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Do DMARDs and biologic agents protect from cardiovascular disease in patients with inflammatory arthropathies?

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1. Introduction

During the past 2–3 decades treatment of rheumatoid arthritis (RA) and other inflammatory arthropathies has made enormous progress. We are now, through the use of new medications, able to dramatically change the prognosis for the majority of patients with RA. These advances started with the improved use of methotrexate, often given in combinations with other DMARDs. From the late 90's the introduction of TNF-α inhibitors, followed by other biologics, has further improved the lives of patients with inflammatory arthropathies. Yet, on a group level, RA patients still face a shorter life expectancy than the general population and many studies have demonstrated that an increased incidence of cardiovascular disease (CVD) is an important contributing factor to the premature mortality observed among patients with RA and other inflammatory arthropathies [1–6]. More recently, and less studied, several studies have observed an increased risk on the venous side of the vasculature, including deep venous thrombosis and pulmonary embolism [7,8].

During the past decades there has been a decline in CVD incidence and associated mortality in the general population [9,10] and similar trends have also been observed among patients with RA [1,2]. It is therefore important to investigate if decreasing frequencies of CVD in inflammatory arthropathies are mainly a mirror of the decline seen in the general population, or if these observations are effects of new and better treatments.

Whether and how anti-inflammatory treatments affect the risk of premature CVD is still not well studied. Importantly, hard CVD outcomes are scarce and thus large cohorts and long observational periods are needed to investigate what causes them.

Risk estimates for CVD are in general complex and depend on many variables including traditional CVD risk factors, cultural and life style habits [11]. In patients with inflammatory arthropathies, disease associated risk factors add an additional burden, and a more severe disease with systemic inflammation seems to be particularly important [12–15]. Furthermore, but less discussed, there may be both additional risks and benefits accompanying specific treatments. Some of these treatments are known to enhance CVD risk, or at least risk factors for CVD, while they at the same time reduce RA associated inflammation. This situation calls for large clinical studies to be truly reliable since the number of variables that need to be included are many, long follow up periods are needed and both the diseases and the outcomes are relatively scarce. Such studies will of course be very difficult and costly to perform and the ideal randomized controlled trial that could estimate the CVD risk in patients with and without RA treatment will for ethical reasons never be performed.

The reality of today, leaves us with many “studies of balance” where we have to weigh pros and cons. Studies have often focused on the influence of medications on traditional risk factors or on measures of subclinical atherosclerosis. Effective treatments should definitely reduce inflammation, but at the same time they may increase traditional risk factors such as lipid levels, hypertension or insulin resistance, or they may be associated with other harmful effects to the vasculature,

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e.g. be pro-coagulant.

Should we perhaps add selected primary CVD prevention medications, e.g. statins or antihypertensives, when using some of our anti rheumatic drugs??

As health professionals, we generally like to think that we can cure or at least reduce symptoms associated with disease. And we tend to bring forward and focus on positive results, while important and well-performed studies with negative findings may be difficult to publish and are often ignored. But, to get a true picture it is important to scrutinize not only those studies that show that our treatment leads to improvements, but also those where treatment causes unfavorable effects and enhance the risks of co-morbidities. In this review, we have extracted studies which indicate both positive and negative effects of commonly used anti-rheumatic treatments on the cardiovascular system.

"YES, the Cardiovascular System is Protected to a great extent by DMARDs and Biologic Agents in Inflammatory Arthropathies".

One meta-analysis of nine randomized controlled trials (RCTs) involving patients with osteoarthritis (OA) and RA has found that, in comparison with placebo, the use of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) has no significant effect on CVD events [16], but no RCT has directly investigated whether any anti-inflammatory agent can reduce the rate of such events in RA patients or the general population, and the published data are conflicting. For example, a systematic literature review assessing CVD risk in RA patients receiving low corticosteroid doses (defined as < 10 mg/day of prednisone) found that they had a protective effect on serum lipid profiles, increased insulin resistance or glycemia, probably had no effect on blood pressure, had no effect on atherosclerosis, ventricular function or heart rate variability, had discordant effects on arterial stiffness, and were associated with major CV events such as myocardial infarction (MI) (hazard ratio [HR]1.7 [1.2–o2.3]), stroke (odds ratio [OR] 4.36 [1.60–11.90]), mortality (HR 2.03 [1.25–3.32]) and, in patients with rheumatoid factor-positive RA, a composite index of CV events (HR 2.21 [1.22–4.00]) [17]. In brief, there was weak association with cardiovascular risk, but a trend toward an increase in major CV events [17,18].

