolled data should therefore be interpreted with caution. However, data suggest that anti-TNF-alpha may be effective in the treatment of severe and resistant BD and/or intolerance to conventional therapy for BD.

Off-label use of anti-TNF-alpha therapy in BD is increasing. Infliximab appears to have a rapid effect on sight-threatening uveitis as evidenced in some uncontrolled case series [53, 54]. The long-term effect of repetitive infliximab infusions at preventing ocular relapses and maintaining visual acuity in patients unresponsive or intolerant to standard treatment was evaluated in a few studies [55-58]. Infliximab may be more effective at reducing acute episodes of uveitis in BD than cyclosporine A (p<0.05) [59]. Moreover, in acute, posterior unilateral uveitis, a single infusion of infliximab 5 mg/kg may be superior to steroids to obtain a rapid resolution of inflammation. When uveitis is bilateral, a single infusion of infliximab could also achieve a rapid response compared to steroids. For instance, Markomichelakis et al. reported that a single infusion of infliximab was faster than corticosteroids (intravenous or intra-vitreal) at decreasing total ocular inflammation scores (p=0.01) and was superior to corticosteroids at clearing retinal vasculitis (p<0.003) as well as resolving cystoid macular oedema (p=0.007). Nevertheless, the beneficial effects of corticosteroids and of infliximab in visual acuity were comparable from baseline to the end of the follow-up [60]. Moreover, due to the lack of comparative data, it is not known whether infliximab has a faster effect at resolving acute ocular inflammation than interferon-alpha or cyclosporine. When ocular inflammation is suppressed after a single infusion of infliximab, immunosuppressive drugs like cyclosporine or azathioprine combined with corticosteroids can be used long-term to avoid relapses. If insufficient, a combination of these immunosuppressive agents with repetitive infusions of infliximab 5 mg/kg every 6-8 weeks should be considered [61].

Arida et al. analyzed published data on 369 patients and reported 16 open prospective studies evaluating the effect of repetitive infliximab injections. Clinical responses were obvious in 90% of patients with resistant mucocutaneous manifestations, 89% of patients with ocular lesions, 100% of patients with intestinal involvement, and 91% of patients with central nervous system involvement [62]. Moreover, the combination of infliximab with azathioprine and/or cyclosporine A appeared to be superior to monotherapy for sustained ocular remission [62].
Infliximab was also reported to be effective at managing intestinal manifestations in 10 patients with BD suffering from ulcerations despite conventional immunosuppressive treatment or who had contraindications or intolerance [63]. Some case reports also suggest that infliximab might be effective for central nervous system involvement in patients refractory to high-dose corticosteroids and cyclophosphamide [58].

Interest in adalumumab for BD is also increasing, especially for patients with severe and refractory disease unresponsive to infliximab. Adalumumab might improve paucivitis, retinal vasculitis and aphthosis [64, 65].

2.4.2. Takayasu’s Arteritis

Some cases reported the effectiveness of anti-TNF-alpha therapy in Takayasu’s arteritis (TA) [66, 67]. In a recent review of the literature, Comarmond et al. reported that anti-TNF treatment, mainly infliximab, may be an effective therapy in refractory TA (37% of patients achieved a complete remission and 53.5% were partial responders), with a good safety profile despite 20% of patients having adverse effects (mainly infections and hypersensitivity reactions) [68]. A French retrospective study reported data from 15 patients with TA treated with infliximab: 13 of the 15 patients (87%) experienced partial or good overall response, with clinical and biological activities significantly decreased within 3 months, along with reduced steroid dose, suggesting a corticosteroid-sparing effect [69]. Another retrospective study using data from 20 TA patients treated with TNF-alpha inhibitors (17 with infliximab, 2 with adalimumab and 1 with etanercept) reported disease remission in 18 patients and sustained remission in 10 patients. However, 6 of the 18 patients achieving remission relapsed while receiving TNF-alpha inhibitors [70].

