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Case Report Open Access

# Heart Failure with Etanercept Therapy: A Case Report

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**Abstract**

Tumour Necrosis Factor-alpha antagonists constitute an important part of the therapeutic armamentarium available for managing autoimmune diseases such as rheumatoid arthritis and psoriatic arthropathy. Here, we present the case of a 68-year old male with severe rheumatoid arthritis who developed chest pains and severe left ventricular systolic dysfunction following etanercept therapy. Etanercept was discontinued while he was commenced on standard heart failure treatment. This, consequently, led to complete resolution of his symptoms and recovery of left ventricular function to near normal. Previous literature involving similar case reports is reviewed and implications for clinical practice are discussed with emphasis on the need for a screening protocol when commencing such therapy.

**Keywords:** Heart failure; Cardiomyopathy; Etanercept; Tumour necrosis factor antagonists; Anticytokine therapy

## Introduction

Etanercept is a tumour necrosis factor-alpha (TNF-α) antagonist. It was the first member of a family of cytokine modulators subsequently used as disease modifying agents for a variety of autoimmune conditions including rheumatoid arthritis, polyarticular juvenile rheumatoid arthritis, ankylosing spondylitis and psoriasis. It acts by binding to cell-surface TNF receptors thus blocking their interaction with circulating TNF. It is produced (by recombinant DNA technology) in the form of a dimeric human TNF receptor p75 Fc fusion protein and behaves as a decoy soluble TNF receptor.

TNF and related chemokines are thought to play an important role in the pathogenesis of heart failure [1,2]. Levine et al. [3] compared 33 patients in NYHA class III with healthy age-matched controls and found that circulating levels of TNF were higher in chronic heart failure as compared to controls and reported a correlation between TNF levels and the severity of heart failure. In the Studies of Left Ventricular Dysfunction (SOLVD) trial TNF-α was increased in patients in NYHA functional classes I to III as compared to healthy controls with levels correlated to NYHA class [4]. This association between TNF-α and heart failure severity led to the assessment of TNF as a potential target in heart failure. Small preliminary studies [5,6] provided encouraging safety and efficacy results of etanercept in lowering levels of biologically active TNF. There was a trend towards improvement in functional heart failure class as well.

Two double-blind placebo-controlled large-scale trials were subsequently conducted to assess the efficacy of Etanercept in the management of heart failure, RENAISSANCE (Randomized Etanercept North AmerIcan Strategy to Study AntagoNism of CytokinEs) in the US and RECOVER (Research into Etanercept CytOkine Antagonism in VEntriculaR dysfunction) in Europe. The two trials enrolled patients in chronic heart failure (NYHA class II-IV) with left ventricular ejection fraction of less than 30%. The primary end-point was based on a composite score of hospitalisation and death. A pre-specified combined analysis of the data called RENEWAL (Randomized EtaNercEpt Worldwide EvALuation) [7] was also planned. However, the trials had to be terminated prematurely due to a lack of effect (as decided by prespecified criteria). There was no statistically significant change in clinical status from baseline between placebo and etanercept arms (in both the trials). Moreover, in RENAISSANCE, etanercept group showed higher proportion of worse outcomes as compared to placebo [8].

Whilst etanercept has proven to be of no benefit in the management of heart failure, it continues to be used as a disease-modifying agent in a number of autoimmune conditions. The present report highlights a rare but potentially life-threatening adverse effect of etanercept in a patient with rheumatoid arthritis and the need to screen such patients for cardiomyopathy (both before and after therapy).

## Case Report

A 68-year old Caucasian male was referred to our rapid access chest pain clinic in order to investigate a 3-week history of recurrent atypical retrosternal chest pains. These episodes were short lived and self-limited without any particular aggravating or relieving factors. His cardiovascular risk factors consisted of smoking, essential hypertension and hyperlipidaemia. He was known to have severe rheumatoid arthritis for which he had recently been started on etanercept infusions with the onset of his symptoms occurring after the second dose. Cardiovascular examination was unremarkable. He was euvolaemic and normotensive. 12-lead ECG was within normal limits and baseline blood tests including complete blood count, renal profile, thyroid function and hepatic enzymes were all within normal limits as well. However, cholesterol levels were elevated (Total Cholesterol 6.2 mmol/L, LDL 3 mmol/L, HDL 2.3 mmol/L).

