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Antirheumatic drugs and cardiovascular disease in rheumatoid arthritis

ABSTRACT

There is increased cardiovascular (CV) morbidity and mortality in rheumatoid arthritis (RA) and other rheumatic and musculoskeletal diseases (RMDs). Systemic inflammation is highly involved in atherogenesis. Non-steroidal anti-inflammatory drugs (NSAIDs), primarily COX-2 inhibitors might increase CV risk. Corticosteroids might act as a double-edged sword as they exert both beneficial and negative effects on the CV system. NSAIDs and corticosteroids are anti-inflammatory, but, on the other hand, they might be potentially atherogenic. Conventional synthetic DMARDs (csDMARDs), such as antimalarials, methotrexate, sulfasalazine, leflunomide and cyclosporine A have good CV safety, however, leflunomide and cyclosporine A might cause hypertension. Biologic DMARDs, by suppressing inflammation and disease activity, might either reduce CV risk or at least not cause any harm in that respect. Recently, tofacitinib and most likely other Janus kinase inhibitors have been associated with increased CV risk, at least in RMD patients with high CV risk at baseline. In clinical practice, EULAR and other recommendations guide the rheumatologist when screening for and managing CV comorbidities.

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KEY WORDS: rheumatoid arthritis; RMDs; atherosclerosis; cardiovascular disease; antirheumatic drugs; csDMARDs; bDMARDs; tsDMARDs

INTRODUCTION

Increased cardiovascular (CV) risk has been associated with rheumatoid arthritis (RA) and other rheumatic and musculoskeletal diseases (RMDs) [1–6]. The CV risk in RA, similarly to diabetes mellitus, is double compared to the general population [7]. RA patients have a 48% higher risk of incident atherosclerotic CV disease (ASCVD) compared to the general population. There is a 68% higher risk of myocardial infarction (MI) and a 41% higher risk of stroke [8]. Both traditional CV risk factors and systemic inflammation/autoimmunity are involved in atherosclerosis associated with these RMDs, which will not be discussed further in more detail (reviewed in [4, 9–12]). Since the "mortality gap" continues to widen, achieving optimal CV management in RA is a major clinical need [12, 13].

Sustained autoimmunity and systemic inflammation are major drivers of CV conditions underlying RMDs, The European Alliance of Associations for Rheumatology (EULAR) recommends that, after CV risk assessment, prevention and management are required to minimize CV risk [4, 5]. Atheroprotective agents, such as statins, aspirin or angiotensin-converting enzyme inhibitors should be administered to RMD patients with increased CV risk [4, 5]. Yet, the optimal control of the RMD might be even more important.

Antirheumatic drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional synthetic (csDMARDs), biologic (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) might serve as double-edged-swords. On one hand, these agents control inflammation and autoimmunity and thus at-

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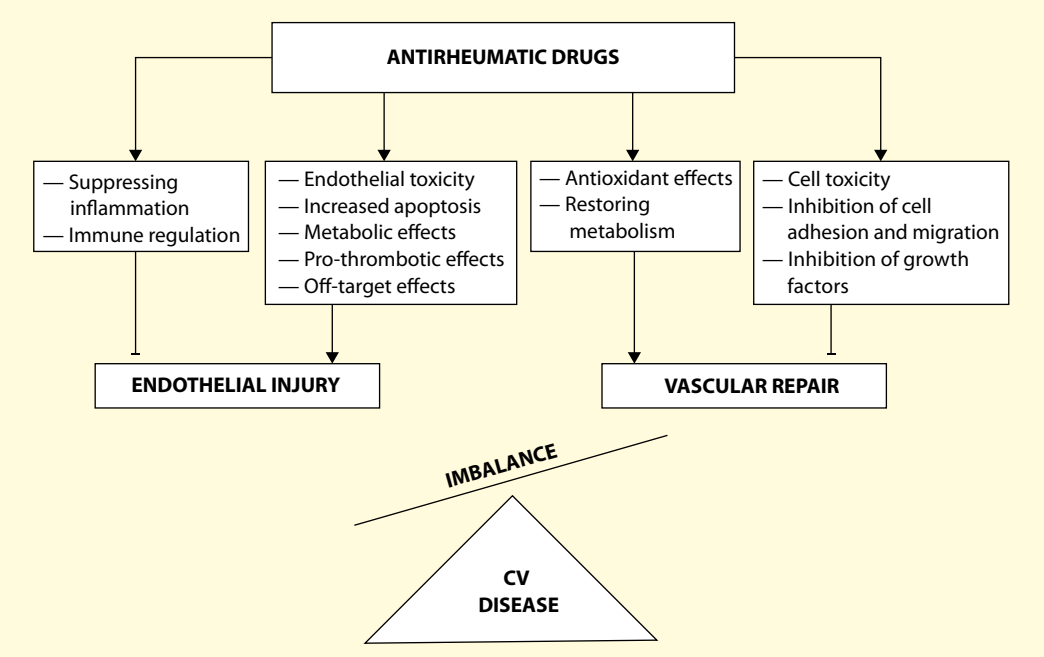

