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REVIEW ARTICLE

TNF Antagonists, the Prevention of Myocardial Infarction in Rheumatoid Arthritis Patients?

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Abstract

Cardiovascular disease (CVD) has been acknowledged to be a major extra-articular comorbidity in patients with rheumatoid arthritis (RA), with myocardial infarction (MI) particularly being the most prominent. Contributory factors include the rise in traditional risk factors and proinflammatory changes seen in RA patients. Two drivers of proinflammatory changes are mainly emphasized in this review: insulin resistance and dyslipidaemia. Among the cytokines involved, tumour necrosis factor alpha (TNF-α) has been identified as one of the major molecules contributing to the proatherogenic state seen in these patients. As such, biological therapies such as anti-TNF drugs are hypothesized to have a secondary function in reducing CVD in these patients. Using TNF-α as an example, this review provides an overview of how chronic inflammation increases the risk of CVD, focusing mainly on the two drivers: insulin resistance (IR) state and dyslipidaemia. The review also investigates if anti-TNF drugs can reduce the effects of these two drivers and hence, determine if anti-TNF drugs can produce a clinical effect of reducing the risk of MI in RA patients.

A literature search was conducted using Medline and Google Scholar (1990–January 2013). Studies were selected if they addressed the pathophysiology of TNF-α in CVD risk for RA patients or the effects of anti-TNF therapy on IR, dyslipidaemia or MI in RA patients. Although the studies were unable to establish if anti-TNF therapy can reduce CVD risk, responders to anti-TNF therapy appears to have a significant lower risk of MI.

Despite its effects, additional studies should be conducted to determine its cost-benefit ratio. This is because of its high cost and its administration limitations. Future studies should also determine if the lipid profile in RA patients truly reflects their risk of CVD, as some studies have reflected an increased CVD risk as compared to the general population.

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Introduction

The link between rheumatoid arthritis (RA) and cardiovascular disease (CVD) has been well established.[1,2] It has been postulated that since atherosclerosis is in part inflammatory, the same inflammatory process that drives RA in patients is also likely to accelerate the rate of atherosclerosis, increasing their risk of CVD. It is estimated that 50% of deaths in RA patients are caused by CVD, making it the largest causative factor in the mortality of these patients.[3] Studies have shown that these patients are more likely to suffer from myocardial infarction (MI), as compared to stroke.[3,4]

Over the past 30 years, medical advances in chronic inflammation allowed us to have a better understanding of the biochemistry behind this pathology. This insight has led to the development of a promising new class of medicine, biologic therapy, now allowing doctors to provide a more targeted approach in managing patients with chronic inflammation. Many cytokines are known to drive the inflammatory process, however tumour necrosis factor alpha (TNF-α) has been touted as one of the main players. Given the role of inflammation in precipitating atherosclerosis, it is inferred that biological drugs such as infliximab should have a positive impact on CVD risk, and hence the incidence of MI. This has prompted many studies to investigate such effects, in hopes to significantly improve the mortality rates of RA patients.[5-11]

This paper is particularly useful to medical students because, by using the example of RA, it will seek to explain why patients with chronic inflammation have an increased risk of MI, bridging the biochemistry of chronic inflammation and the pathophysiology behind the rise in CVD risk. In particular, it focuses on one main cytokine of inflammation, TNF-α. It will also explore the role of a new class of biological drugs, TNF-α antagonists, and determine if these drugs have a potential role in reducing CVD risk. One of the challenges in studying if TNF-α antagonists can prevent MI is that a substantial decrease in CVD risk does not necessarily correspond to a decrease in MI. Hence, we will conclude by discussing whether TNF-α antagonists have a possible clinical endpoint of preventing MI and if sufficient evidences are present to warrant the use of TNF-α antagonist in the prevention of MI. We will also look at possible gaps in the present knowledge and identify potential studies to strengthen the present evidence.

Methodology

A literature search was conducted using Medline and Google Scholar. Terms used in search involved combinations of "rheumatoid arthritis", "myocardial infarction", "anti-TNF/TNF antagonist", "dyslipidaemia", and "insulin resistance". The results were limited within the period of 1990–January 2013. Abstracts from potentially relevant literature were vetted and only included in the review if they addressed the topic. They were also included if discussions about the effects of TNA-α antagonist on CVD risk were made. 6 articles were also obtained by conducting a manual search on the references in the above articles.