Keeping in view the coronary risk factors, he was referred for a dobutamine stress echocardiogram. The images, surprisingly, revealed a globally hypokinetic and dilated left ventricle (LV end diastolic diameter 7.1 cm) with LV ejection fraction (LVEF) of 15-20% (Figures 1 and 2). Severe functional mitral regurgitation was noted. Low dose

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dobutamine resulted in global but mild myocardial recruitment and no evidence of stress induced regional wall motion abnormalities. The overall impression was that of a dilated cardiomyopathy. The patient, nevertheless, denied any symptoms suggestive of congestive cardiac failure and was in NYHA functional class I. He was commenced on a beta-blocker, ACE-inhibitor and statin. Given the temporal association, etanercept was withheld pending further investigations.

Consequent coronary angiography demonstrated essentially normal coronary arteries. We repeated echocardiography following a period of 6 months, which revealed improved left ventricular dimension (LVEDD 5.7 cm), mild mitral regurgitation and LVEF of 40%. He remained asymptomatic from a heart failure perspective and the chest pains had not recurred. Further echocardiography (10 months from the original presentation) reassuringly revealed a non-dilated LV (LVEDD 5.2 cm) with an LVEF of around 50% (Figures 3 and 4). Etanercept infusions were not repeated.

## Discussion

Cytokine modulators or "biologics" are widely used in clinical practice as therapy in a variety of disease states such as rheumatoid arthritis, juvenile idiopathic polyarthritis, ankylosing spondylitis, psoriasis, inflammatory bowel disease and systemic vasculitides. Further research may extend clinical use to yet other conditions such as idiopathic pulmonary fibrosis and resistant uveitis.

An association between etanercept and new-onset HF has not been widely reported in literature. Manufacturers list heart failure and chest pain among possible side effects of the drug and advise caution in known heart failure due to potential risk of exacerbation.

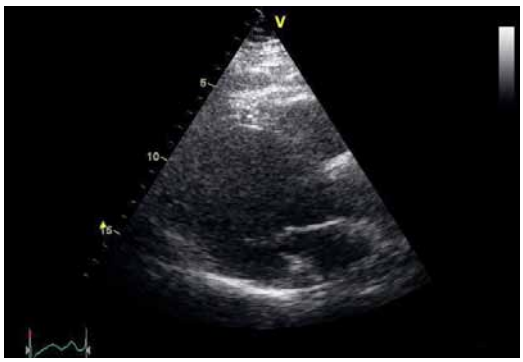

**Figure 1:** Echocardiogram (parasternal view) showing dilated and globally hypokinetic LV.

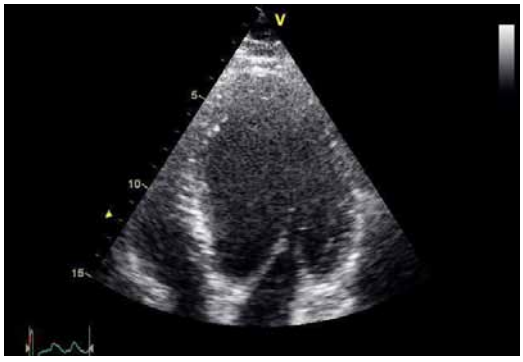

**Figure 2:** Echocardiogram (apical view) showing dilated LV.

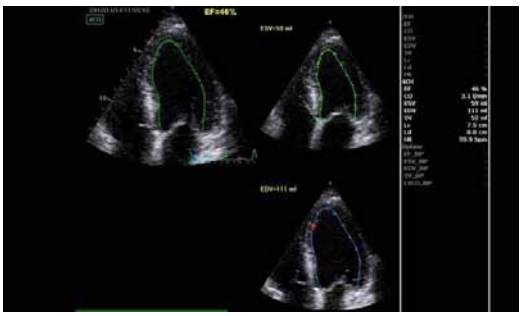

**Figure 3:** Echocardiogram (apical 4-chamber view) after discontinuing etanercept showing non-dilated LV recovery in LV function.