2.4.3. Giant Cell Arteritis

Small series or case reports have suggested the possible utility of TNF-alpha inhibitors in treating patients with refractory or corticosteroid-dependent giant cell arteritis (GCA), including infliximab [71-73], etanercept [74] and adalimumab [75]. However, these data have not been confirmed in two controlled studies evaluating infliximab and etanercept. Hoffman et al. [76] reported that infliximab 5 mg/kg had no effect on relapse in 44 patients, the rate of which was high: 50 to 57% of patients with GCA at 22 weeks. All patients received corticosteroid but the dosage was tapered rapidly so that patients stopped receiving corticosteroids within 6 months. This study was then stopped prematurely at 22 weeks because only 43% of the patients in the infliximab group achieved relapse-free remission compared to 50% of the patients in the placebo group (p=0.65). Moreover, infliximab did not increase the number of patients whose corticosteroid dosages were tapered to 10 mg/day without relapse (p=0.31). Perhaps the number of patients assessed was too small, or perhaps it would have been more relevant to use standard corticosteroid therapy, i.e. prolonged, and add infliximab or placebo instead of a short-term corticosteroid regimen. Concerning etanercept, Martinez-Tanboada et al. showed in 17 patients that after 12 months, 50% of patients in the etanercept group and 22.2% in the placebo group controlled the disease without corticosteroids; however, the difference did not reach statistical significance [77]. Finally, these two RCTs demonstrate that there may be no clear benefit of adding infliximab or etanercept to corticosteroids in managing patients with GCA. Another RCT assessing adalimumab in GCA to spare corticosteroids (HECTHOR study – http://clinicaltrials.gov - NCT 00305539) is completed but data are not yet published. This study evaluated the influence of an initial treatment of 3 months of adalimumab 40 mg/2 weeks in the patients achieving a decrease in their corticosteroid treatment to a dose equal to or lower than 0.1 mg/kg at 6 months.

2.4.4. Systemic Necrotizing Vasculitides

Anti-TNF-alpha have been suggested to be of interest in the treatment of systemic necrotizing vasculitides. Booth et al. reported that infliximab in combination with standard treatment (prednisolone and cyclophosphamide) could have led to clinical remission in 88% of patients with acute or persistent ANCA-associated vasculitis (AAV) and to a reduction in corticosteroid doses [78]. In an open study, Bartolucci et al. demonstrated that infliximab used in 10 patients (7 with Wegener’s granulomatosis) with severe vasculitides refractory to corticosteroids and immunosuppressive agents could also have led to complete or partial remission in all patients [79]. Moreover, infliximab may have a suspensive and transient beneficial effect because of relapses evidenced after discontinuation [80]. Etanercept has also been evaluated in association with conventional therapy to reduce the relapse rate versus placebo in the WGET trial. When combined with induction therapy (corticosteroids and cyclophosphamide or methotrexate for limited diseases), etanercept was not effective at preventing relapses and patients also developed solid cancers [81]. Anti-TNF-alpha might therefore be considered as an ultimate therapeutic option for some rare patients with refractory vasculitides. Results from another RATTRAP trial (http://clinicaltrials.gov – NCT00307593), comparing infliximab to rituximab for the treatment of relapsing or refractory AAV are awaited.

3. IL-6 BLOCKADE AND THE CARDIOVASCULAR SYSTEM

3.1. IL-6 Blockade in RA Patients

IL-6 is a pro-inflammatory cytokine with pleiotropic activity which is involved in many inflammatory diseases such as RA and atherosclerosis. Tocilizumab is a humanized anti-IL-6R monoclonal antibody of the IgG1 class used in RA therapy.