Rheumatoid Arthritis: An Independent Risk Factor

Several studies have shown that patients with RA have increased mortality[12-14] and morbidity rates[1,12,15] associated with CVD. In particular, a meta-analysis conducted by the University of British Columbia and Arthritis Research Centre of Canada showed that an increase of 50% in CVD-related mortality risk was observed for RA patients, versus the general population (meta-SMR 1.50, 95% CI 1.39–1.61).[3] Of this, 59% of RA patients were more likely to die from MI (meta-SMR 1.59, 95% CI 1.46–1.73) while 52% of them were more likely to die from cerebrovascular accidents (CVAs) (meta-SMR 1.52, 95% CI 1.40–1.67).[3] It was also noted that the increase in CVD-related mortality is not significantly different between sexes. The paper also identified that although not all studies included in the meta-analysis demonstrated that CVD-related mortality is higher in RA patients, most of these studies had smaller samples. As such, lack of persuasive power was a plausible reason for not identifying a similar pattern in those studies.[3]

Role of TNF And Anti-TNF Therapy in the Pathophysiology of CVD

TNF-α

In the early 1980s, among the multitude of cytokines produced in RA, researchers found that TNF-α seemed to be the pivotal proinflammatory mediator in the big inflammatory cascade.[16] Early animal studies showed that transgenic mice expressing human TNF-α developed an inflammatory arthritis similar to RA.[17]

TNF-α has many effects on the human body. However, it can be broadly classified into 2 groups: acute effects and chronic effects (Figure 1.1).[18-20]

The biological effects of TNF-α are initiated by the ligand-binding of TNF-α and its receptors, TNF-RI and TNF-RII.[21] These receptors are present on the membrane of all cell types except erythrocytes.[20] While TNF-RI is the main receptor that establishes the effects of TNF-α,[22] TNF-RII determines the severity of the effects.[23] This is because both receptors have different intracellular signalling pathways and they differ in their binding affinity to TNF-α. When stimulated, the intracellular domain of TNF-RI binds to the TNF receptor associated death domain (TRADD) protein.[20] TRADD protein proceeds to initiate apoptosis via the Fas associated death domain (FADD) protein or promote inflammation via THNK receptor associated factor 2 (TRAF2).[20] This activates the nuclear factor-κB. In TNF-RII, the signalling pathway only allows for the promotion of inflammation via the TRAF2 pathway.[20]

TNF-α exists in two forms (Figure 1.2): a functional membrane protein and a soluble protein that is cleaved from the membrane by TNF-α converting enzyme.[21] Due to the significant role that TNF-α plays in RA, new biological therapies targeting TNF-α have been very efficient in treating RA.[24] Some studies also suggest that these anti-TNF-α drugs have cardioprotective effects for RA patients.[5,6] They will be discussed in detail below.

At present, there are 5 anti-TNF drugs that are approved by the United States Food and Drug Administration for the treatment of RA: infliximab, etanercept, adalimumab, golimumab, certolizumab. Table 1.1 provides a summary of these drugs.[25]

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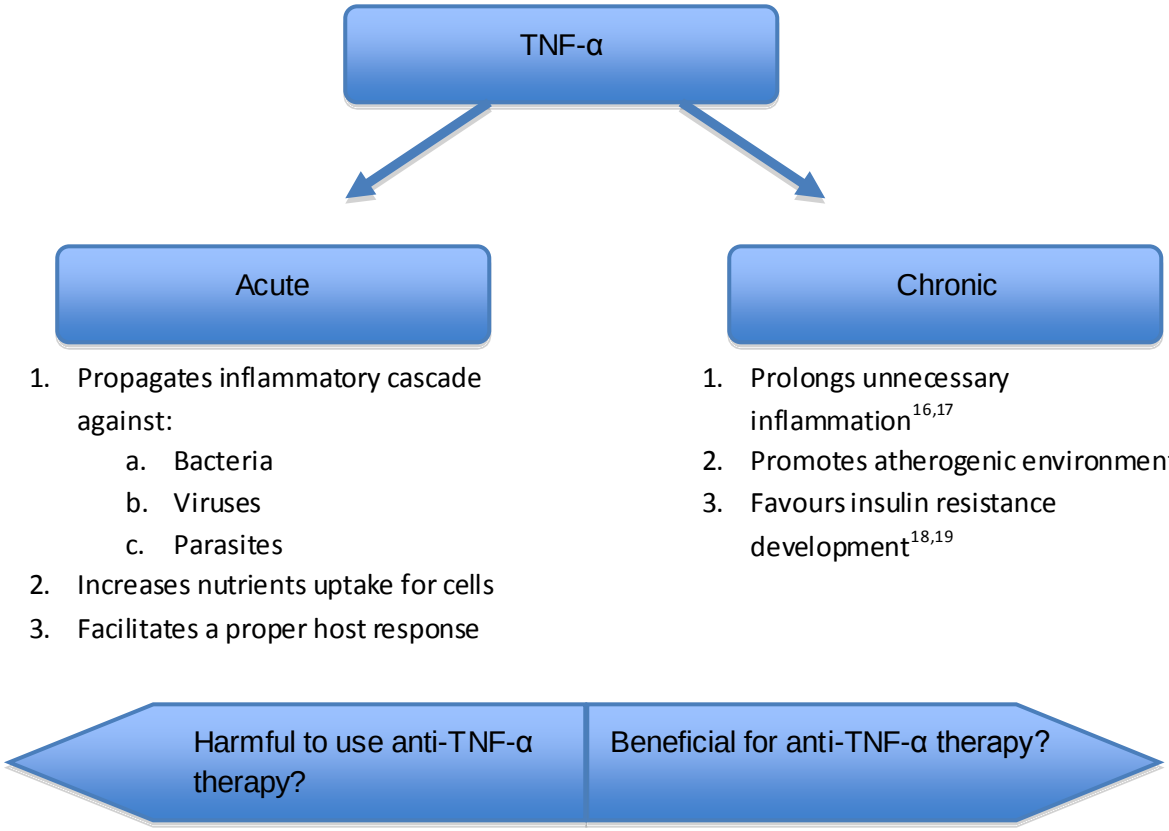