Figure 1. Beneficial and harmful CV effects of antirheumatic drugs. These compounds might inhibit vascular damage and promote repair by various mechanisms. On the other hand, the drugs themselves might carry side effect that enhance endothelial damage and delay vascular repair. The net CV outcome will depend on the imbalance between positive and negative CV effects; CV — cardiovascular

tenuate inflammatory atherosclerosis. As CV pathology starts developing before the clinical diagnosis of RMDs, very early control of the underlying disease is crucial to prevent the progression of CV comorbidities. On the other hand, some of these compounds might exert some unfavourable effects on the vasculature (Fig. 1) (reviewed in [4, 12, 14–16]).

Despite the considerable development in disease control, already in the early phases of arthritis, throughout the years, the CV burden in RA remains elevated [13]. Although the treat-to-target approach has been introduced and treatment aims at clinical remission in the joints [17], this may not necessarily fully match CV risk reduction [12, 18]. Moreover, as discussed later, some antirheumatic drugs might exert deleterious effects on the vasculature, mainly by interfering with vascular repair mechanisms [12, 14]. Finally, corticosteroids and some DMARDs, while dampening inflammation, can unfavourably influence traditional risk factors, such as lipids [12, 14, 19].

Here the authors review the, sometimes controversial, data on the effects of antirheumatic drugs on the CV system. Most data have arisen when RMD patients were treated with these compounds. However, a few larger trials have also been initiated in non-RMD patients with CV disease. The metabolic effects of these compounds (e.g., metabolic syndrome, obesity, lipids, adipokines, glucose metabolism) will not be discussed in detail.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Recently, both traditional NSAIDs and coxibs have drawn attention to CV diseases [14]. Early studies suggested that non-selective NSAIDs, similarly to coxibs, can also increase CV risk [14, 20–23]. Kearney et al. [21] performed a meta-analysis. In that study, the use of coxibs resulted in a 42% relative increase in the incidence of major cardiovascular events (MACE) when compared to a placebo. The overall CV risk was comparable between coxibs and traditional NSAIDs. High doses of ibuprofen and diclofenac but not naproxen exerted a moderate increase in overall CV risk [21]. In the systematic review of Scott et al. [24], the odds ratio (OR) for MI of COX-2 inhibitors was 1.6. The highest CV risk was observed with rofecoxib. No or very slow CV risk increases were observed in relation to other NSAIDs [24]. Roubille et al. [15] performed a meta-analysis to determine the CV risk of NSAIDs in RA, psoriasis or psoriatic arthritis (PsA). The relative risk (RR) of all CV diseases using all NSAIDs, coxibs or traditional NSAIDs were 1.18 (1.01; 1.38), 1.36 (1.10;

1.67) and 1.08 (0.94; 1.24), respectively. Concerning MI, stroke and MACE, these RR values were 1.13 (0.93; 1.37), 2.15 (1.19; 3.87) and 1.56 (0.82; 2.97), respectively [15]. On the other hand, in the PRECISION trial conducted in RA and osteoarthritis patients, the selective COX-2 inhibitor celecoxib was not inferior to non-selective NSAIDs (ibuprofen or naproxen) in terms of MACE [25]. These studies indicated that, although NSAIDs might increase the risk of CV events and stroke in RA, there were no differences between coxibs and traditional NSAIDs [15, 25].