It is known that treating RA with traditional DMARDs is associated with an increase in total cholesterol and low-density lipoprotein (LDL) levels, and a decrease in high-density lipoprotein (HDL) levels. In order to evaluate long-term changes in cholesterol levels, the Treatment of Early Aggressive Rheumatoid Arthritis (TEAR) trial randomized patients with early RA to begin treatment with methotrexate (MTX) alone, MTX plus etanercept, or MTX plus sulfasalazine plus hydroxychloroquine. The results showed a decrease in the 28-joint Disease Activity Score (DAS-28), C-reactive protein (CRP) levels and the erythrocyte sedimentation rate (ESR) associated with increased levels of HDL, LDL and total cholesterol in all of the treatment groups ($p < 0.001$–0.035) [19]. Triple therapy was more closely associated with higher levels of HDL cholesteral, lower levels of LDL cholesterol, and higher total cholesterol: HDL cholesterol ratios ($p < 0.001$ for all) than MTX alone or in combination with etanercept during the 2-year follow-up period. The decrease in RA disease activity during the long-term follow-up were associated with increased cholesterol levels regardless of whether the patients received biological or non-biological treatment.

A meta-analysis of 13 prospective studies has shown that anti-tumor necrosis factor α (TNF-α) drugs administered to RA patients for 52 weeks increase the levels of triglycerides (+0.28 mmol/L, $p < 0.001$) and HDL (+0.27 mmol/L, $p < 0.0001$) and total cholesterol (+0.27 mmol/L, $p = 0.03$), without affecting LDL levels or AI and decrease apolipoprotein A/B levels (−0.3, $p < 0.0001$) [20].

Increased lipid concentrations are associated with the use of the interleukin-6 (IL-6) inhibitor, tocilizumab, and the oral Janus kinase inhibitor tofacitinib, as has been shown in a recent meta-analysis of 25 placebo-controlled RCTs [21]. RA patients treated with tocilizumab were more likely to have hypercholesterolemia and increased levels of both HDL and LDL cholesterol than those treated with placebo but, although the patients treated with tofacitinib showed increased HDL and LDL cholesterol levels, they were not hypercholesterolemic [21]. It is important to assess the lipid profiles of RA patients as they have implications in terms of the risk of CVD, especially given that DMARDs and biological therapies can affect lipid fractions without affecting the total cholesterol/HDL cholesterol ratio. It seems that tocilizumab and tofacitinib can transform HDL cholesterol particles from a pro-inflammatory to an anti-inflammatory phenotype [22].

It has been demonstrated that traditional DMARDs protect against the risk of CVD [23], but the mechanisms underlying this protection are not clear. MTX increases triglyceride and total, LDL and HDL cholesterol in RA patients [24], but it is believed that this does not increase but actually reduces the risk of CVD. A study evaluating the associations between MTX treatment for different times and the risk of cardiovascular events in RA patients found that the recent continuous use of MTX was associated with a 20% reduction in the number of events [25]. Furthermore, it has been demonstrated that, despite the increase in lipid levels, anti-TNF drugs decrease the risk of CVD, reduce endothelial dysfunction, enhance HDL anti-oxidative capacity, and improve insulin sensitivity [26]. Anti-TNF-α treatment also reduces inflammation (including CRP levels and the ESR), and has been associated with a reduction in the risk of CVD in the patients responding to it [27]. A retrospective study of data from the MarketScan claims database of 113,677 RA patients found that 35.8%, 41.1% and 23.1% respectively received anti-TNF-α agents, methotrexate and other DMARDs for an average of 7.6 months, and showed that the use of anti-TNF-α agents for one, two or three years can be expected to reduce cardiovascular event risks by respectively 21%, 38% and 51% in comparison with non-use [28]. In brief, anti-TNF-α therapy is associated with a significantly lower risk of cardiovascular events, particularly in responding RA patients and longer users [29].

Tocilizumab, which inhibits IL-6 signaling, is associated with increased lipid levels and a decrease in the levels of inflammatory markers [21]. Although the reason for the increase in lipid levels is not yet fully understood, it has been noted that it relates to all of the main lipoproteins (HDL, LDL and triglycerides) without significantly affecting LDL:HDL and total cholesterol: HDL ratios, which are closely associated with the risk of CVD [21]. The five phase III studies of tocilizumab showed that both of the doses used led to lower rates of myocardial infarction in comparison with controls [28], while analyses of the long-term safety of tocilizumab in 4171 patients with a median treatment duration of 3.9 years have shown that the rate CV events remains stable.