Figure 1.1. A breakdown of the physiological role of TNF-α on the human body. Adapted from Popa et al, 2007.[20]

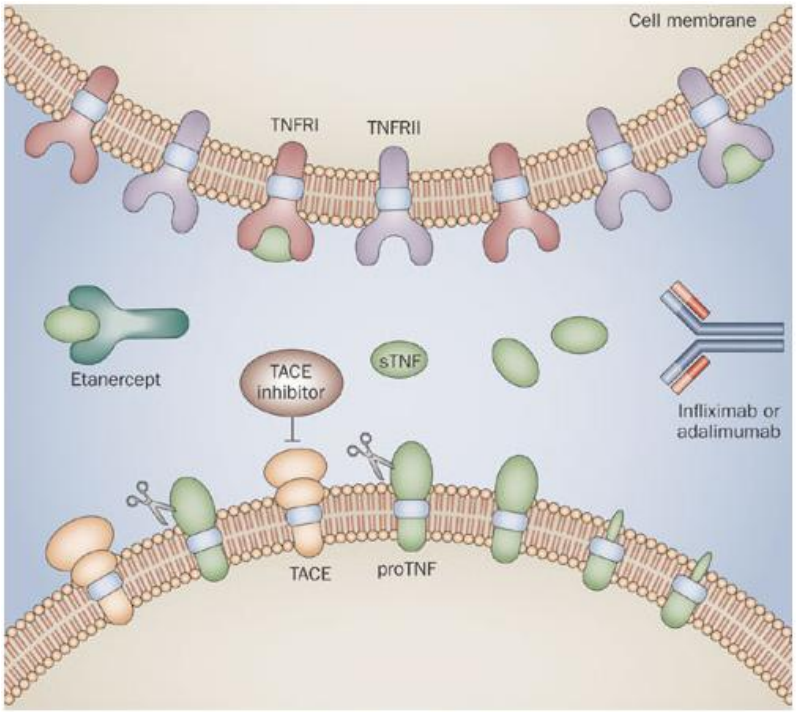

Figure 1.2. A diagram demonstrating the key proteins involved in extracellular signalling of TNF-α and some of the key anti-TNF drugs used in the treatment of RA. TACE-TNF-α converting enzyme; sTNF-soluble TNF; proTNF-membrane-bound TNF-α protein. Adapted from McKellar et al, 2009.[21]

Insulin resistance

The link between RA and insulin resistance (IR) has long been established and it correlates with the activity of RA in patients.[26-28] In a study that consists of 124 RA patients, it was estimated that the RA cohort are 10% more likely to have IR compared to the general population.[27] A similar study by Dessein *et al.* also yielded similar results.[28] Several studies attribute TNF-α for this phenomenon.[18-19]

There are several mechanisms to explain how TNF-α can induce IR in the body. Its effects are mainly seen in adipose tissue (Figure 1.3).

