Biological Therapy on Cardiovascular Risk Factors in RA

Subjects: Rheumatology

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Rheumatoid arthritis (RA), one of the most common of the chronic inflammatory autoimmune diseases (CIADs), is recognized as an independent cardiovascular risk factor. Therapies used in RA include disease-modifying antirheumatic drugs (DMARDs), categorized into conventional synthetic DMARDs (csDMARDs), targeted synthetic DMARDS (tsDMARDs), and biological DMARDs (bDMARDs). csDMARDs are used as first-line therapy in the absence of contraindications, with Methotrexate (MTX) being the first option. Moreover, when disease activity is high, low doses of glucocorticoids can be used for a short period of time as a bridging therapy.

atherosclerosis autoimmune disease rheumatoid arthritis inflammation

1. Anti-IL-6

Interleukin-6 (IL-6) is a cytokine with pleiotropic effects in inflammation, modulation of immune responses, regenerative processes, hematopoiesis, and metabolism. Synthesized from the initial stage at the site of inflammation by several cell types—such as macrophages, adipocytes, endothelial cells (ECs), or smooth muscle cells—IL-6 causes the release of acute-phase reactants from the liver, such as C-reactive protein (CRP), fibrinogen, haptoglobin, and serum amyloid A (SAA). It is important to note that the transition from the acute to the chronic phase of inflammation is made by the recruitment of the leukocyte infiltrates, while neutrophils are transformed into monocytes or macrophages. In this stage, an important role is played by the soluble IL-6 receptor α (sIL-6Rα) [1][2]. Its important role in the acute and chronic phases of inflammation has made this particular cytokine a key player in the development and progression of atherosclerosis. There are studies that have demonstrated the role of IL-6 as a risk factor for coronary atherosclerosis. For example, Saremi et al. [3] showed an association between IL-6 values and coronary artery calcium (CAC), independent of other cardiovascular risk factors. Another study [4] highlighted a link between increased IL-6 levels and myocardial infarction (MI) risk. Studies in this direction have laid the groundwork for the hypothesis that IL-6 could be a therapeutic target for atherosclerosis.

The first anti-IL-6 drug approved for the treatment of RA, tocilizumab (TCZ), has been investigated in several studies. Clear data showing changes in lipid profiles—specifically in the serum lipid levels—have raised concerns about increased cardiovascular risk secondary to the dyslipidemic process. The MEASURE study [5] showed that adding TCZ to MTX increased total cholesterol (TC), low-density-lipoprotein cholesterol (LDL-C), and triglycerides more than MTX alone; in addition, another report compared monotherapy with TCZ with monotherapy with MTX,

with the results favoring MTX in terms of lipid profile [6]. In another study, TCZ alone resulted in greater increases in TC and LDL-C than the combination of two csDMARDs (MTX plus hydroxychloroquine) [7]; meanwhile, in the ADACTA study, comparing TCZ with another bDMARD, TCZ had a more pronounced impact on serum lipid levels than adalimumab [8]. Further analysis concluded that although these changes in lipid profile occurred, long-term use of TCZ reduced the cardiovascular risk due to atherosclerosis. The explanation was found in the same studies, which showed that although TCZ had a negative impact on serum lipid levels, its effects on lipid function and quality were beneficial. Therefore, it was observed that the increase in serum lipids led to an improvement in inflammation, with a reduction in inflammatory markers such as fibrinogen, D-dimer, phospholipase A2, and SAA [5][7][8]. This makes the lipid changes more anti-atherogenic than pro-atherogenic [9]. Furthermore, using TCZ was linked to lower lipoprotein(a) (Lp(a)) concentrations [5][8][10]. Future studies should aim to translate these pro-atherosclerotic risk reduction effects of TCZ to patients without RA. The ASSAIL-IM study, still in phase II, has already demonstrated some data and aims to assess whether TCZ can reduce myocardial damage in patients with atherosclerotic cardiovascular disease (ASCVD) [11][12].

Aside from quantitative and qualitative changes, TCZ improves endothelial function and decreases oxidative stress, expression of vascular cell adhesion moll=ecule (VCAM), and pro-thrombotic status by modulating the pro-thrombotic and pro-inflammatory phenotype of monocytes; it also induces NETosis [13].

