

# Is there a future role for anti-TNF therapy in cardiovascular disease?

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Rheumatoid arthritis (RA) is a chronic inflammatory disease resulting in tissue destruction, disability and increased mortality. The latter is chiefly explained by a substantial increase in cardiovascular morbidity. This observation is in line with increasing evidence, supporting the importance of inflammatory mechanisms in the progression of atherosclerosis and plaque rupture often preceding cardiovascular events in general. A key cytokine, both in the inflamed synovia and in several of the pathophysiological processes leading up to cardiovascular events, is tumor necrosis factor (TNF). Both experimental data and observational data from patients with RA treated with TNF blockers support that elimination or blocking of the TNF effect can reduce the progression of atherosclerosis and the risk for cardiovascular events. Furthermore, a substantial proportion of patients with acute coronary events develop new events during the first year, illustrating the need for improved therapies in this group. We think that the time is right to test, in the setting of a randomized controlled trial, whether TNF inhibitors can reduce this risk of reoccurrence, first in patient groups with RA and subsequently in non-RA groups.

## Lessons from rheumatoid arthritis

Rheumatoid arthritis (RA) has a prevalence in the western part of the world of 0.5–1.0% [1]. The disease is characterized by progressive disability, socio-economic consequences and, in addition to this, a higher risk for the development of comorbidities, such as cardiovascular disease (CVD) [2], infection [3] and malignant lymphoma [4], which eventually may lead to premature death. Most previous studies have demonstrated an increased mortality rate in RA patients, with a relative risk of 1.3–3.0 [5], although some recent studies published during the last decade have indicated that this increased risk is becoming less obvious or perhaps delayed [6]. If this trend of improved survival is confirmed, it could be speculated that it is secondary to more efficient therapy since it parallels the more extensive use of anti-rheumatic drugs. Starting in the late 1990s, biological agents, particularly tumor necrosis factor (TNF) blockers, have become available and extensively used in the treatment of RA and other inflammatory disorders. In randomized controlled trials, TNF blockers have been shown to decrease disease severity and tissue destruction [7–9], and in observational studies to also reduce cardiovascular morbidity [10] and total mortality [11]. It has also been demonstrated that treatment with methotrexate, which is often used in combination with TNF inhibitors, decreases the risk for overall and

CVD mortality [12], and effective therapy with disease-modifying antirheumatic drugs is likely to reduce the use of nonsteroidal anti-inflammatory drugs (NSAIDs), for which there is increasing evidence that they may increase the risk for CVD events [13].

## Tumor necrosis factor, rheumatoid arthritis & cardiovascular disease

Inflammatory mechanisms have been increasingly acknowledged as being important in the pathophysiology of atherosclerotic plaques, their progressive development and for the occurrence of cardiovascular events [14,15]. In line with this, it is also well established that there is increased morbidity and mortality from CVD in RA patients [16,17]. The explanation for this increase is probably complex. First, RA and CVD share some common risk factors, such as coming from a poor socio-economic background and being predicted by the exposure to previous smoking [18]. Against this background, both traditional CVD risk factors (hypertension, obesity, hyperlipidemia and diabetes) and markers of inflammation (joint counts and erythrocyte sedimentation rate) contribute with independent and additive risk fractions [19,20]. This is also in line with the observed prediction of CVD events by moderate elevations of C-reactive protein observed in population studies [21]. The increase in CVD-event occurrence in RA patients with active disease seems to be

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more pronounced for coronary events and peripheral arterial disease and less apparent for cerebrovascular events [17].

Together, these epidemiological findings indicate that reducing inflammation may be important when aiming to decrease CVD morbidity and mortality, not just in RA but possibly also in non-RA populations.

#### Atherosclerotic plaque formation

Multiple support exists for the importance of TNF in the development and rupture of atherosclerotic plaques subsequently leading to cardiovascular events. The formation of the atherosclerotic plaque is enhanced by endothelial activation, migration of monocytes into the vascular wall and scavenging of oxidized low-density lipoprotein [14,15], which are all factors that are augmented by high levels of TNF [18]. Activation of these processes may lead to a vicious circle promoting growth of the atherosclerotic plaque. Histopathological studies have also demonstrated that there is an abundance of inflammatory cells at the border of atherosclerotic plaques, which probably promotes the rupture of the plaque with subsequent development of cardiovascular events [14,15,18]. Inflammation driven by cytokines such as TNF appears to be crucial for this development. This is further supported by experimental studies. It has, for instance, been demonstrated that knockout of the TNF- $\alpha$  gene in atherosclerosis-prone apolipoprotein E knockout mice inhibits growth of atherosclerotic plaques. Moreover, treatment with a soluble receptor for TNF resulted in a dose-dependent inhibitory effect on the development of atherosclerosis in the same strain [22].

