

Non solum... sed etiam: added cardiac benefits of TNF α blockade in rheumatoid arthritis

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ABSTRACT Tumour necrosis factor alpha (TNF α) has emerged as one of the key cytokines in the fields of infection and inflammation, and has been linked with disease activity and joint damage in rheumatoid arthritis. Acute myocardial infarction remains the leading cause of death in rheumatoid arthritis, and there is now a large body of evidence placing TNF α and other inflammatory cytokines at the centre of the development of atherosclerotic plaques and their subsequent rupture, which is in keeping with the observation of accelerated atherosclerosis in rheumatoid arthritis patients. TNF α might also have a role to play in the increased incidence of congestive cardiac failure seen in rheumatoid arthritis.

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Although anti-TNF α therapies were originally developed with a view to controlling joint disease in rheumatoid arthritis, evidence is emerging of a positive benefit in reducing heart disease as well. A range of mechanisms has been suggested by which anti-TNF α treatment might achieve a reduction in incidence of myocardial infarction and cardiac failure, some of which will have implications for the treatment of cardiovascular disease in general.

KEYWORDS Anti-TNF α therapy, cardiovascular disease, congestive heart failure, ischaemic heart disease, rheumatoid arthritis

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ANTI-TNF α THERAPY IN RHEUMATOID ARTHRITIS

The therapeutic management of rheumatoid arthritis (RA) has traditionally been a challenge for both physician and patient, and the introduction almost ten years ago of anti-TNF α therapy was therefore a major advance. The cytokine tumour necrosis factor alpha (TNF α) emerged over almost 30 years as a key player in infection and inflammation, and during the 1990s advances were made in the understanding of its importance in the pathophysiology of RA. These included its role in the induction of interleukin-1 (IL-1), known to be a key player in joint destruction,¹ and its presence within synovium, endothelium and at the site of cartilage destruction within the inflamed joint.²

Since 1999, three TNF α blocking drugs have been licensed for use in clinical practice: infliximab – a chimeric monoclonal antibody that binds both soluble and membrane-bound TNF α ; etanercept – a human TNF α receptor fusion protein that binds soluble TNF α ; and adalimumab – a fully humanised monoclonal antibody against TNF α . All three are potent anti-inflammatory agents and have also been shown to be the first drugs to irrefutably prevent joint damage.³ In the UK, TNF α blockers are used according to strict guidelines as defined by NICE for patients with active RA that has failed to respond to two disease-modifying anti-rheumatic drugs (DMARDs).

There is also an emerging body of evidence to support the use of these drugs early in the course of the disease.⁴

THE HEART IN RHEUMATOID ARTHRITIS

Many studies have reported increased mortality rates in RA compared with the general population, and much of the excess mortality has been attributed to cardiovascular causes.⁵ A number of factors might explain this:

- Increased incidence of myocardial infarction (MI), related to atherosclerosis (although it is suggested by some that low-grade vasculitis or abnormal coagulation might also have a role to play). Females with RA for more than ten years have a relative risk of 3.10 for MI, compared with those without,⁵ and RA patients have a higher incidence of diastolic dysfunction, angina and stroke.
- Increased incidence of congestive cardiac failure. Although it is difficult to separate out heart failure caused by co-existing ischaemic heart disease, even when other factors have been excluded, one large study in the US put the hazard ratio for heart failure in RA as high as 1.87.⁶ Other work has shown clear associations between higher levels of C-reactive protein (CRP) and both worsening cardiac function and mortality related to cardiac failure in non-RA subjects.⁷
- Increased incidence of sudden or unexplained death. Rheumatoid patients are more likely to suffer from silent ischaemia or atypical ischaemic symptoms,⁸

and physical disability may mask ischaemic heart disease until it is well advanced. Autonomic dysfunction may also have a role to play.

At present, ischaemic heart disease associated with accelerated atherosclerosis is viewed by most as the main driver of cardiovascular mortality in RA. Traditional Framingham risk factors, such as smoking and hypertension, have an important role to play in the development of atherosclerosis, but the traditional cardiovascular disease risk factors do not fully account for the increased cardiovascular risk in RA compared with the general population.⁹ It is likely that the chronic inflammatory process in RA is implicated in the pathogenesis of this accelerated atherosclerosis: CRP and oxidised LDL are among several molecules found in excess in RA, also located in the atherosclerotic plaque, and linked with accelerated cardiovascular disease.^{10,11}

TNF α AND THE HEART

TNF α is a key inflammatory cytokine in RA, with strong links to both articular disease and premature atherosclerosis. Elevated levels of TNF α are found in the synovial fluid and serum of RA patients, and TNF α has been localised to atherosclerotic plaques. TNF α increases insulin resistance, and impaired handling of glucose is seen in chronic active RA.¹² TNF α reduces levels of nitric oxide synthase mRNA, which is responsible for the generation of nitric oxide (consequently affecting endothelial mediated dilatation).¹³ There are TNF α mediated changes in lipid metabolism, which in the acute setting are beneficial to the host. However, prolonged exposure to chronically elevated levels of TNF α has a pro-atherogenic effect on lipoprotein metabolism.¹⁴

While the healthy heart is not believed to produce TNF α , the failing heart produces significant amounts, broadly proportional to the degree of failure. It has also been demonstrated that exposing healthy myocardium in animal models to TNF α produces changes identical to those seen in heart failure,¹⁵ including myocyte apoptosis, fibrosis and cardiac hypertrophy; blocking of TNF α reverses the process.