Tocilizumab does not seem to have clinically significant CV adverse effects in available data from RA trials. However, tocilizumab-treated patients showed moderate reversible elevations of the mean serum total cholesterol, LDL-C, HDL-C and triglycerides [82]. However, the implication for long-term CV safety remains uncertain. A post-marketing analysis in Japan recently reported 25 cardiovascular events in 24 of 3,881 patients (1.39/100 patient-years (PY)) [83]. Of these patients, 13 (54.2%) had a concurrent or medical history of cardiac disturbance. Schiff et al. [84] reported the safety profile of tocilizumab evaluated in five core trials in...
patients with RA, assessing the pooled data from these Phase 3 trials. The all-control population included all patients randomly assigned in the five core studies, and the all-exposed population included all patients who received tocilizumab (randomized + open-label extension trial). Rates of MI were similar to those reported in epidemiologic studies of RA patients [1]. In the all-exposed population, the MI rate was 0.25/100 PY (95% CI 0.16-0.38) at 9,414 PY of exposure. In the all-control population, the MI rate was 0.49/100 PY in the control group (MTX/DMARDs or placebo), 0.18/100 PY in the tocilizumab 4 mg/kg group and 0.17/100 PY in the tocilizumab 8 mg/kg group. Finally, tocilizumab was shown to reduce arterial stiffness in RA patients, like TNF-alpha inhibitors [85, 86], and to improve endothelial dysfunction [86].

3.2. IL-6 Blockade: Beneficial for Coronary Diseases?

IL-6 inhibitors might have some beneficial effects on coronary artery disease. Indeed, increased levels of IL-6 have been associated with higher risk of coronary events [87, 88]. Recently, it was reported that IL-6 receptor blockade could be considered in the prevention of coronary heart diseases [89], or even be useful for the treatment of acute MI, as suggested in an ongoing study investigating the effect of the IL-6 receptor antagonist tocilizumab in non-ST elevation MI (http://clinicaltrials.gov - NCT 014901074).

3.3. IL-6 Blockade in Vasculitides

Small recent studies and case reports found some clinical and laboratory improvement in patients suffering from large vessel vasculitides (giant cell arteritis, Takayasu’s arteritis) and treated with tocilizumab [90, 91].

4. ANTI-CD 20 AND THE CARDIOVASCULAR SYSTEM

4.1. Rituximab May Cause Acute Infusion Reactions

Rituximab (RTX), a chimeric monoclonal antibody that selectively depletes B cells expressing the CD20 antigen, is licensed for the treatment of RA and lymphomas.

The most common adverse effect reported by patients receiving RTX is acute infusion reactions occurring within 24 hours after initiation of the treatment, including many possible symptoms such as headache, nausea, pruritus, flushing, tachycardia, hypertension or hypotension [92]. These infusion reactions may occur in approximately one fourth of patients during the first administration and may be due to a release of cytokines into the blood coming from the rapid destruction of circulating B cells, justifying a slow initial infusion rate. They can be managed with an appropriate premedication including acetaminophen, antihistamine and corticosteroids.

There are only a few case reports of severe cardiac events during RTX infusions, such as MI, ventricular fibrillation and cardiogenic shock. For example, one patient with dilated cardiomyopathy died after RTX infusion [93] and three cases of reduced cardiac function in non-Hodgkin’s lymphoma patients treated with RTX were reported [94]. Other case reports reported a cardiogenic shock in a young patient suffering from thrombotic thrombocytopenic purpura, where HF discharged after therapeutic plasma exchange [95], and a fatal MI in a 60-year-old diabetic patient who received RTX, whereas the baseline echocardiography and electrocardiogram were normal [96]. Release of cytokines following B cell lysis may cause vasoconstriction, platelet activation and rupture of pre-existing asymptomatic plaque, leading to MI.

In larger cohorts, no long-term cardiovascular side effects were reported. For instance, the addition of RTX to CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine-oncovin and prednisolone) did not increase the risk of doxorubicin-induced cardiotoxicity [97]. Siano et al. did not find any cardiac toxic effect of RTX treatment, monitoring troponin, BNP, echocardiogram and electrocardiogram, even with a fast infusion rate in patients having received at least one RTX in the previous three months [98]. They only described a specific increase in BNP values 24 hours after rituximab infusion which remained within the reference range values and which afterwards returned to baseline values, possibly caused by the slight volume overload due to the fast infusion rate.

4.2. Rituximab and Atherosclerosis

The role of RTX in vessels remains controversial and overall not well-known. RTX has been reported to increase brachial artery flow-mediated vasodilatation (FMD) in RA patients, thus to have beneficial effects on endothelial function [99, 100]. However, it has also been found to provide no change in arterial stiffness [101].