Potential methods to break this vicious circle of inflammation in the atherosclerotic plaque include treatment with statins [23] and more experimental approaches, such as the development of vaccines against the protein component of LDL cholesterol [24]. It is likely that specific inhibition of certain cytokines, such as TNF, could be added to such possible pharmacological approaches.

#### Hemostasis & endothelium

TNF- $\alpha$  and other cytokines activate the endothelium, which is reflected by endothelial dysfunction and increased expression of adhesion molecules. In addition, TNF- $\alpha$  has a systemic effect in upregulating proteins involved in hemostasis. Patients with RA have increased

serum levels of fibrinogen, von Willebrand factor and tissue-plasminogen-activator antigen compared with controls, and these prothrombotic markers have been shown to predict cardiovascular events in RA patients [25,26].

#### Postevent repair

The role of TNF in the postevent repair after a cardiovascular event is less well studied and is probably pleotropic. TNF has, for instance, been demonstrated to have a protective role in limiting the infarct size, although overexpression has also been demonstrated to promote maladaptation with left ventricular dysfunction of the heart (see below) [18].

#### Immunology

It is increasingly recognized that immunological pathways are important in the development of CVD and that such pathways are modulated by proinflammatory cytokines, including TNF. The major histocompatibility complex class II subtypes human leucocyte antigen (HLA)-DR, -DQ and -DP are regulators of T-cell-dependent immune responses and aberrant expression of these tissue antigens has been demonstrated in autoimmune diseases such as RA and systemic lupus erythematosus [27]. Recent data suggest an association between such endothelial expression and diffuse endothelial dysfunction [28]. This upregulation may also be important for the activation and migration of T cells and monocytes into the vascular wall. A specific T-cell subset, the CD4<sup>+</sup>CD28<sup>null</sup> T cells, has been the focus of interest recently. Increased levels of such T cells have been demonstrated in patients with RA [29], especially those with extra-articular RA associated with CVD [30], unstable coronary artery disease and Wegener's granulomatosis [31]. These T cells are characterized by high production of interferon- $\gamma$  [32], cytotoxic capabilities and expression of natural-killer-cell markers, including CD56 [33] and killer immunoglobulin-like receptors, which are ligands for certain HLA-C subtypes [34]. CD4<sup>+</sup>CD28<sup>null</sup> T cells can also be isolated from culprit lesions in unstable coronary artery plaques [35], but not from stable plaques and have, in addition, been demonstrated to correlate with intima-media thickness and impaired arterial-flow-mediated vasodilatation in RA [36]. Taken together, these data suggest a role for such cells in explaining the association between autoimmune vascular disease and CVD. The concept of modulation of such pathomechanisms by potent anti-inflammatory treatment, such as

TNF inhibitors, is supported by Bryl and coworkers, who observed upregulation of CD28 expression on T cells in patients with RA treated with the anti-TNF antibody infliximab [37]. In addition, in a recent study of CD4<sup>+</sup>CD28<sup>null</sup> T cells isolated from patients with unstable angina, such cells were depleted *in vitro* when infliximab was added to whole blood samples, suggesting that the persistence of this T-cell phenotype is TNF dependent [38].

In addition to TNF and interleukin (IL)-1, new cytokines with potential importance to chronic inflammation and atherosclerosis are continuously being described. In RA, for example, IL-17 has recently been identified as an important proinflammatory cytokine in the inflamed synovium [39], and there are data to suggest that IL-17 is also important in the inflammation of the atherosclerotic plaque [40].

#### Congestive heart failure

It was previously demonstrated that patients with congestive heart failure (CHF) had higher circulating levels of TNF compared with healthy subjects and that TNF could lead to progression of heart failure. On the other hand, it has also been shown that low levels of TNF are necessary for repair of the myocardium [41,42]. These observations triggered a number of randomized controlled studies of both infliximab and etanercept to evaluate whether TNF inhibition could have beneficial effects on patients with severe CHF. These studies were, however, disappointing in that they demonstrated no beneficial effect. Especially noteworthy was an increased mortality rate associated with the administration of a high dose of infliximab [43]. The mechanisms behind these disappointing findings in patients with severe CHF (New York Heart Association class III and IV) are not clear. They could represent a class difference between different TNF blockers or that the doses were too high, decreasing TNF below the physiological levels required for repair of the myocardium [41,42]. Since the available data suggest that TNF inhibition in RA does not lead to an increased risk for developing CHF in RA patients [44], it is likely that this negative effects is confined to patients already suffering from severe established CHF.