Regarding spondyloarthritis (SpA), Tsai et al. [26] assessed CV risk in patients receiving sustained NSAID therapy. Some NSAIDs might exert disease-modifying capacity in SpA [27, 28]. Therefore, the attenuation of disease progression in SpA might also have beneficial CV effects [4]. Indeed, in the study of Tsai et al. [26], longer *vs*. shorter use of NSAIDs including coxibs resulted in lower CV morbidity in SpA.

The CV risk of NSAIDs might be different in inflammatory RMDs compared to the general population. NSAIDs that exert a detrimental CV profile in otherwise healthy subjects might not increase CV risk in arthritis patients, where the anti-inflammatory action of NSAIDs could override their negative CV effects [29–31]. In a Danish study, the CV risk associated with NSAIDs was lower in arthritis (RR 1.22 [1.09; 1.37]) compared to controls (RR 1.51 [1.36; 1.66]) [30].

Thus, from the CV perspective, the long-term use of any NSAIDs is not recommended, especially in elderly patients and in those with a history of CV disease or with CV risk factors [15, 32, 33]. According to the EULAR recommendations, in RA and PsA, traditional NSAIDs and coxibs should be administered with caution to patients with documented ASCVD or with CV risk factors [5, 32, 33]. On the other hand, in atherosclerosis, NSAIDs should be used as a first-line option unless NSAIDs are contraindicated [33].

CORTICOSTEROIDS

Corticosteroids exert harmful effects on body fat distribution, blood pressure and glucose metabolism [14, 34–38]. Again, corticosteroids are double-edged swords being anti-inflammatory and atherogenic at the same time [14, 35–37, 39, 40]. For example, in systemic lupus erythematosus (SLE), both disease activity and recent corticosteroid use have been independently correlated with the development of ASCVD [5, 40].

In the study of del Rincón et al. [41] that included 779 RA patients, corticosteroid use was associated with increased CV-related mortality independent of RA severity. These authors recommended treating RA patients by applying the lowest possible dose (< 7.5 mg/day prednisolone equivalent) for the shortest possible time [41]. In the CARRE study, higher CV risk was found in patients receiving corticosteroids. After adjustment for the DAS28 and HAQ scores, greater disease activity was associated with higher CV risk [42]. In the study of Roubille et al. [15] already discussed above in relation to NSAIDs, corticosteroids increased the risk of all CV events, MI, stroke and MACE with RR values of 1.47 (134; 1.60), 1.41 (1.22; 1.63), 1.57 (1.05; 2.35) and 1.62 (1.22; 2.16), respectively. On the other hand, in a meta-analysis of 4381 patients, Boers et al. [43] could not find increased CV risk. Very recently, in the GLORIA trial, the long-term use of low-dose (5 mg/day) prednisolone as an add-on therapy was effective and safe in elderly (65+ years) patients with RA [44]. The exact benefit-to-harm ratio of corticosteroids needs further clarification.

Certainly, the duration of the underlying disease and cumulative corticosteroid dose also matter. Ajeganova et al. [45] assessed CV risk in early RA patients treated with 7.5 mg/day prednisone in combination with DMARDs *vs.* DMARD monotherapy. The incidence of ASCVD was similar in the two groups, however, the long-term risk of cerebrovascular events was higher in patients receiving corticosteroids [45]. In the CARRE study, a longer duration of exposure or cumulative exposure to corticosteroids could be associated with increased CV risk. However, there was no such association after adjustment for disease activity [42]. Moreover, del Rincon et al. [41] determined the daily threshold corticosteroid dose of 8 mg. Above this dose mortality increased in a dose-dependent manner. This study suggests that low corticosteroid doses (< 8 mg/day) might be safe [41].

In conclusion, the favourable anti-inflammatory effects of corticosteroids might be associated with their detrimental CV effects, especially after long-term exposure [12, 14, 42]. In line with this, the EULAR CV recommendations suggest using the lowest effective dose possible (ideally < 7.5 mg of prednisone or equivalent) and the dose should be tapered

when clinical remission or low disease activity is reached [4, 5, 32]. This notion supports corticosteroid use as a bridge therapy before initiating DMARDs [4, 17]. Moreover, the potential CV risk associated with corticosteroids might be different in inflammatory RMDs and non-inflammatory conditions [42, 46].