Firstly, i*n vitro* studies using murine cell cultures have observed that TNF-α is able to inhibit the activity of tyrosine kinase found on insulin receptors. This was possible due to serine phosphorylation of insulin receptor substrate 1 (IRS-1), converting it to an inhibitor of tyrosine kinase. This would effectively inhibit the insulin receptor intracellularly, rendering it useless even when the insulin molecules bind to its receptor. This effect is initiated by the activation of TNF-RI.[29]

Secondly, the rise in TNF-α levels also stimulates an increase in the levels of free fatty acid (FFA). This results from the rise in the rate of lipolysis from adipose tissue.[30] Stimulation of gluconeogenesis in hepatic cells and a decrease in the rate of glucose uptake and metabolism would follows in skeletal muscle cells. The end result would help contribute to an insulin-resistant state.[20]

Thirdly, TNF-α has been known to downregulate the expression of some proteins in adipocytes. These include glucose transporter type 4 (GLUT-4), IRS-1, peroxisome proliferator-activated receptor gamma (PPAR-γ) and adiponectin.[31-33] A reduction in insulin-sensitive GLUT-4 indicates that the rate of glucose uptake in adipose tissue would be reduced, causing a rise in blood glucose level. Also, adiponectin, a protein hormone that modulates insulin sensitivity, has an inverse relationship with the overall systemic insulin resistance.[34] Hence, the overall increase in insulin resistance could increase the CVD risk of RA patients.

Lastly, proinflammatory proteins such as leptins and monocyte chemoattractant protein-1 (MCP-1) have been observed to be upregulated in patients with elevated TNF-α. It is believed that these proteins further worsen the degree of insulin resistance.[34,35] However, the pathogenesis has yet to be fully established.

Effects of anti-TNF therapy on IR

In many studies, the homeostatic model assessment index[36] (HOMA) calculation was used to quantify the level of IR while the quantitative insulin sensitivity check index[37] (QUICKI) measures the level of insulin sensitivity. As such, these measures will be used below to discuss about the effects of anti-TNF therapy on IR.

A study conducted using infliximab on 45 patients with either RA or ankylosing spondylitis has shown some benefits on the level of IR.[38] Although it was observed that there were no significant changes of the HOMA and QUICKI in the whole study, patients with the highest IR (n=14) showed significant improvement in HOMA and QUICKI. This translates that the level of IR in these patients was reduced while the

insulin sensitivity improved.[38] Another study involving 10 patients also showed that infliximab does not result in an overall significant improvement of HOMA and QUICKI.[39] In that study, however, a separate analysis on the highest IR subjects were not conducted due to the small cohort size. Other studies involving diabetic patients who have IR also failed to show the hypothetical beneficial effects of anti-TNF therapy.[40,41]

Dyslipidaemia

Based on the ATP III classification, dyslipidaemia is defined as a state of high low-density lipoprotein (LDL), high total cholesterol (Tchol) and low high-density lipoprotein (HDL) levels. It has been well established that this state can greatly increase the risk of CVD.[42] Hence, we will focus on these three types of cholesterol in this discussion.

Dyslipidaemia appears to be elevated in the RA cohort. However, the evidence seems conflicting. Several studies found that RA patients tend to have highly atherogenic dyslipidemic patterns, as compared to their age and gender matched controls.[43,44] However, in another population-based case control study, an opposite effect was seen. It was observed that RA patients have lower Tchol and LDL levels as compared to the control cohort. The study also found that the LDL levels in the RA cohort were reduced significantly 5 years before the diagnosis of RA.[45] Hence, it appears that RA seems to create an antiatherogenic lipid profile in patients. However, a population based study of RA in 2011 showed that such antiatherogenic lipid profile in RA patients can paradoxically increase the risk of CVD.[46] This phenomenon will be further elaborated below.

Patients with a high RA activity also tend to have lower HDL levels.[47-49] There are also studies that suggest HDL, an established cardioprotective marker, could be modified into a proinflammatory product, accelerating the progression of atherosclerosis.[50,51] As such, it is widely agreed that systemic inflammation can alter the lipid profile in human body.[52-54] Studies have suggested that the interference of TNF-α in cholesterol metabolism and the reverse cholesterol transport are the main reasons why the lipid profiles in these patients are highly proatherogenic.[20]

Cholesterol Metabolism

Cell lines using human hepatoma cells showed that TNF-α decreases the secretion of apolipoprotein A and B (apo-A and apo-B).[55] As these proteins are necessary to form lipoproteins, their reduced expression will decrease levels of HDL and LDL found in the circulatory system (Figure 1.4).[55]

CYP7A1 is an enzyme that helps eliminate cholesterol by converting it to become bile acid. This enzyme is found to be the rate-limiting step in the classical pathway of bile acid formation. Studies have found that in times of inflammation, cytokines such as TNF-α are able to reduce the activity of CYP7A1.[56] In addition, downregulating the activities of mitochondrial sterol 27-hydroxylase and oxysterol 7α-hydroxylase further dampens the synthesis of bile acid via the alternative pathway.[57] Although it is not known if this alteration helps promote a proatherogenic state in RA patients, it redirects available cholesterols for other hepatic processes in times of inflammation.[56]

In vitro studies also showed that TNF-α promotes the clearance of LDL from the circulatory system.[52] This could explain the reduction of LDL levels found in patients with RA. This is achieved by promoting the synthesis of LDL receptor on hepatocytes, allowing an increase in uptake of LDL.[52] Such mechanisms appear to look antiatherogenic.