4.3. Rituximab: an Effective Therapy for Vasculitides

Randomized controlled trials demonstrated the efficacy of RTX in the treatment of vasculitides, which appears to be a strong alternative therapy to cyclophosphamide (CYC) for the induction of remission in severe ANCA-associated vasculitides (AAV) [102, 103].

RTX has been licensed for the treatment of both Wegener’s granulomatosis and microscopic polyangiitis, in combination with glucocorticosteroids, since the non-inferiority of RTX compared to cyclophosphamide at inducing disease remission has been demonstrated. Indeed, in the RAVE trial (Rituximab for ANCA-associated vasculitis), BVAS/WG (Birmingham Vasculitis Assessment Score for Wegener’s Granulomatosis) was achieved at 6-month follow-up by 64% of RTX treated patients and by 53% of control patients treated with CYC (non-significant) [102]. In the RITUXVAS (Rituximab in vasculitis) trial, complete remission was achieved at 12-month follow-up by 82% of patients who received RTX and 91% of patients who received CYC (non-significant) [103].

RTX is as effective as CYC for remission induction of previously untreated patients and suggested to be an effective treatment for refractory and/or relapsing forms of AAV. In fact, RTX seems to be more effective in relapsing patients when compared with CYC retreatment, hence RTX might be recommended when conventional therapy has failed [104]. However, it is important to note that in RITUXVAS, two doses of CYC were administered within the first RTX course whereas in the RAVE trial, no CYC was added to RTX.

Nevertheless, follow-up and long-term data are needed to confirm whether RTX has a sustained effect. Indeed, using
RTX in daily practice equal to CYC to treat newly diagnosed AAV may be premature because of the lack of head-on comparative data beyond 6-12 months [105].

Data from a retrospective study evaluating RTX for remission maintenance in refractory or relapsing AAV reported that a 2-year fixed-interval routine RTX-retreatment was associated with a reduction in relapse rates during the re-treatment period [106].

Results from the MAINRITSAN trial (http://clinicaltrials.gov – NCT00748644) comparing RTX to azathioprine for maintenance therapy in systemic AAV are awaited.

5. IL-1 ANTAGONISM AND THE CARDIOVASCULAR SYSTEM

5.1. Pleiotropic Involvement of IL-1 in Cardiovascular Diseases

Elevated levels of IL-1 result in secretion of chemokines, pro-inflammatory cytokines including IL-6, increased expression of adhesion molecules, activation of endothelial and smooth muscle cell proliferation and increased vascular permeability. IL-1 can also induce expression of inducible nitric oxide synthase (iNOS) and vascular endothelial growth factor (VEGF).

IL-1 was found to be involved in many mechanisms of cardiovascular diseases such as atherosclerosis, MI, myocarditis and hypertrophic cardiomyopathy (see review in [107]).

5.1.1. IL-1 Promotes Atherosclerosis

In clinical studies, IL-1 concentrations were found in high levels in atherosclerotic human coronary arteries [108]. In atherothrombotic coronary disease IL-1 may promote atheromatous lesions, modulate cholesterol metabolism, enhance vascular inflammation and support plaque rupture. Indeed, IL-1 showed pro-adhesive activity by stimulating adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) [109] and may promote atheromatous plaque destabilization and rupture via upregulation of MMPs [110]. The adhesion molecules VCAM and monocyte chemotactic protein-1 (MCP-1) may attract monocytes to the arterial intima, which will differentiate into macrophages and foam cells, leading to atherogenesis. Furthermore, MMPs are able to degrade the extracellular matrix and induce collagen breakdown in atheromatous plaques. Increased expression of MMPs by IL-1 may therefore induce atheromatous plaque rupture and lead to thrombosis. IL-1 may also modulate cholesterol plasma levels by serum amyloid A (SAA) induction [111], and stimulate angiogenesis and vessel wall inflammation, via VEGF [112] and inflammatory pathway induction [113]. Hence, mice lacking the IL-1 receptor antagonist (IL-1Ra) (an endogenous protein binding the IL-1 receptor type I and preventing the IL-1 effect) exhibit elevated levels of plasma cholesterol [114]. The important role of IL-1 in atherosclerosis has been highlighted by experimental studies showing less atherosclerosis in IL-1 knock-out [109] or IL-1 type I receptor knock-out mice [115].