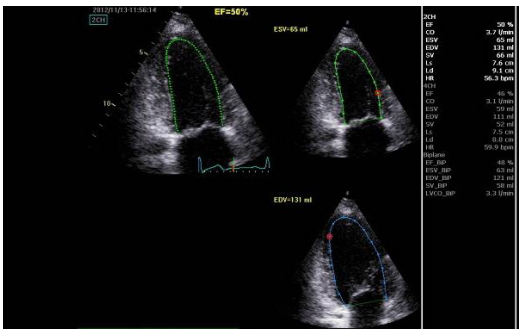

**Figure 4:** Echocardiogram (apical 2-chamber view) after discontinuing etanercept showing recovery in LV function.

Kwon et al. analysed data from the US Medwatch Program [9] looking for adverse effect reports of heart failure in patients being treated with TNF antagonists. They excluded reports that were associated with other potential precipitants of heart failure such as myocardial infarction. A total of 47 patients were highlighted who had developed heart failure after therapy with etanercept or infliximab. Out of these, 29 had received etanercept. 26 had new onset heart failure (12 without coronary risk factors and 14 with risk factors documented) while 3 cases had worsening of already known heart failure. Median time from commencing etanercept to heart failure diagnosis (in patients under 50 years of age) was 8.5 months. There was a similar picture with Infliximab as well.

Similarly, Castro Rocha et al. reported a case of a 42-year-old man with ankylosing spondylitis who developed severe heart failure on etanercept therapy. Discontinuation of the drug led to improvement in cardiac function [10]. Reports of CHF in patients of psoriasis on etanercept are likewise rare [11]. Solomon et al. showed the risk of heart failure was very low [12]. Other investigators also reported similar low risk [13].

Although, the present case does not establish an unequivocal cause-effect relationship between etanercept and heart failure yet the circumstantial evidence is hard to ignore. It can be argued that the patient may have had a pre-existing latent cardiomyopathy due to alternative aetiology including rheumatoid arthritis (very rare), yet the strong temporal relationship between our patient's symptoms and etanercept infusions is highly significant. Furthermore, the patient had near normal exercise tolerance prior to etanercept initiation and had no symptoms consistent with heart failure. Finally, near-complete recovery of cardiac function on discontinuing the drug points towards etanercept as the most likely offending agent. Admittedly, beta-blocker

and ACE-inhibitor therapy contributed to the recovery observed. As voluntary under-reporting of drug adverse effects is relatively common, reported events may represent a smaller percentage of the actual number of such cases. In contrast to previous reports, this was an acute presentation with left ventricular dysfunction and chest pains following etanercept therapy.

It is not entirely clear why TNF antagonists have an adverse effect on the heart. The excellent review by Mann sheds light on this subject [14]. The deleterious cardiac effects of pro-inflammatory cytokines are well known. Although etanercept blocks the biological effects of TNF at the cell-surface receptors (and this is useful therapeutically in inflammatory disease states), yet this cytokine-drug complex also leads to higher levels of TNF in the peripheral circulation. TNF can then dissociate quite rapidly and it is speculated that this higher peripheral bioactivity may adversely affect the cardiomyocytes. In addition, etanercept may also lead to enhanced TNF-mediated effects by a second mechanism. TNF exists as soluble (sTNF) and trans-membrane (tmTNF) forms and these act through two cell-surface receptors R1 and R2. sTNF binds preferentially to R1 while tmTNF has equal affinity for both. TNF-R1 signalling is pro-apoptotic and anti-inflammatory as opposed to TNF-R2 signalling which mediates anti-apoptotic and pro-inflammatory actions. Now, etanercept binds and selectively inactivates sTNF while leaving the tmTNF signalling unaffected. This in turn shifts the balance from TNF-R1 signalling to unopposed tmTNF-R2 signalling leading to anti-apoptotic and pro-inflammatory actions including increased TNF synthesis [15].

Clinicians should be aware of this potential adverse effect of etanercept and should screen for cardiomyopathy both before and after commencing such therapy. This will become increasingly important as therapy with anti-TNF agents becomes more widespread. Any reports of chest pain should prompt complete evaluation with an electrocardiogram (and cardiac enzymes if clinically appropriate). It is also noteworthy that such patients may not necessarily have an abnormal ECG and cardiac enzymes and only echocardiography would pick up asymptomatic left ventricular dysfunction (as in our case). We propose a baseline echocardiogram or BNP / NT-pro BNP before commencing therapy followed by repeat echocardiography or BNP / NT-pro BNP 8 weeks later while ensuring on-going surveillance for any symptoms/signs that may suggest heart failure. Etanercept should only be commenced if LV systolic function is within normal limits (LVEF above 50%) and any clinical suspicion of heart failure should prompt immediate withdrawal of etanercept therapy followed by further cardiological evaluation.

## Conclusion

Heart failure is an infrequent but well-recognized adverse effect of TNF-alpha inhibitor therapy. Patients who need such treatment should be pre-screened and monitored for myocardial dysfunction accordingly. There is a need to incorporate such screening/monitoring /reporting protocols into clinical practice.

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