A sub-analysis of the Tocilizumab in Combination With Traditional DMARD Therapy (TOWARD) study found that tocilizumab significantly improved insulin resistance in RA patients, probably because CRP levels were regarded as a precursor of the development of insulin resistance [30]. Furthermore, one small study has shown that six months' treatment with tocilizumab reduced inflammation and (more significantly) the levels of the circulating CD4+/CD28− cells involved in accelerated atherosclerosis in RA patients who achieved a DAS28 score of < 2.6 in comparison with those who did not. Finally, vascular imaging studies have shown that tocilizumab improves endothelial function and arterial stiffness [31].

Relatively little is known regarding the effects of other biological agents (rituximab, abatacept or anakinra) on the lipid profiles or CV risk of RA patients, but a recent analysis suggests that six months' treatment with rituximab has beneficial effects on cholesterol profiles and induce a change in the composition of HDL from a pro-atherogenic to a non-atherogenic form [32]. In addition, another study [33] has shown that rituximab reduces the progression of accelerated atherosclerosis (as measured by the improvement in percentage flow-mediated dilation and the decrease in common carotid intima-media thickness) in RA patients [33].

Oral Janus kinase (JAK) inhibitors seem to affect lipid profiles in a manner that is similar to that of tocilizumab without increasing the risk of CVD [21]. A recent systematic review with meta-analysis has found no significant change in the CV risk among all JAK inhibitor treated RA patients [34].

The effect of inflammation on lipid profiles and the lipid paradox involved in RA patients make lipid levels unreliable markers of CV risk and mean that traditional CV risk algorithms are less accurate in predicting CVD. The use of biological drugs to control inflammation in RA patients is accompanied by increases in various lipid parameters, thus making it advisable to monitor lipid profiles closely and, if necessary, start treatment with lipid-lowering drugs [35].

"Cardiovascular System is NOT Protected to a great extent by DMARDs and Biologic Agents in Inflammatory Arthropathies".

Although it is widely believed that treatment of RA with DMARDs leads to a decreased cardiovascular risk there are some suggestions that DMARD treatment could also imply an increased cardiovascular risk. The current state of art treatment for early RA patients is that we should aim at remission and in principle start with methotrexate, generally combined with glucocorticoids for a short period of time [36].

Methotrexate, our anchor drug, works in the folate reduction pathway by blocking dihydrofolate reductase leading to less conversion of homocysteine to methionine with subsequent increased homocysteine levels and this could imply an increased cardiovascular risk [37]. Consequently, homocysteine leads to generation of reactive oxygen species and this leads to damaging of the endothelium, hypertension and thus atherosclerosis but also through oxidized LDL and formation of foam cells. One may argue that we administer folic acid and that this reduces homocysteine levels (and this cardiovascular risk) but it has never been adequately investigated whether or not it indeed reduces the cardiovascular risk. Moreover, rather outdated studies show only a moderate risk reduction of about 20% [38].

The only way to test whether or not methotrexate reduces cardiovascular risk in RA is a randomized controlled trial, but such a trial has never been performed. However, there is one randomized, double-blind trial of low-dose methotrexate (at a target dose of 15 to 20 mg weekly) or matching placebo in 4786 general population patients with previous myocardial infarction or multivessel coronary disease who additionally had CV risk factors [39]. The primary end point at the onset of the trial was a composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. The trial was stopped after a median follow-up of 2.3 years. The cumulative number of major adverse cardiovascular events did not differ between methotrexate and placebo, in other words MTX doesn't work in antirheumatic doses in a population that has a similar background CV-risk as our RA patients.

If we look at the cardiovascular side effects of glucocorticoids then we know that there are numerous CV-side effects that could ultimately result in more cardiovascular events. Therefore, the EULAR states that glucocorticoids, should only be given for a short period of time and tapered as soon as possible. However, in daily clinical practice this is hardly possible.

The Barfot study investigated the effect of prolonged low-dose steroid administration [40]. This was a 2-year open randomized trial in early RA patients comparing prednisolone 7.5 mg/dayin addition toDMARDs and participants were followed for 10 years and it appeared that cardiovascular events occurred much less when patients were not treated with glucocorticoids.

For other DMARDs, there are no adequate studies, but we know that leflunomide is frequently associated with hypertension that could ultimately lead to a cardiovascular event and from a cardiovascular point of view it is important to realize that virtually all non steroid anti-inflammatory drugs (NSAIDs) and Cox inhibitors (COXIBs) are associated with a doubled CV risk.

If we look at the effects of biologics and new chemical entities on lipids then a first systematic review and meta-analysis was published in 2015. When looking at total cholesterol, as a proxy for dyslipidemia, then the TNF-α inhibitors are associated with increased cholesterol, the same holds for anti-IL 6 agents [21]. Obviously this could ultimately lead to an increased cardiovascular risk.