5.1.2. IL-1 and Myocardial Infarction

Patients with MI have increased levels of IL-1 [116]. IL-1 may exert direct pro-thrombotic actions by enhancing endothelial tissue factor expression [117] and promote adverse ventricular remodeling via modulation of collagen deposition [118]. Moreover, IL-1 has been implicated in HF via its negative inotropic effects and is involved in harmful left ventricular remodeling. Mice lacking IL-1 receptor type I show decreased adverse remodeling after MI [118]. IL-1 also contributes to endothelial dysfunction by stimulating the release of endothelin-1, a potent vasoconstrictor, and nitric oxide synthase leading to oxidative and nitrosative stress. IL-1 exerts a pro-apoptotic effect on cardiomyocytes, associated with activation of Bak and Bcl-xl through pathways involving nitric oxide. Nevertheless, like TNF-alpha, IL-1 may also exert beneficial effects during MI and be involved in cardiac repair mechanisms, stimulating for example the expression of plasminogen activator inhibitor 1 (PAI-1) [119].

5.1.3. IL-1 and Myocarditis

IL-1 levels have been reported to be increased in several cases of coxsackievirus-induced myocarditis [120]. IL-1 activates iNOS and results in increased production of nitric oxide, cytotoxicity, and negative inotropic effects on myocardium [121].

5.2. IL-1 Antagonism by IL-1Ra in Cardiovascular Diseases

As IL-1 is an important mediator in atherosclerosis, and associated with plaque destabilization in acute coronary syndromes, involved in post-infarction remodeling, and in the pathogenesis of myocarditis, IL-1Ra could be a therapeutic option for a wide variety of cardiovascular conditions but further studies need to be done.

IL-1 mediated inflammatory effects can be neutralized by the physiological inhibitor IL-1Ra, which is found in both soluble and intracellular isoforms. The soluble IL-1Ra molecule binds the IL-1 receptor but does not lead to the activation of the signaling pathway. Anakinra is a recombinant form of human IL-1 Ra that competitively inhibits IL-1 by binding the IL-1 type I receptor, acting as IL-1Ra.

5.2.1. IL-1Ra in Atherosclerosis

Studies on IL-1Ra highlight the key role of IL-1 in atherogenesis. Mice lacking the IL-1Ra gene develop lethal arterial inflammation [113]. IL-1Ra may inhibit neoimtima formation after coronary artery injury [122]. The ratio of IL-1 to IL-1Ra was suggested to be critical in the pathogenesis of vascular inflammation and atherosclerosis [123]. In obese patients, IL-1Ra levels are increased [124], partly secreted by adipose tissue. In this population, IL-1Ra promotes leptin and insulin resistance and weight gain [124]. An association between certain IL-1Ra gene polymorphism and coronary disease as well as the development of restenosis after stenting has been reported [125, 126].

5.2.2. IL-1Ra and Myocardial Infarction

Patients with MI have increased levels of IL-1Ra compared to patients with stable coronary disease or with no
Table 1. Trials evaluating biologics in inflammatory and non-inflammatory cardiovascular diseases as reported on http://clinicaltrials.gov, July 2012.