CONVENTIONAL SYNTHETIC DISEASE-MODIFYING DRUGS

ANTIMALARIALS

Chloroquine (CQ) and hydroxychloroquine (HCQ) might exert anti-atherogenic nature. Their use can improve lipid and glucose metabolism. They might also have anti-thrombotic and atheroprotective effects [12, 14, 47].

In the ARAMIS study, HCQ decreased the risk of developing diabetes mellitus by 38%. Moreover, the RR decreased with sustained HCQ treatment. Thus, prolonged use of antimalarials might reduce the risk of diabetes mellitus [48]. The VARA registry data confirmed that HCQ improves lipid profiles. In addition, HCQ use was associated with less frequent MI [49].

Overall, antimalarials, either in monotherapy or in combination with bDMARDs, are beneficial in RA patients with CV risk factors. However, whether HCQ and CQ have direct atheroprotective effects or if they counteract the detrimental effects of other compounds, need further clarification [12, 14]. Nevertheless, in previously defined heart failure patients HCQ might worsen CV outcomes compared with methotrexate (MTX) [50].

The latest EULAR CV recommendations state that in patients with SLE, treatment with HCQ, which is recommended for all lupus patients anyway, should be considered to reduce CV risk [5].

SULFASALAZINE

There has been limited data available for the possible CV effects of sulfasalazine (SASP). Van Halm et al. [51] conducted a case-control study in RA patients, where SASP was associated with lower CV risk in comparison to patients who never used SASP, HCQ or MTX. SASP, similarly to MTX, might also exert its anti-inflammatory activity by inducing adenosine production [52].

METHOTREXATE

Increasing evidence suggests that MTX can lower CV risk. Although MTX itself increases the release of pro-atherogenic homocysteine, on the other hand, MTX also dampens systemic inflammation. MTX also exerts beneficial effects on cholesterol efflux in RA, increases adenosine release and suppresses AMPK-mediated vascular injury [53–55].

In various studies carried out in arthritis patients, MTX reduced rather than increased CV risk [15, 55–57]. In an earlier study, Suissa et al. [58], MTX use was associated with a significantly lower rate of MI (RR = 0.81) compared to RA patients not receiving MTX. In the study of Choi et al. [59], which included 1240 RA patients, MTX, but not other csDMARDs, decreased all-cause mortality by 60% and CV-related mortality by 70% [59]. Westlake et al. [55] carried out a systematic review and compared inflammatory *vs.* traditional CV risk. Methotrexate was able to reduce ASCVD risk and mortality in RA patients most likely due to its anti-inflammatory effects [55]. In the study of Roubille et al. [15] already mentioned above, MTX decreased the risk of all CV events, as well as MI, stroke and MACE with RR values of 0.72 (0.57; 0.91), 0.81 (0.68; 0.96), 0.78 (0.40; 1.50) and 0.38 (0.05; 2.84), respectively [15]. In the meta-analysis of De Vecchis et al. [60] MTX significantly decreased the risk of MACE (OR = 0.73).

All these studies were carried out in patients with inflammatory RMDs. In contrast, to date, the largest prospective trial assessing the CV effects of MTX, the CIRT trial, was conducted in non-arthritic individuals with previous ASCVD [61]. Ridker et al. [61] administered 15–20 mg/week MTX or placebo to 4786 patients with previous MI or multivessel coronary disease who also had either diabetes mellitus or metabolic syndrome. The primary endpoint of the trial was a composite of nonfatal MI, nonfatal stroke, CV death or urgent need for revascularization (major cardiovascular events, MACE). The trial was terminated after a median follow-up of 2.3 years. In this non-arthritic cohort, MTX did not lower C-reactive protein (CRP), interleukin 6 (IL-6) or IL-1β levels. In addition, low-dose MTX therapy did not result in fewer CV events than the placebo [61]. Moreover, in the THETYS trial conducted in acute MI patients without previous inflammatory arthritis, the administration of MTX resulted in decreased left ventricular ejection fraction [62]. Thus, MTX might exert beneficial CV effects only under inflammatory conditions.

In conclusion, although MTX might increase homocysteine levels and thus CV risk,

which could be abrogated by folate supplementation, MTX use might lead to an overall positive CV balance [15, 55, 59]. The EULAR recommendations suggest MTX use to suppress systemic inflammation to prevent ASCVD [4, 32].