The impact of TCZ on arterial stiffness—an independent predictor of cardiovascular risk—has also been evaluated. The results were either conflicting [7] or showed that TCZ reduces pulse wave velocity (PWV) [14][15], while carotid intima-media thickness (cIMT) was not influenced [15]. Regarding traditional cardiovascular risk factors, there were no significant changes in blood pressure (BP) [15], but there was a higher prevalence of arterial hypertension among patients treated with TCZ than among those treated with MTX [16]. TCZ also improved the distribution of fat to peripheral tissues and the skeletal muscle mass index [17].

Compared to other bDMARDs, TCZ has a reduced risk of major acute cardiovascular event (MACE), being superior to abatacept [18] and anti-TNF-α [19], but with no major differences between it and adalimumab or etanercept [19].

Sarilumab, the other monoclonal antibody that binds to the IL-6 receptor, seems to have similar efficacy to TCZ in terms of clinical and radiological improvement of RA [20], while being clinically and functionally superior to adalimumab [21]. The incidence of MACE with sarilumab, whether in combination with csDMARDs or as monotherapy, did not differ from that in patients without DMARDs [22]. Although the changes in lipid profile are the same, studies on the relationship between sarilumab and cardiovascular risk are limited compared to those on TCZ.

2. Anti-TNF-α

Tumor necrosis factor-α (TNF-α), a cytokine produced by activated macrophages and monocytes as well as natural killer (NK) cells, plays a key role in the pathogenesis of RA, due to its pro-inflammatory effects. It is also involved in

defending organisms against infection, bone remodeling, and cancer. Increased endothelial permeability to circulating blood cells, nitric oxide (NO) reduction, reactive oxygen species (ROS) production, and the ability to promote dyslipidemia and insulin resistance are mechanisms underlying atheromatous plaque formation [23][24]. It is worth noting that patients with MI who were being monitored for recurrence of MACE showed steadily increased TNF-α levels [25]. Understanding the mechanisms of action of this cytokine has led to the development of targeted therapies such as TNF-α inhibitors.

Data from studies and clinical trials show a reduction in cardiovascular risk in patients treated with TNF-α inhibitors. Comparative studies between anti-TNF-α drugs and csDMARDs demonstrated a 20–30% reduction in cardiovascular risk in the first six months after the introduction of anti-TNF-α drugs [26]. Moreover, anti-TNF-α drugs may reduce the risk of all acute cardiovascular events, but especially of MI or stroke, as suggested by two meta-analyses. [27]. The cardioprotective effect increases proportionally the faster the bDMARDs with anti-TNF-α activity are introduced, but also the longer they are maintained [28]. This is also supported by two other studies in which an increased cardiovascular risk was observed upon [29] and within 6 months of [30] bDMARDs' discontinuation. In addition to the impact on the occurrence of an acute cardiovascular event such as MI, anti-TNF-α therapy may influence the prognosis of patients after such an event. As regards post-MI mortality, Low et al. [28] demonstrated that patients in whom bDMARDs were stopped 3 months prior to the MI had a threefold higher mortality rate than those receiving anti-TNF-α drugs. No correlation was found between severity or mortality rate and TNF-α inhibitors versus csDMARDs in this study [28]. However, these effects do not apply to all patients, since Ljung et al. [31] showed that patients with low disease activity (as assessed by DAS-28)—referred to as responders—had a 50% lower rate of developing acute coronary syndrome compared to non-responders.

Insights on the effects of anti-TNF-α drugs on the lipid profile have conflicting results. Some studies have reported a significant increase in TC, LDL-C, HDL-C, or ApoA1 and ApoB [32][33], while others have shown no effect on TC and its fractions or triglycerides [34][35] for adalimumab. There was no effect of adalimumab on cholesterol efflux despite inhibiting cholesterol uptake in macrophages [35]. Infliximab, on the other hand, seems to have greater effects on serum lipid levels, with most of the studies proving that it can induce long-lasting increases in TC, LDL-C, HDL-C, and triglycerides [36][37]. In patients treated with golimumab and MTX, increases in TC, LDL-C, and HDL-C were observed compared to those receiving monotherapy with MTX [38], while for certolizumab there are non-specific data available [31][32]. As for etanercept, the ApoB/ApoA ratio was significantly lower in responders among RA patients, while HDL-C increased significantly, with these results demonstrating its favorable effects on the lipid profile [39]. No significant change in LDL-C or triglycerides was reported [39][40].