However, as mentioned previously, these antiatherogenic profiles increase the risk of CVD in RA patients. This is because TNF-α stimulates changes in the composition of LDL, making it more atherogenic. Patients with elevated TNF-α were found to have a higher concentration of oxidized LDL in their circulation as TNF-α increases the expression of secretory phospholipase A_2 in LDL, hence increasing the hydrolysis of phospholipids. This would generate higher levels of fatty acids that would eventually result to an increase in oxidized LDL.[58] It was also noted that TNF-α could stimulate hepatic sphingolipid synthesis, significantly altering the structure of circulating lipoprotein to make them more atherogenic.[53]

Reverse Cholesterol Transport

Reverse cholesterol transport is a widely accepted hypothesis that explains the role of HDL in removing excess cholesterol from the circulation and transferring them to the liver for excretion. Impairment to this mechanism is known to promote atherosclerosis, and many believe that the interference of TNF-α explains the increased risk of CVD in RA patients (Figure 1.5).[20,59-61]

Studies conducted in primates have suggested that TNF-α decreases the synthesis and activity of lecithin cholesterol acyltransferase (LCAT).[59] This is an important enzyme that catalyses the conversion of free cholesterol into cholesteryl ester, an essential molecule for the formation of HDL. A decrease in LCAT would result in a decrease in HDL concentration, and this could account for the drop in cholesterol concentration after a TNF-α infusion.[54]

TNF-α is also known to impair the uptake and excretion by hepatocytes by downregulating the expression of scavenger receptor class B.[60] This receptor is known to bind oxdized LDL, normal LDL and HDL, promoting the catabolism of these molecules.[62-65] It is believed that during acute-phase inflammation, the reduced uptake of these molecules would help direct cholesterols towards inflammatory cells, such as macrophages, to aid in host defences. However, a prolonged inflammatory process would encourage deposition of cholesterol in macrophages, contributing to the formation of atherosclerotic plaques.[60]

Elevated levels of TNF-α have been observed to modify the structure of HDL. Compounds such as apoJ and apolipoprotein serum amyloid A (apoSAA) were elevated while others such as apolipoprotein A-I (apoA-I) and paraoxonase-1 (PON1) were decreased.[61,66] This is important because apoA-I is greatly associated to the ability of a type of HDL, pre-β HDL, in attracting cholesterol from the circulation. As such, the protective effects of HDL are significantly decreased in these patients. PON-1 is a major antiatherogenic molecule in HDL because it promotes antioxidant properties in HDL. This allows HDL to protect LDL and itself from oxidation, preventing them from becoming proatherogenic molecules.[67]

Types of anti-TNF	Structure
Infliximab	A chimeric, monoclonal IgG1 antibody. It is made of 75% human and 25% murine.
Etanercept	A recombinant human TNF dimeric fusion protein receptor. Combination of extracellular domain of p75 TNF receptor and the Fc domains of human IgG1 antibody.
Adalimumab	Full human monoclonal antibody, indistinguishable from the naturally occurring IgG1 in the human body.
Golimumab	A human monocloncal IgG1 antibody. Similar to Adalimumab.
Certolizumab	An antibody that is made up of Fab fragment of humanised TNF, combined with polyethylene glycol.

Table 1.1. A summary of the structures of different anti-TNF drugs.[25]