LEFLUNOMIDE

Leflunomide inhibits the NFκB pathway that is involved in both inflammatory processes and cardiovascular pathology [63, 64]. Leflunomide has also been implicated in the inhibition of leukocyte-endothelial adhesion [64, 65]. Thus, leflunomide might be beneficial for inflammatory atherosclerosis.

In RA, leflunomide use was associated with a significantly lower MI rate compared to several other drugs (RR = 0.28) [58]. In a prospective study carried out in early RA patients, leflunomide exerted favourable effects on disease activity, however, hypertension relatively frequently occurred [66]. Moreover, leflunomide-eluting stents have been used in invasive cardiology due to the possible atheroprotective effects of these agents. Indeed, leflunomide stents preserved endothelial function, improved vascular healing and were found to be safe in various studies [67].

Thus, leflunomide might be atheroprotective in RA. On the other hand, it might have limited use in patients with hypertension [12, 14].

CYCLOSPORINE A

Cyclosporine A (CyA) might promote the development of atherosclerosis, hypertension and dyslipidaemia. It can induce hypertension. A Cochrane review assessing the incidence of hypertension in randomised controlled trials associated with a significant dose-related increase in blood pressure during CyA treatment [68]. In SLE, CyA exerted neutral associations with CV events [5].

Blood pressure should be assessed before and monitored during CyA treatment of RA. CyA should be administered at the lowest possible dose [4]. The evidence about the effects of CyA on efficacy and safety for CV outcomes in RMDs is rather limited.

BIOLOGIC DISEASE-MODIFYING DRUGS

ANTI-TNF-α AGENTS

Tumour necrosis factor alpha (TNF-α) inhibitors might exert variable effects on the CV system in RA [18, 69]. TNF-α is involved in almost all mechanisms underlying atherogenesis. TNF-α is a major pro-inflammatory and pro-atherogenic cytokine. TNF-α promotes cellular adhesion molecule expression on endothelial cells and thus leukocyte migration through the vessel wall [10, 70]. TNF-α has been implicated in the development of obesity, insulin resistance and dyslipidaemia [10, 70].

TNF-α blockers, at least transiently, improve endothelial function indicated by brachial artery flow-mediated vasodilation (FMD), decrease carotid (cIMT) and coronary atherosclerosis, as well as arterial stiffness indicated by pulse-wave velocity in arthritides (reviewed in [18]). Anti-TNF agents might stimulate endothelial progenitor cells and thus vasculogenesis [71] and also suppress platelet activation and tissue factor production in arthritis [72].

There have been numerous cross-sectional and very few prospective clinical trials that studied the CV effects of TNF-α inhibitors. In the Swedish national registry, as reported by Jacobsson et al. [73] 531 RA patients were treated with anti-TNF agents. In patients receiving TNF-α inhibitors, the incidence rate of first CV events was less than half compared to that observed in patients not treated by bDMARDs. In the systematic review carried out by Westlake et al. [74], anti-TNF therapy decreased the likelihood of ASCVD. Dixon et al. [75] analysed the British registry and compared RA patients treated with TNF-α inhibitors with those receiving csDMARDs only. There was no difference in the incidence of MI between these two patient subsets. However, ASCVD risk was significantly lower in patients responding well to 6 months of anti-TNF therapy in comparison to non-responders [75]. Greenberg et al. [76] performed a meta-analysis of five available studies. Most of these earlier studies indicated that TNF-α blockade resulted in the reduction of CV risk. The overall RR was 0.46 (0.28; 0.77) [76]. Barnabe et al. [77] carried out a systematic review of 16 studies. In this analysis, TNF-α inhibitors also reduced the risk of all CV events (RR = 0.46 [0.28; 0.70]) including MI (RR = 0.81 [0.68; 0.96]) [77]. Ljung et al. [78] studied the incidence of acute coronary syndrome in the Swedish ARTIS registry. Rheumatoid arthritis patients receiving anti-TNF agents had better event-free survival in comparison to bDMARD-naive patients [78]. Roubille et al. [15] also reported that TNF-α inhibitors lowered CV risk. The RR values for all CV events, MI, stroke and

MACE were 0.70 (0.54; 0.90), 0.59 (0.36; 0.97), 0.57 (0.35; 0.92) and 0.30 (0.15; 0.57), respectively [15].