#### Can inhibition of TNF reduce the rate of cardiovascular events?

Data published in 2005, based on an observational cohort study from southern Sweden, suggested that the risk for first CVD events was

decreased in patients being treated with TNF blockers compared with a population-based cohort of RA patients receiving conventional treatment [10]. These results have later been partly confirmed by studies from the British Society of Rheumatology's register in the UK, which demonstrated a decreased risk for cerebrovascular accidents in anti-TNF-treated subjects and for acute myocardial infarction in responders to TNF blockade [45]. In addition, preliminary data from the US CORRONA database [46] and the Swedish national biologics register [44] have yielded similar results. Based on these studies, and the circumstantial evidence mentioned above concerning the importance of TNF and inflammation in the atherosclerotic plaque, it appears reasonable to hypothesize that anti-inflammatory medication with, for example, TNF blockade could protect against cardiovascular events in RA patients, and possibly also in non-RA populations.

On the other hand, it is not completely clear from these observational studies [10,11,45–47] whether some of the effects observed could be attributed to differences in baseline CVD risk profile in the comparison groups or differences in medication with NSAIDs, statins or methotrexate, which have all been demonstrated to affect the risk for CVD events or mortality.

Over the last decade, the primary and secondary prophylaxis against cardiovascular events has been largely improved, with the introduction of thrombolysis and intravascular procedures in acute coronary syndromes and a continuously improved secondary pharmacological prophylaxis, including the use of aspirin, clopidogrel, acetylcholine esterase inhibition,  $\beta$ -blocker and statin treatment. In the observational studies suggesting a protective effect of TNF blockers in RA patients, the extent of such pharmacological prophylaxis has often not been included in the analysis and may very well have been insufficient [10,11,45–47]. It is thus possible that some of the effects demonstrated in observational studies by TNF inhibitors might have been achieved with optimal standard secondary prophylactic treatment with, for example, statins. However, even with optimal secondary pharmacological prophylaxis the overall risk of a new cardiovascular event or death, is still greater than 20% the first year after hospitalization for acute coronary syndrome in non-RA populations [Jovinge S, Unpublished Data] and probably worse in RA groups [48], demonstrating that there is room for improvements in therapy.

**Conclusion & future perspective**

There are unmet needs for improved strategies aimed at reducing CVD events in general and specifically in patients with RA. Furthermore, there is an abundance of circumstantial evidence indicating that anti-inflammatory treatment

would reduce this rate in general, and probably to an even larger extent in RA patients. The potential of anti-inflammatory treatment should be tested in randomized, controlled trials in risk populations, including patients with RA. The most obvious candidate for such trials are statins, which have already been shown to be effective in non-RA groups and should also be investigated in RA patients. Based on the known effects of TNF it is possible that TNF inhibitors may be an even more effective anti-inflammatory approach, especially in RA patients.

We suggest that the time has come to test in an experimental fashion if TNF inhibition can achieve such improvement, which can ultimately only be done in the setting of a randomized, controlled trial. Such studies should probably first be conducted in patients with RA, although it would be logistically difficult owing to the relatively low prevalence of the disease and hence low absolute rate of cardiovascular events to perform a study of sufficient size. To test the hypothesis that TNF blockers protect against CVD events would therefore ultimately require trials on patients with atherosclerotic manifestations, irrespective of whether rheumatic disease is present or not.

**Executive summary****Introduction**

- Inflammation is important for the progression of atherosclerosis and the development of disabling events.

**Tumor necrosis factor, rheumatoid arthritis & cardiovascular disease**

- Tumor necrosis factor (TNF) is a key cytokine in many of the pathophysiological processes that lead up to a cardiovascular event.
- Rheumatoid arthritis (RA) has an increased occurrence of cardiovascular morbidity.
- RA can be considered as a model for accelerated cardiovascular disease.
- Observational data from RA patients and experimental data support that TNF inhibition is likely to protect against cardiovascular events.
- There are still unmet medical needs with regard to preventing reoccurrence of cardiovascular events.

**Perspectives & conclusion**

- The time appears right to test if TNF inhibition can prevent reoccurrence of cardiovascular events in the setting of a randomized controlled trial.
- Such trials should initially be carried out in patients with RA, but may later be expanded to non-RA populations.

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