<table>
<thead>
<tr>
<th>Name of the Study</th>
<th>NCT</th>
<th>Design of the Study</th>
<th>Primary Endpoint</th>
<th>Estimated Enrollment</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects of TNF-alpha antagonism (Etanercept) in patients with the metabolic syndrome and psoriasis</td>
<td>00477191</td>
<td>Randomized open-label versus placebo</td>
<td>Effects of etanercept on CRP levels from baseline to 6 months of treatment in patients with psoriasis and metabolic syndrome</td>
<td>40</td>
<td>USA</td>
</tr>
<tr>
<td>Escape II Myocardium</td>
<td>01548768</td>
<td>Randomized Single blind</td>
<td>Improvement of left ventricular mass and left ventricular ejection fraction (LVEF) after 6 months of treatment: TNF inhibitors versus triple therapy (sulfasalazine+hydroxychloroquine+methotrexate)</td>
<td>50 patients who had not responded to methotrexate</td>
<td>USA</td>
</tr>
<tr>
<td>Etanercept safety and efficacy treating patients with acute ST-segment elevation MI</td>
<td>01372930</td>
<td>Randomized open-label</td>
<td>Composite of major cardiovascular adverse events = cardiac death, fatal MI and fatal stroke (30 days) comparing etanercept 25 mg at 2 hours and 72 hours after percutaneous coronary intervention (PCI) versus saline at 2 hours and 72 hours after PCI</td>
<td>200</td>
<td>China</td>
</tr>
<tr>
<td>A study of tocilizumab in comparison to etanercept in patients with RA and cardiovascular risk factors</td>
<td>01331837</td>
<td>Randomized open-label</td>
<td>Time from randomization to occurrence of the primary cardiac adverse event defined as a composite of cardiovascular death, non-fatal MI and non-fatal stroke (5 years) to evaluate the rate of ischemic events of tocilizumab 8 mg/kg/4 weeks to etanercept 50 mg/week</td>
<td>2,800</td>
<td>USA</td>
</tr>
<tr>
<td>Cardiovascular effects in psoriasis patients treating with adalimumab</td>
<td>01320293</td>
<td>Open-label single-group assignment</td>
<td>Adalimumab Percentage change in endothelial function compared to baseline at 6 months</td>
<td>52</td>
<td>USA</td>
</tr>
<tr>
<td>Efficacy of adalimumab in Behcet’s disease patients with arthritis</td>
<td>01497717</td>
<td>Open-label single-group assignment</td>
<td>Adalimumab Reduction in DAS28 at week 24</td>
<td>15</td>
<td>Israel</td>
</tr>
<tr>
<td>Etanercept: single blind controlled study in ocular manifestations of Behcet’s disease</td>
<td>00931957</td>
<td>Randomized single-blind</td>
<td>Visual activity and disease activity index for posterior uveitis and retinal vasculitis comparing etanercept 50 mg/week +methotrexate+prednisolone versus methotrexate+prednisolone</td>
<td>80</td>
<td>Iran</td>
</tr>
<tr>
<td>Effect of tocilizumab in non-ST elevation MI</td>
<td>01491074</td>
<td>Randomized double-blind</td>
<td>High sensitivity CRP area under the curve 0-56 hours after inclusion comparing tocilizumab versus placebo Non-STEMI</td>
<td>120</td>
<td>Norway</td>
</tr>
<tr>
<td>Tocilizumab for patients with giant cell arteritis</td>
<td>01450137</td>
<td>Randomized double-blind</td>
<td>Proportion of patients who have achieved complete remission of disease (12 weeks) comparing tocilizumab+steroids versus placebo+steroids</td>
<td>27</td>
<td>Switzerland</td>
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<tr>
<td>Pilot feasibility study of the safety and efficacy of anakinra in heart failure (HF) with preserved ejection function</td>
<td>01542502</td>
<td>Randomized double-blind</td>
<td>Peak oxygen consumption (peak VO2) (14 days) comparing anakinra 100 mg SC versus placebo Giant cell arteritis</td>
<td>14</td>
<td>USA</td>
</tr>
<tr>
<td>Anakinra to prevent adverse post-infarction remodeling (VCU-ART2)</td>
<td>01175018</td>
<td>Randomized double-blind</td>
<td>Differences between the anakinra arm and the placebo arm in changes in left ventricular end-systolic volume indices from baseline to follow-up exam at cardiac magnetic resonance imaging (MRI) (10-14 weeks)</td>
<td>30</td>
<td>USA</td>
</tr>
<tr>
<td>Pilot study of the safety and efficacy of anakinra in HF</td>
<td>01300650</td>
<td>Non-randomized open-label</td>
<td>Median interval change from baseline in peak VO2 (14 days) and in the minute ventilation and carbon dioxide production (14 days) HF</td>
<td>10</td>
<td>USA</td>
</tr>
</tbody>
</table>
coronary disease [127] and IL-1Ra levels in MI correlate with infarct size [128]. Release of IL-1Ra occurs early in patients with ST-segment elevation MI, earlier than traditional markers of necrosis [129]. The role of increased IL-1Ra is not completely established: is it a simple marker of damage or a potential cardioprotective agent?