There have been only two major prospective, hard endpoint studies, where a TNF-α was chosen as a comparator. In the ENTRACTE study, the IL-6 receptor inhibitor tocilizumab was compared to etanercept [79], while in the ORAL Surveillance trial, RA patients received either the Janus kinases (JAK) inhibitor tofacitinib or anti-TNF agents (adalimumab or etanercept) [80]. These trials will be presented later.

It is still important to note that TNF-α inhibitor therapy is not recommended for RA patients with NYHA III-IV stage congestive heart failure. In this situation, anti-TNF agents might aggravate heart conditions [6, 81].

IL-6 RECEPTOR BLOCKADE

IL-6 is also a key pro-inflammatory cytokine, which also increases the production of CRP, an independent risk factor for ASCVD [10, 70]. IL-6 has been implicated in the pathogenesis of atherosclerosis and ASCVD. IL-6 also promotes platelet and endothelial activation and increases adhesion molecule expression [10, 70]. Plasma CRP and IL-6 levels correlated with CV risk in healthy men [82]. A correlation was found between plasma IL-6 concentrations, impaired FMD and increased ccIMT in RA patients [83]. Thus, IL-6 blockade might have favourable vascular effects.

IL-6 receptor blockade, due to the "lipid paradox", might result in lipid level elevations. However, no changes in lipid indices (total cholesterol/high-density lipoprotein and low-density lipoprotein/high-density lipoprotein ratios) were observed, suggesting that the lipid changes would not reflect increased CV risk [19, 84].

IL-6 receptor inhibition by tocilizumab improved endothelial function (FMD) and decreased arterial stiffness (pulse-wave velocity) [18, 85]. Rao et al. [86] conducted a retrospective, *post hoc* analysis of about 4000 RA patients. In this cohort, tocilizumab did not increase the frequency of MACE. At baseline, the future development of MACE correlated with age, positive history of ASCVD and RA disease activity (DAS28) [86].

Singh et al. [87] performed a meta-analysis to compare the CV effects of various bDMARDs and csDMARDs in RA. In comparison to TNF-α inhibitors, tocilizumab use was associated with a decreased risk of MACE. No difference was found between tocilizumab and abatacept [87]. These data also support that the increased lipid levels associated with tocilizumab do not translate into increased CV risk. In contrast, tocilizumab might even have more favourable CV effects than anti-TNF agents [12, 87].

In the prospective, randomized, open-label ENTRACTE trial, 3080 patients with active seropositive RA were enrolled. These patients had an inadequate response to csDMARDs and had one or more CV risk factors. Patients received either tocilizumab (8 mg/kg/month) or etanercept (50 mg/week) and were undergoing follow-up for an average of 3.2 years. The primary endpoint was time until the first CV event. In this trial, the frequency of MACE was similar in tocilizumab- *vs.* etanercept-treated patients [79].

IL-1β BLOCKADE

IL-1β is involved in the pathogenesis of RA, as well as atherosclerosis [10, 88]. IL-1 blockade improved endothelial function in RA patients [89]. The recombinant IL-1 receptor antagonist 8IL-1Ra) anakinra improved endothelial function markers, oxidative stress and left ventricular function in a group of RA patients with ASCVD [90]. In ASCVD patients, the anti-IL-1β antibody canakinumab reduced CRP, IL-6 and fibrinogen plasma levels [91]. In clinical trials, canakinumab appeared to be safe [92–94].

The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study) trial was conducted in thousands of non-arthritis patients with stable ASCVD, but with elevated CRP levels [95]. In this trial, patients received 150 mg of canakinumab every 3 months. This resulted in a significantly lower rate of recurrent MACE compared to placebo. The atheroprotective effects of canakinumab appeared to be independent of its lipid-level lowering effects [95]. Positive CV outcomes as associated with CRP level reduction [96] suggesting that even under non-inflammatory conditions, the suppression of systemic inflammation rather than metabolic changes might lead to beneficial CV outcomes.