There is evidence that TNF-α inhibitors have a positive effect on endothelial dysfunction, although this has been observed mainly in patients without many cardiovascular risk factors [41]. Improvements have also been seen in NO bioavailability and ROS production in patients treated with both infliximab and MTX [42]. Low levels of SAA [33] and ADMA [43], along with reduced levels of inflammatory markers such as CRP, phospholipase A2, or fibrinogen, further help to improve cardiovascular risk.

Effects of anti-TNF-α therapy on arterial stiffness showed significant reduction for adalimumab, etanercept, and infliximab after 8–56 weeks of follow-up, independent of other factors such as clinical response or age. The impact appeared to be more pronounced for the first two than for infliximab [44][45][46]. There were no effects reported on cIMT [14][33][45], except for one study showing that anti-TNF-α therapy may be effective in slowing the progression of cIMT, but this is dependent on the long-term disease [47]. As for the impact on traditional cardiovascular risk factors, insulin resistance appeared to improve with infliximab therapy [36]. Although there is evidence that patients receiving TNF-α inhibitors present a risk of developing arterial hypertension [48], many studies do not show a direct correlation between them [34][37]. Nevertheless, monitoring BP during bDMARDs should be part of the therapeutic management.

Regarding the risk of developing acute cardiovascular events, there is evidence showing that the risk for the occurrence of MACE is lower in patients treated with etanercept compared to TCZ [49] or tofacitinib (a janus kinase inhibitor) [50], while another study found no difference in the risk of MACE between patients treated with tofacitinib and with adalimumab [51].

3. Anti-CD20

In addition to previously described mechanisms involved in the pathogenesis of atherosclerosis, B-cell activation plays an important role by stimulating T-helper1 (Th1), with a pro-atherogenic effect, and inhibiting IL-17, with an anti-atherogenic effect [52]. Both B1 (by producing IgM antibodies) and B2 have been shown to promote atherosclerosis [53]. Moreover, B cells stimulate the production of different cytokines, such as IL-6, IL-8, IL-10, and TNF-α [54]. Finally, anti-CD20 treatment, through the consumption of B2 cells, slows the progression of atherosclerosis [55]. There is some evidence demonstrating the potential anti-atherogenic role of anti-CD20 treatment. Treatment with anti-CD20 drugs in mice led to decreased infarct area and improved cardiac remodeling [56].

Rituximab (RTX), a monoclonal CD20 antibody, works by depleting B2 cells. It has been shown to be effective in the treatment of RA, by improving clinical symptoms and slowing disease progression. RTX is a second-line biologic agent, used in case of therapeutic failure of another bDMARD [57].

Significant increases in HDL-C along with decreases in the ApoB/ApoA1 ratio (seen as an atherogenic index) have been reported, while TC and triglycerides were increased in two studies [58][59]. However, other studies showed no changes in HDL-C or triglycerides, along with significant increases in TC and LDL-C [15][58]. Due to conflicting findings, further studies are needed to elucidate the impact of RTX on lipid profiles.

There was no significant effect on BP, or on PWV, as demonstrated in three studies [15][60][61], although in one study an improvement in cIMT was observed [61].

Improved cardiovascular risk in patients treated with RTX may also result from reduced inflammatory status, with studies showing decreases in CRP, VSH, DAS-28 [59], and SAA [58], as well as enhanced endothelial function [62].

According to the literature, the reduction in the risk of acute cardiovascular events such as MIs using RTX is similar to that from using anti-TNF-α drugs [63].

4. Anti-CD80/86

T cells play a pivotal role in the immune response in native atherosclerosis. Abatacept shows strong clinical promise for cardiovascular risk prevention, since T-cell CD28-CD80/86 co-stimulation is essential for accelerated atherosclerosis [64].

Assessing factors that influence cardiovascular risk, studies have not reported changes in TC, triglycerides, LDL-C, or HDL-C levels for abatacept [15][65]. There is one study showing an increase in LDL-C [66], while there two showing improvements in HDL-C, both quantitatively and qualitatively [66][67]. No significant modification in cIMT [15][68] or BP [15] was observed, while BMI showed an upward trend; however, insulin sensitivity appeared to be improved [69].

Compared to other bDMARDs—specifically, to TNF-α inhibitors—abatacept demonstrated better cardioprotective effects [18][70]. Jin et al., in their review [68], noted that patients treated with abatacept had a 28% lower risk of MACE compared with anti-TNF-α therapy and a 36% increased risk of MACE compared with those starting TCZ; nevertheless, only the composite outcome showed this effect of TCZ. In another study, this characteristic was only found in patients with diabetes mellitus [71].

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