Looking at biologics and heart failure, then the evidence that TNF-α blocking agents induce heart failure comes from the Attach trial [41]. This was a double-blind RCT in 150 patients with moderate to severe heart failure, who were randomized to placebo, infliximab 5 mg/kg or 10 mg/kg. However, no improvement of cardiac functioning was observed, in contrast, the highest dose revealed worsening of heart failure. Considering the percentage of patients that died due to heart failure, then infliximab was associated with a much higher death rate in comparison to placebo. Ultimately, this was one of the main reasons why anti-TNF-α therapy is contraindicated in patients with NYHA III-IV heart failure.

Several systematic reviews have been done in this area and an important one was published in 2015 and this one comprised 52 studies and found that treatment with anti-TNF-α was not contraindicated in inflammatory arthritis with mild- moderate CHF [42]. However, a harmful effect in older patients could not be excluded.

If we look at the other side of our vascular system, thus venous thrombo-embolism it's becoming more and more acknowledged that patients with RA also have an increased risk of venous thromboembolism [8]. What then about the effect of anti-rheumatic therapy on clinical venous thromboembolism? In a database study there were 29,481 patients with newly diagnosed rheumatoid arthritis with 39,647 treatment episodes [43]. The incidence rate of hospitalization for venous thromboembolism per 1000 person-years was 5.5 in biologic DMARD initiators versus 4.4 in the nonbiologic DMARD initiators. Thus, initiation of a biologic DMARD seemed to be associated with an increased short-term risk of hospitalization for venous thromboembolism compared with initiation of methotrexate or another nonbiologic DMARD. This might be due to the fact that initiation of a biologic DMARDs might acutely cause a paradoxical pro-coagulating phase. Production of both immunoglobulinM and G anti-cardiolipin antibodies, as well as other autoantibodies, have been reported in patients treated with etanercept and infliximab.

The last years there have been some rumours regarding the induction of VTE by JAK -inhibitors actually this was the reason that the 4 mg dose baricitinib was not approved in the US due to an imbalance in thromboembolic events in baricitinib treated patients vs placebo, and recently the SPC text in Europe has been updated accordingly. With respect to tofacitinib: Analysis of DVT and PE across randomized clinical studies for RA, PsO, PsA, and UC showed, until recently no evidence of an increased risk of events with tofacitinib. However, very recently the FDA sent out a warning that a safety clinical trial found an increased risk of blood clots in the lungs and death associated with the 10 mg twice daily dose of tofacitinib [44,45].

Altogether, methotrexate gives a little cardiovascular benefit, if any, but adequate studies in RA have never been conducted. It is important to realize, that among the commonly used drugs, steroids, NSAIDs/COXIBs give an increased cardiovascular risk. Biologics and JAK inhibitors might induce an increased CV risk due to increasing lipids, particularly total cholesterol. Furthermore, TNF-α blockers might induce heart failure in susceptible patients. TNF-α inhibitors and JAK inhibitors are associated with more venous thromboembolism, that could sometimes be fatal.

But we do know that RA is an important cardiovascular risk factor and you may wonder what's nowadays the contribution of disease activity vs the traditional CV risk factors. This was addressed in the multicountry ATTAC –RA study where > 5600 patients with RA, at baseline free from cardiovascular disease, were followed for 6 years during which period there were around 400 CVD events [46]. It was found that both inflammation and traditional CVD risk factors contribute to the increased risk of CVD in RA. The investigators performed their study though investigating the populaton attributable risk, PAR, and this is the proportion of cardiovascular disease in a population that could be

prevented by elimination of an exposure or risk factor. It's important to realize that 49% of the events were due to cardiovascular risk factors and only 30% of CVD events were due to RA characteristics. So from a cardiovascular point of view it is also or even more important to take care of the cardiovascular risk factors of our patients.

Altogether, if we look at the conventional synthetic DMARDs, biologics and new chemical entities, when studying the literature appropriately, it appears that there is no substantial decrease of cardiovascular disease in RA, sometimes there is even increased cardiovascular disease risk, including not only atherosclerotic disease, but also venous thromboembolism. Therefore, we should focus on the traditional CV risk factors, particularly as cardiovascular risk management is nowadays still performed poorly in daily clinical practice and this should be optimized [47].

Hence, nowadays, the most appropriate way to lessen the cardiovascular burden of our patients is to focus on the traditional cardiovascular risk factors, as the cardiovascular system, is only to a limited extent protected by DMARDs and biologic agents.

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