IL-12, IL-23 AND IL-17 INHIBITORS

IL-12, IL-17 and IL-23 are also pro-inflammatory cytokines involved in the pathogenesis of various arthritides [88, 97]. There has been limited data on CV safety concerning novel bD-

MARDs including IL-12/23, IL-17 and IL-23 inhibitors. These agents have been used to treat non-RA conditions including PsA, axial spondyloarthritis (axSpA), as well as non-rheumatic conditions [97]. No CV safety signals emerged in clinical trials of ustekinumab, secukinumab, ixekizumab, bimekizumab, guselkumab, risankizumab and tildrakizumab [18, 98–100].

B-CELL DEPLETING ANTIBODIES

Rituximab is an anti-CD20 monoclonal antibody, which leads to B-cells depletion. This results in the attenuation of disease activity in RA [101]. In a pilot study on five RA patients, 16-week rituximab treatment improved FMD and decreased ccIMT [101]. Other investigators also found that rituximab improved micro- and macrovascular endothelial function [102, 103]. The improvement of endothelial function was associated with the attenuation of systemic inflammation as indicated by decreased CRP and DAS28 [102–104].

In clinical trials, rituximab showed good CV safety [105]. In an analysis of the US registry, rituximab and anti-TNF agents had comparable CV safety profiles [106]. The rate of MI is similar in rituximab-treated RA patients and the general RA population [12, 107]. Gottenberg et al. [108] investigated drug survival after 2 years in more than 3000 RA patients receiving rituximab, tocilizumab or abatacept. No significant differences in the frequency of MACE were seen between the three groups [108]. In a 5-year study carried out on almost 1000 RA patients, the overall CV risk of rituximab was similar compared to other bDMARDs [109].

Very rarely, the development of acute MI was reported in association with rituximab administration [110]. The underlying mechanisms remain unknown. However, a rapid release of pro-inflammatory cytokine has been suggested to occur during acute infusion reactions. In turn, coronary vasoconstriction and/or plaque rupture might occur. In addition, the role of medium- or high-dose corticosteroid premedication usually administered before rituximab treatment cannot be ruled out [12, 109, 110]. Therefore, in patients with a history of ASCVD, rituximab should be administered with caution and close monitoring should be applied.

T-CELL COSTIMULATION BLOCKADE

T-cells play an important role in both synovial inflammation and atherosclerosis [10, 111, 112]. Among T-cell subsets, type 1 T helper cells might be involved in RA and ASCVD pathogenesis [10, 111, 112].

There have been relatively few studies on the T-cell costimulation inhibitor abatacept (CTLA4-Ig fusion protein) and CV safety. In the meta-analysis of phase III trial data, abatacept exerted a good CV safety profile [113]. Zhang et al. [114] performed an insurance database analysis. In this study, abatacept treatment resulted in lower MI risk compared to anti-TNF agents in elderly RA patients [114]. As discussed above, Gottenberg et al. [108] did not find any differences in the frequency of MACE between abatacept, rituximab and tocilizumab. Moreover, as reported by Singh et al. [87], there were no differences in the incidence of MACE and/or stroke between RA patients receiving abatacept, tocilizumab or anti-TNF agents. Abatacept also improves insulin sensitivity, therefore the administration of abatacept to RA patients with diabetes mellitus might be beneficial [115, 116]. Indeed, abatacept treatment resulted in a 26% decrease in CV risk when administered to RA patients who also have diabetes mellitus [115, 116].

TARGETED SYNTHETIC DMARDS

Janus kinases mediate the signalling of multiple cytokines in RA [117, 118]. JAKs have also been implicated in atherosclerosis and ASCVD [119, 120]. JAK3 inhibition in mice was found to be protective against myocardial ischaemia and reperfusion injury [119].

Up to now, four JAK inhibitors (JAKi), tofacitinib, baricitinib, upadacitinib and filgotinib have been approved for the treatment of RA [121]. Available data from clinical studies and integrated safety analyses did not suggest increased CV risk in RA patients [121–126]. As numerous cytokines signalling through JAKs might be involved in the pathogenesis of inflammatory atherosclerosis and ASCVD, JAKi might be vasculoprotective by inhibiting these cytokine pathways [9, 12, 127]. For example, in the authors' ^{18}F-FDG-PET/computed tomography study, the pan-JAK inhibitor tofacitinib suppressed aortic wall inflammation in RA patients [128]. JAK inhibition also inhibited the progression of endothelial function and arterial stiffness in RA [120].