THE CARDIOVASCULAR EFFECTS OF TNF α ANTAGONISM

At the cellular level

Given that TNF α -mediated systemic inflammation has been shown to accelerate atherosclerosis in RA patients, it is therefore reasonable to hypothesise that therapies targeting the inflammatory response may also have cardiovascular benefits. In addition to the articular benefits seen in RA, the TNF α blocking drugs have a role to play in the prevention of premature atherosclerosis: animal studies have shown TNF α blockade leads to an improvement in endothelial function (an independent

predictor of cardiovascular events),¹⁶ which may be partially mediated by nitric oxide.¹⁷ There is evidence that patients with RA responding to TNF α antagonism have an associated reduction in carotid artery intima-media thickness (another sub-clinical marker of atherosclerosis) after 12 months of treatment,¹⁸ but despite early improvements in HDL levels¹⁹ there is no significant long-lasting improvement in lipid profiles. There is also evidence that infliximab therapy improves insulin sensitivity in patients with rheumatic diseases.²⁰ But do these effects confer any clinical benefit?

At the clinical level

There is good reason to believe that effective immunosuppression can positively influence cardiovascular outcome, and it has been clearly shown that the use of methotrexate reduces cardiovascular mortality in RA.²¹ Initial data suggested that the risk of a first MI may be reduced in those treated with anti-TNF α therapy compared with those not. However, this did not fully exclude all confounding factors, such as disease activity.²² More robust evidence has recently been published from the British Society for Rheumatology Biologics Register (BSRBR), a large prospectively recorded database for monitoring biologic therapy. This demonstrated a lower incidence of MI in those responding to anti-TNF α therapy compared with non-responders. There was a non-significant trend towards a reduced incidence of MI in all RA patients treated with anti-TNF α therapy compared with those treated with conventional DMARDs.²³ These findings are striking, as a short-term reduction in the incidence of MI might suggest an effect on plaque stability in addition to the long-term regression of atherosclerosis. We can expect more compelling data to follow from the BSRBR, which will further inform our understanding of the cardiovascular benefits of TNF α blockade.

Given the potential role of TNF α in heart failure, it was a natural progression for TNF α blockers to be suggested as an attractive treatment for the disease, and initial work in animals gave further impetus to large trials of anti-TNF α therapy as a potential treatment in (non-rheumatoid) patients with established cardiac failure.

The results of RENEWAL, a combined analysis of more than 1,200 patients in the RECOVER and RENAISSANCE programmes, were published in 2004, after the two studies had been terminated early due to pre-specified criteria for lack of benefit.²⁴ Although the experience with TNF α blockers in heart failure was considered negative in these studies, wider experience of biological drugs in rheumatology patients has given rheumatologists cause to reconsider the results. The only statistically significant result was that patients who received etanercept 25 mg twice weekly in the RENAISSANCE trial were more likely to have clinically worsened after 24 weeks. However, many of the patients receiving smaller or less frequent doses of the drug seemed to do better, and there were

trends in these patients towards improvement. Similarly, in the ATTACH study, patients who received 10 mg/kg infliximab (a substantially higher dose than used in most rheumatoid arthritis patients) tended to do less well, despite slight improvements in ejection fraction and CRP; by contrast, those receiving lower doses, more relevant to RA treatment, tended to do better.²⁵

This impression has been borne out recently by observational studies on the effect on heart failure of TNF α blockers used to treat rheumatoid arthritis patients without significant heart failure to begin with. Although RA patients have a greater incidence of heart failure than controls and there have been case reports of worsening heart failure with TNF α blockers, in many patients it seems that the trend is towards benefit.

In a recent retrospective study, RA patients treated with TNF α antagonists were no more likely to die, or to be admitted to hospital with congestive heart failure, than RA patients treated with conventional therapy, or non-RA controls, and there was a strong trend towards reduced mortality in the anti-TNF α group.²⁶ This reflected an older study actually suggesting that the risk of heart failure was marginally lower in RA patients treated with TNF α blockers as compared with those without (3.8% v 3.1% over a two-year period).²⁷ Although these results are encouraging, it seems that for the foreseeable future the dose and timing of anti-TNF α therapy in RA will be decided on the basis of articular function rather than cardiac ejection fraction.

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SUMMARY

Atherosclerosis The link between the sustained systemic inflammatory response in RA and the development of accelerated atherosclerosis is well established and is linked with significant morbidity and mortality. TNF α -blocking therapies have revolutionised the management of RA, and current evidence suggests that anti-TNF α therapy favourably affects some lipid profiles, insulin sensitivity and the development of sub-clinical atherosclerosis. There are grounds for optimism that these effects will translate into reduced cardiovascular events.

Heart failure The role of TNF α blockers in cardiac failure is far from clear. Large prospective trials suggest that TNF α blockers are not a breakthrough in treatment of heart failure and that high doses may be deleterious. By contrast, retrospective papers on the use of anti-TNF α therapy in rheumatological patients with mild heart failure suggest no hazard, and perhaps even a slight benefit. Pragmatism is perhaps the order of the day, and while most rheumatologists would avoid TNF α blockers in patients with severe heart failure, mild to moderate congestive heart failure does not rank high on the list of potential worries when prescribing these drugs to the wider population of patients with inflammatory arthritis.

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