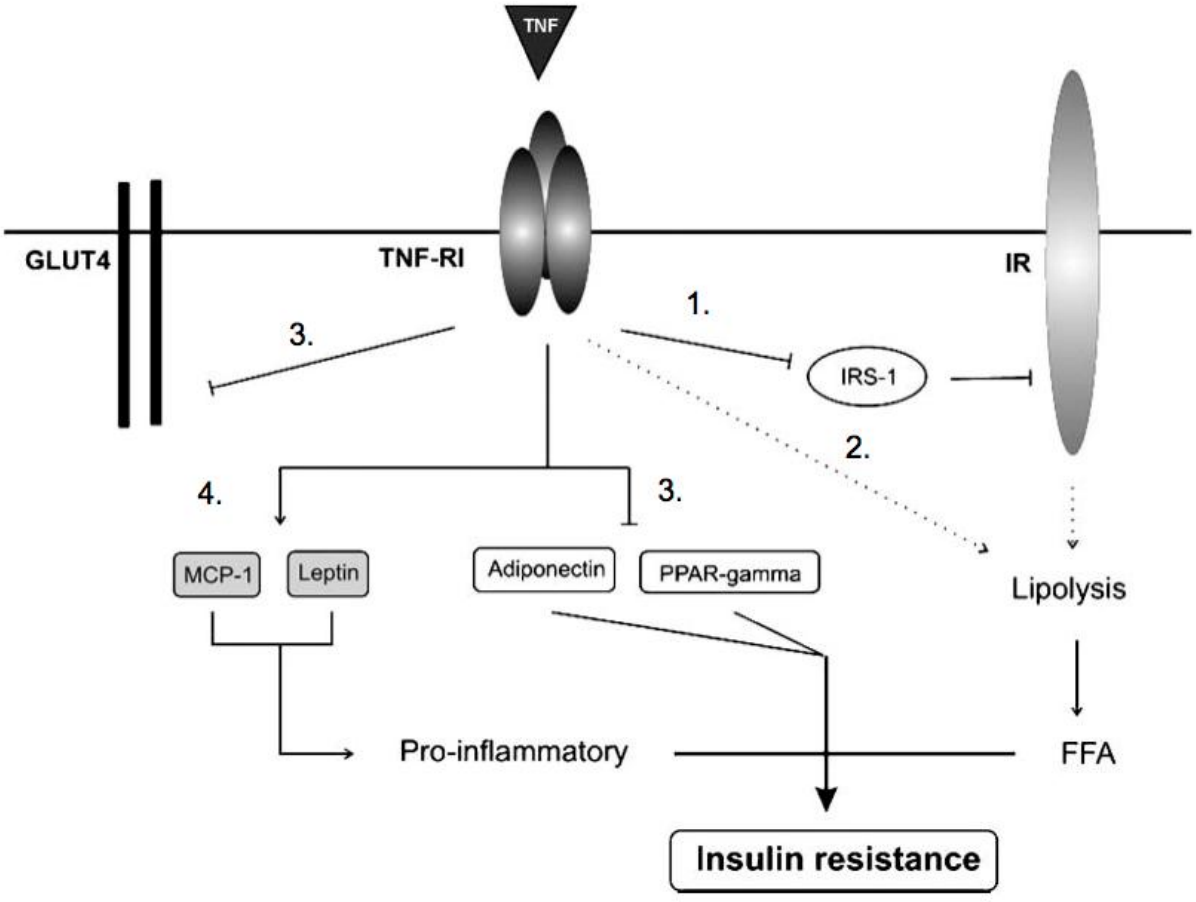

Figure 1.3. A diagram illustrating the possible mechanisms of TNF-α on IR. Adapted from Popa et al, 2007.[20]

Based on the studies shown above, the rise in TNF-α levels could induce a hypocholesterolaemia state in RA patients. However, the effects of TNF-α on lipoproteins make these patients highly atherogenic. In view of the positive correlation between RA and CVD, it would appear that the increased atherogenic effect of the lipoprotein surpasses the cardioprotective effects of a hypocholesterolaemia state. However, further studies will be required to confirm this hypothesis.

Effects of Anti-TNF Therapy on Dyslipidaemia

Several studies looking at the effects of anti-TNF therapy on the lipid profile of patients have been conducted. A summary can be seen in Table 1.2.

It appears that the effects of anti-TNF on the lipid profile are rather complicated. Although the studies did not yield identical results, there were some similarities. In general, anti-TNF therapies appear to elevate the total cholesterol and HDL levels. Some of these studies noted that the effects were still sustained after 6 weeks of therapy.[49] Even so, no improvements in the atherogenic index were seen, given the rise in levels of protective HDL. The only exception was in a study where adalimumab was used.[68]

Clinical End-Point: Myocardial Infarction

Based on the effects of TNF-α on reducing the clearance rate of cholesterol in the body and making lipoproteins more reactive to oxidation, one would assume that the use of anti-TNF therapy will, in theory, reduce the rate of plaque formation and hence the incidences of MI in RA patients. However, this direct correlation has yet to been seen.

Data obtained from the British Society for Rheumatology Biologics Register (BSRBR) has shown some encouraging results.[5] The cohort study concluded that when compared to patients using the traditional disease-modifying antirheumatic drugs (DMARDs), anti-TNF therapy does not reduce the risk of MI (incidence rate 1.44, 95% CI 0.56–3.67). However, further analysis of the data observed that responders to anti-TNF therapy had a significant reduction in the incidence rate of MI as compared to non-responders (incidence rate 0.36, 95% CI 0.19–0.69). Due to the nature of the study, the risk of bias was low. Coupled with such hopeful results, it appears that anti-TNF therapy could in fact reduce the risk of MI in RA patients that respond to these treatments.[5]

A cross sectional study using data collected from the QUEST-RA study further indicated that the prolonged exposure to anti-TNF drugs could reduce MI by 58% as compared to RA patients with no DMARDs (HR 0.42, 95% CI 0.21–0.81).[6] This was observed to be even better than the improvement seen in methotrexate treatment (HR 0.85, 95% CI 0.81–0.89). However, 4 other case-control studies showed differing outcomes. They observed that there was no significant decrease in the risk of MI when comparing anti-TNF therapy (monotherapy or combined therapy)[7-10] with no DMARDs. No segregation between responders and non-responders was conducted in these studies. As such, the possibility of non-responders skewing the results in these studies must be considered.