Recently, ORAL Surveillance, the very first trial that prospectively assessed the safety of tofacitinib in comparison to TNF-α inhibitors has been conducted [80]. ORAL Surveillance was a randomized, open-label, noninferiority,

safety trial, which included patients with active RA, with an age of ≥ 50 years. All recruited patients had ≥ 1 CV risk factor. Patients received either 5 mg or 10 mg bid tofacitinib or a TNF-α inhibitor. One of the primary endpoints was adjudicated MACE. The trial included 4362 patients with a median follow-up of 4.0 years and a mean disease duration of 10 years. In this trial, the incidence of MACE was higher with both tofacitinib doses (3.4%) compared to the TNF-α inhibitor (2.5%). The hazard ratio for MACE was 1.33 (95% CI: 0.91–1.94) and the non-inferiority criterion for tofacitinib was not met. Thus, in this RA population of high baseline CV risk, the risk of MACE was higher with tofacitinib compared to bDMARDs [80]. A *post hoc* analysis of the ORAL Surveillance trial has been performed with respect to MACE. MACE occurred mostly in RA patients with a positive history of ASCVD. In patients with no history of ASCVD, the hazard ratio of MACE was similar in patients receiving 5 mg bid tofacitinib or anti-TNF therapy [129].

Much fewer data have become available regarding other JAKi. Again, no CV safety signals emerged from clinical trials and integrated safety analyses of baricitinib, upadacitinib and filgotinib [121–126, 130–133]. A meta-analysis of all JAKi assessed 26 randomized clinical trials (11 799 patients), finding no increase in the risk of MACE [134]. Prospective trials with baricitinib, such as RA-BRIDGE (NCT03915964) and RA-BRANCH (NCT04086745), which have venous thromboembolism as the primary endpoint are underway (www.clinicaltrials.gov).

Based on results from the ORAL Surveillance trial conducted with tofacitinib, as well as preliminary data from an observational study with baricitinib, in November 2022, the European Medicines Agency (EMA) stated to minimise the risk of serious side effects with JAKi in chronic inflammatory disorders [135]. The EMA suggests that in various inflammatory diseases, patients at the age of ≥ 65 years, those with a history of ASCVD or heavy smokers should only be treated with JAKi if no other therapeutic alternatives are available [135]. Similar statements have been included in the latest RA treatment EULAR recommendations [17]. The EULAR task force concluded that the data from the ORAL Surveillance trial currently pertain only to RA patients at high CV risk. The task force found no evidence of higher CV risk of tofacitinib versus anti-TNF agents in RA patients without CV risk factors. Although similar data for other JAKi have not yet been available, the task force, in accordance with EMA, suggested that similar considerations should be made with respect to JAKi other than tofacitinib [17].

CONCLUSIONS

Inflammatory atherosclerosis and increased CV risk have been associated with RA. Chronic inflammation and disease activity, in addition to traditional CV risk factors, are major contributors to atherogenesis. NSAIDs, primarily COX-2 inhibitors might increase CV risk, therefore, these drugs should be prescribed with caution. Corticosteroids might exert both beneficial and harmful effects on the CV system. The CV risk of NSAIDs and corticosteroids might be different in inflammatory diseases, such as RA or non-inflammatory conditions. It is possible that the anti-inflammatory action of NSAIDs and corticosteroids might be superior to their potential atherogenic nature. Among csDMARDs, antimalarials and MTX might be cardio-protective. Leflunomide might not promote atherosclerosis, but it can cause hypertension. Biologic DMARDs and tsDMARDs effectively suppress systemic, as well as synovial inflammation. Targeted therapies might also have beneficial effects on vascular pathophysiology including overt atherosclerosis, endothelial dysfunction and vascular stiffness. In several trials, TNF-α inhibitors have been associated with decreased CV risk. Other bDMARDs also appeared safe, however, long-term prospective trials are still lacking. In the ORAL Surveillance trial conducted in RA patients with long disease duration and higher CV risk, tofacitinib increased the risk of MACE. Based on these data, both the funding agencies (EMA) and EULAR recommend caution when administering any JAKi to elderly patients, smokers and patients with increased CV risk. In clinical practice, EULAR and other recommendations help the rheumatologist during the prevention and management of CV comorbidities in patients with RA and other RMDs.

CONFLICT OF INTEREST

None declared.

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