Expression of IL-1 Ra in an animal model has been shown to be cardioprotective against ischemia-reperfusion injury by reducing infarct size and cardiomyocyte apoptosis [130]. Administration of anakinra prior to reperfusion may limit myocardial ischemia-reperfusion injury [131].

Moreover, IL-1 antagonism may contribute to the modulation of post-MI remodeling. Administration of anakinra within 24 hours of acute experimental MI ameliorates the post-infarction remodeling process by inhibiting apoptosis induced by ischemia (inhibiting caspase-1 and -9 activities) [132]. Murtuza et al. showed that transplantation of skeletal myoblasts secreting IL-1 Ra improves systolic function, by modulating adverse remodeling and reducing myocyte hypertrophy [133].

More recently, the VCU-ART study (http://clinicaltrials.gov – NCT01175018) reported that anakinra in acute MI assessed in 10 patients was safe and beneficial on left ventricular remodelling [134]. The VCU-ART2 study, again evaluating anakinra to prevent adverse post-infarction remodeling, is presently recruiting patients. This study will compare anakinra with placebo in the assessment of change in left ventricular end-systolic volume indices from baseline to 10-14 weeks by cardiac magnetic resonance imaging in 30 patients with ST-segment elevation MI (STEMI). Another trial, MRC-ILA-HEART, a randomized, placebo-controlled, multicenter study comparing 14 days of anakinra therapy to placebo in patients with non-STEMI, is completed but the data are not yet published [135].

In summary, many considerations should be taken into account if one wants to use IL-1Ra in MI. Like TNF-alpha, the actions of IL-1 on the circulatory system are complex and an imbalance between IL-1 and IL-1Ra might have an important impact on the cardiovascular function. It may be beneficial but could also be harmful if IL-1 is involved in cardiac repair after MI, for example. Moreover, atherosclerosis may require long-term therapy and chronic IL-1 blockade may increase vulnerability to infections and malignancies.

5.2.3. IL-1Ra and Ventricular Function

Ikonomidis et al. reported that anakinra may improve vascular and left ventricular function in patients with RA but without coronary disease [136]. This improvement was related to a concomitant reduction in nitrooxidative stress and endothelin-1 levels. It is not known if results from this non-randomized study may be extrapolated to patients without RA but suffering from coronary disease, which would be more relevant. Nevertheless, an ongoing study is evaluating whether anakinra also improves vascular and left ventricular function in patients with coronary diseases and coexistent RA (http://clinicaltrials.gov – NCT 01566201).

6. CONCLUSION

In summary, data showed that patients with chronic inflammatory diseases have a higher risk of cardiovascular diseases partly due to systemic inflammation. Pro-inflammatory cytokines such as TNF-alpha, IL-1, and IL-6 could be major actors in this pathophysiology. Specific treatments targeting these proinflammatory cytokines are promising tools to control the burden of cardiovascular diseases. Although experimental data are consistent with this hypothesis, preliminary large clinical trials with anti-TNF-alpha therapies in heart failure were disappointing.
Nevertheless, new drugs inhibiting or regulating these pathways remain of interest in atherosclerosis, heart failure or ischemia-reperfusion lesions and further trials will address these issues (Table 1). Anti-IL-6 and anti-IL-1 strategies are currently under study to further investigate the complex relationship between inflammation, its therapies, and cardiovascular diseases.