Further studies looking at the combined effects of anti-TNF therapy with other DMARDs were also conducted.[11] Although the monotherapy of anti-TNF did not reduce the rate of MI (RR 1.17, 95% CI 0.50–2.75), the combined therapy of methotrexate with anti-TNF was seen to be superior in reducing the risk of MI as compared to methotrexate monotherapy. An 80% reduction of risk was obtained (RR 0.8, 95% CI 0.05–0.88).[11]

Discussion

Present studies conducted do support the idea that TNF-α is a major contributor to the increased risk of CVD. However, the association between anti-TNF therapy and its benefits on IR and dyslipidaemia remains unestablished.

Many studies[38-41] have already indicated that anti-TNF therapy does not significantly improve the IR status seen in RA patients. However, one study by Kiortsis *et al.* noted significant improvement in the IR with patients having the highest IR.[38] As other studies mentioned did not perform a separate analysis on patients with the highest IR, it is difficult to determine if anti-TNF therapy does produce significant benefit to only patients with the highest IR. As such, future studies looking at patients with the highest IR will be necessary before one can definitively conclude the lack of effectiveness of anti-TNF therapy on IR.

The effects of anti-TNF therapy on dyslipidaemia however, appears to be more promising. Evidence presented has indicated similar results, showing that anti-TNF therapy increases the Tchol and HDL in RA patients.[5,47,49] However, as the cardio-protective effects provided from HDL in the RA population appears to be less than the general population, a rise in HDL after anti-TNF therapy cannot definitively indicate a reduction in CVD risk. Future studies will first be required to establish if the lipid profile levels of the RA population truly reflects the same level of CVD risk in the general population. A longer-term study will also be required to determine if these improved lipid profile levels are sustainable in the long run.

Studies looking at the effects of anti-TNF therapy in the prevention of MI indicated that it may be effective in the prevention of the disease for responders of the treatment. Results from the BSRBR, one of the largest observational study conducted to date, brought forth an interesting point: although the overall risk of MI was not reduced, when compared to the control cohort that used DMARDS, there was a significant reduction in the events of MI when comparing responders and non-responders to anti-TNF therapy.[5] This study may indicate that anti-TNF therapy only prevents MI in a particular group of patients. However, it may also show that the reduction of MI is attributed to a more well controlled RA disease. A comparison study looking at responders to DMARDS and anti-TNF therapy would be useful as it can better attribute the prevention of MI to the drugs used, instead of the level of inflammation. Future studies should also focus mainly on responders to anti-TNF therapy as this would prevent the non-responders from skewing the results, as seen in this study.

One of the main limitations in this review is the use of mainly infliximab in studies of anti-TNF therapy. As infliximab was the first anti-TNF drug to be marketed, it has the greatest number of published studies carried out to determine its effects.

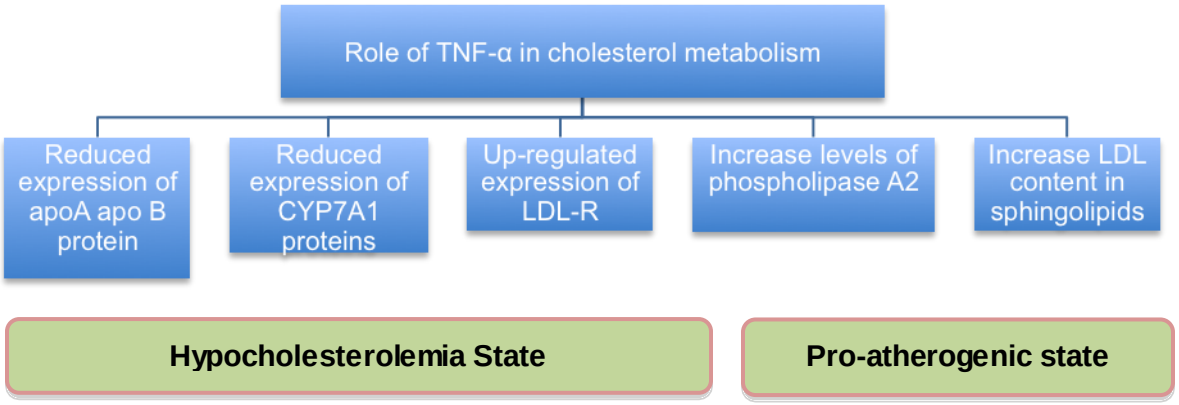

Figure 1.4. A summary of the mechanisms of TNF-α affecting cholesterol metabolism. Adapted from Popa et al, 2007.[20]

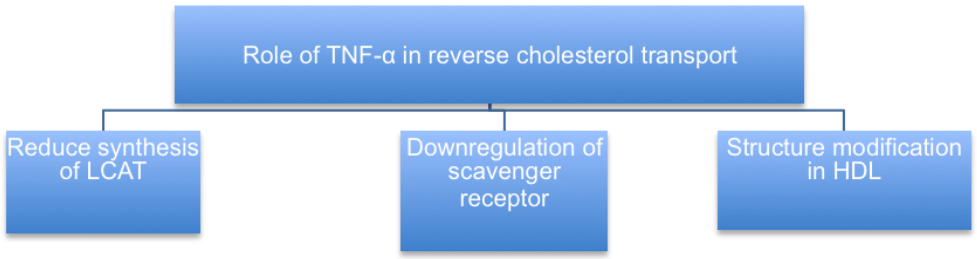

Figure 1.5. A summary of the mechanisms of TNF-α affecting reverse cholesterol transport. [59-61]

Study	Cohort size	Treatment regime	Effects on lipid profile
Allanore *et al.*	RA patients n=56	Infliximab (3mg/kg) weeks:0,2,6,14,22,30	Total Chol ↑, LDL↑, HDL↑, Triglyceride ↔, Total Chol/HDL↔, LDL/HDL ↔
Vis *et al.*	RA patients n=69	Infliximab (3mg/kg) weeks:0,2,6	Total Chol ↑,HDL↑, Total Chol/HDL↔
Popa *et al.*	RA patients n=33	Adalimumab, weeks:0,2	HDL↑, LDL↔, Triglyceride↔, Total Chol/HDL↓
Peters *et al.*	RA patients n=80	Infliximab (3mg/kg) Weeks 0,2,6 and every 8 weeks after	Total Chol ↑, HDL↑, Triglyceride↑, Total chol/HDL↓
Popa *et al.*	RA patients n=67	Inflximab (3mg/kg) weeks: 0,2,6 nad every 8 weeks after	Total Chol ↑, LDL↑, HDL↑, Triglyceride ↔, Total Chol/HDL↔, LDL/HDL ↔

Table 1.2. A table of the summary of studies conducted on the effect of anti-TNF therapy on lipid profile. Adapted from McKellar et al, 2009.[21]

As such, there is a high risk of bias that the effects of infliximab may not be a true reflection of other anti-TNF therapy. This review also focuses on only RA and thus, its results cannot be generalized to other types of inflammatory rheumatic disorder. Another source of limitation is the lack of statistical techniques to collectively conclude the results from the studies used. Future reviews can use a wider range of anti-TNF drugs and other types of inflammatory rheumatic disorder when such information are more readily available. A systemic review can also be conducted to provide a stronger case for the use of anti-TNF therapy in the prevention of MI.

In view of its potential role in the prevention of MI, clinical implications of the use of anti-TNF therapy must also be considered. With the drug costing about GBP 13,000 per year per patient[69] and the need to administer the drug via intravenous infusion every 6 to 8 weeks,[69] it may be impractical at present to administer such drugs to prevent MI. However, future studies should still weigh the cost-benefit ratio of this therapy as such studies may motivate pharmaceutical companies to discover alternative routes to deliver this drug. Possible side effects of the medication should also be further monitored. A randomized controlled trial conducted in 2003 noted that when used in high doses, infliximab adversely worsened the conditions of patients with moderate to severe chronic heart failure.[70] However, the association has yet to be firmly established.

Conclusion

In summary, although it remains controversial if anti-TNF therapy improves the IR and dyslipidaemia state in RA patients, there are indications that responders to anti-TNF therapy may benefit in the prevention of MI. Further studies targeting this group should be initiated and a wider range of anti-TNF drugs can be investigated.

Key Learning Points

- TNF-α plays a pivotal role in the inflammatory process.
- TNF-α increases CVD risk in RA patients by promoting dyslipidaemia and insulin resistance.
- Although the overall risk of MI is not reduced, responders to anti-TNF therapy displayed a significant reduction in risk of MI.
- There is some evidence to support the secondary role of anti-TNF therapy in the reduction of MI risk in RA patients, however, more studies are necessary to cement the findings.

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