**CONFLICT OF INTEREST**

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**ACKNOWLEDGEMENTS**

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**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AAV</td>
<td>ANCA-associated vasculitides</td>
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<tr>
<td>ACPA</td>
<td>Anti-citrullinated peptide antibodies</td>
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<td>ACS</td>
<td>Acute coronary syndrome</td>
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<tr>
<td>ATTACH</td>
<td>Anti-TNF-alpha Therapy Against Congestive Heart Failure</td>
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<tr>
<td>BD</td>
<td>Behcet’s disease</td>
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<tr>
<td>BNP</td>
<td>B-type natriuretic peptide</td>
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<tr>
<td>BSRBR</td>
<td>British Society for Rheumatology Biologics Register</td>
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<tr>
<td>BVAS/WG</td>
<td>Birmingham Vasculitis Assessment Score for Wegener’s Granulomatosis</td>
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<tr>
<td>ccIMT</td>
<td>Common carotid intima-media thickness</td>
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<tr>
<td>CHOP</td>
<td>Cyclophosphamide, doxorubicin, vincristine-oncovin and prednisolone</td>
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<tr>
<td>COX</td>
<td>Cyclooxygenase</td>
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<tr>
<td>CV</td>
<td>Cardiovascular</td>
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<tr>
<td>CYC</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular diseases</td>
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<tr>
<td>DMARDs</td>
<td>Disease-modifying anti-rheumatic drugs</td>
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<tr>
<td>EULAR</td>
<td>The European League Against Rheumatism</td>
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<tr>
<td>FGF</td>
<td>Fibroblast growth factor</td>
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<tr>
<td>FMD</td>
<td>Flow-mediated vasodilatation</td>
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<tr>
<td>GCA</td>
<td>Giant cell arteritis</td>
</tr>
<tr>
<td>HF</td>
<td>Heart failure</td>
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<tr>
<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>IL-1Ra</td>
<td>IL-1 receptor antagonist</td>
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<tr>
<td>iNOS</td>
<td>Inducible nitric oxide synthase</td>
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<tr>
<td>JAK</td>
<td>Janus kinase</td>
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<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
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<td>MAINRITSAN</td>
<td>Maintenance of remission using rituximab in systemic ANCA-associated vasculitis</td>
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<tr>
<td>MCP-1</td>
<td>Monocyte chemotactic protein-1</td>
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<td>MI</td>
<td>Myocardial infarction</td>
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<tr>
<td>MMPs</td>
<td>Matrix degrading metalloproteinases</td>
</tr>
<tr>
<td>MTX</td>
<td>Methotrexate</td>
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<tr>
<td>NMD</td>
<td>Nitroglycerine-mediated vasodilation</td>
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<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drugs</td>
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<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>PAI-1</td>
<td>Plasminogen activator inhibitor 1</td>
</tr>
<tr>
<td>PDGF</td>
<td>Platelet derived growth factor</td>
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<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>RAVE</td>
<td>Rituximab for ANCA-associated vasculitis</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trials</td>
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<td>RECOVER</td>
<td>Research into Etanercept CytOkine Antagonism in VentriculaR dysfunction</td>
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<td>RENAISSANCE</td>
<td>Randomised Etanercept North American Strategy to Study Antagonism of CytokinEs</td>
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<tr>
<td>RENEWAL</td>
<td>Randomized EtaNercept Worldwide evaluation</td>
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<td>RITUXVAS</td>
<td>Rituximab in vasculitis</td>
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<tr>
<td>RTX</td>
<td>Rituximab</td>
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<tr>
<td>SAFE</td>
<td>Survivor activating factor enhancement</td>
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<td>SAA</td>
<td>Serum amyloid A</td>
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<tr>
<td>SC</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>S1P</td>
<td>Sphingosine-1-phosphate</td>
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<tr>
<td>STAT</td>
<td>Signal transducer and activator of transcription</td>
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<tr>
<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
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<tr>
<td>TA</td>
<td>Takayasu’s arteritis</td>
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<tr>
<td>TNF-alpha</td>
<td>Tumor necrosis factor-alpha</td>
</tr>
<tr>
<td>TNFR1 and 2</td>
<td>TNF-alpha receptors type I and II</td>
</tr>
<tr>
<td>VCAM</td>
<td>Vascular cell adhesion molecule</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular endothelial cell growth factor</td>
</tr>
<tr>
<td>WGET</td>
<td>Wegener’s Granulomatosis Etanercept Trial</td>
</tr>
</tbody>
</table>

**REFERENCES**


in patients with Takayasu arteritis: Experience from a referral center with long-term followup. Arthritis Care Res. (Hoboken), 2012, 64(7), 1079-1083.


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