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ORIGINAL ARTICLE

The incidence of new onset congestive heart failure and heart failure exacerbation in Veteran's Affairs patients receiving tumor necrosis factor alpha antagonists

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Abstract The objective of this study was to evaluate the incidence of new onset or worsening congestive heart failure in Veteran's Affairs (VA) patients who have received infliximab, etanercept, or adalimumab, and to compare mortality rates in these patients to control populations. We enrolled three groups of patients for this retrospective study: TNF-α group ($n = 103$), a rheumatoid arthritis (RA) control group ($n = 100$), and a control group without RA ($n = 100$). All patients at our VA facility who had received at least one dose of the TNF-α antagonists were included in the TNF-α group. Admissions for CHF did not differ between the three groups: TNF-α 7 (6.7%), RA control 8 (8%), non-RA control 7 (7%); $P = 0.940$. Mortality rates were not significantly different: TNF-α 4 (3.8%), RA control 7 (7%), non-RA control 11 (11%); $P = 0.147$. Our study showed no difference between the three groups in either CHF exacerbation or mortality.

Keywords Tumor necrosis factor · Heart failure · Congestive · Rheumatoid arthritis

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Introduction

The tumor necrosis factor (TNF)-α antagonists infliximab (Remicade®), etanercept (Enbrel®), and adalimumab (Humira®) all have proven efficacy in the treatment of rheumatoid arthritis (RA). They exert their effects by neutralizing TNF-α, which has been known to be involved in the pathogenesis of RA. Infliximab has also been approved by the Food and Drug Administration (FDA) for the treatment of Crohn's disease, while etanercept has additional FDA indications for the treatment of psoriatic arthritis, ankylosing spondylitis and juvenile RA. It is known that worsening congestive heart failure (CHF) has been associated with elevated serum levels of TNF-α [1–3]. Accordingly, studies have also been done to determine if TNF-α blockade would be beneficial in patients with class III and IV heart failure. The smaller, pilot studies suggested that these agents may be beneficial to heart failure patients, whereas larger studies showed that TNF-α blockade may worsen CHF [4–7]. Chung et al. [6] demonstrated in the anti-TNF therapy against congestive heart failure trial (ATTACH) that infliximab therapy in patients with NYHA class III and IV heart failure produced no benefit in clinical outcomes after 10 weeks despite a decrease in inflammatory markers. In addition, doses of infliximab were associated with an increased risk of death or hospitalization after 28 weeks. As a result of this study,

the product insert (PI) for Remicade® has listed doses greater than 5 mg/kg as a contraindication in patients with any class of heart failure and all doses are contraindicated in class III/IV heart failure.

In the Research Into Etanercept Cytokine Antagonism in Ventricular Dysfunction (RECOVER) and Randomized Etanercept North American Strategy to Study Antagonism of Cytokines (RENAISSANCE) trials, a combined total of 2,048 patients with NYHA class II–IV were given either etanercept as a 25 mg subcutaneous injection (once, twice, or three times a week) or placebo with a primary endpoint of death or hospitalization. Both studies were terminated early because they failed to meet a prespecified target of benefit [7].

A recent case series was done to evaluate adverse event reports of TNF-α antagonists through the FDA's MedWatch program [8]. The authors reported 47 cases of heart failure associated with TNF-α antagonists. Nine of these patients had a history of heart failure before starting therapy. The other 38 patients were considered to have developed new onset heart failure, and of these 19 (50%) had no identifiable risk factors. There is an additional published case report of a 64-year-old man who died suddenly after a single infusion of infliximab; he had no previous signs or symptoms of heart failure [9]. Further data are needed to fully understand the cardiovascular risk versus benefit of TNF-α antagonistic therapy. To date there have been no studies evaluating this in the Veteran's Affairs (VA) population which has a high prevalence of CHF and risk factors for CHF, making it an ideal group to study this question in. The focus of this study was to retrospectively evaluate the incidence of new onset or worsening heart failure in VA patients who had received infliximab, adalimumab, and/or etanercept.

Materials and methods

This was a single-center, retrospective study at a VA Medical Center in Dallas, Texas. Three groups of patients [TNF-α group ($n = 103$), the RA control group who did not receive TNF-α antagonists ($n = 100$), and the non-RA control group ($n = 100$)] were identified for the study. A RA control group was used because it has been suggested that RA patients have a higher incidence of CHF than the general population [10, 11]. A non-RA control was also identified to make comparisons to the general VA patient populations. All three therapeutic agents were readily available to the Department of Rheumatology and up to the discretion of the clinicians.

Patients were identified for inclusion in the TNF-α group through a retrospective search of pharmacy profiles to include every patient who had received at least one dose of the three TNF-α antagonists (infliximab, adalimumab or etanercept) between 01/01/1999 and 07/31/2003. The RA control and non-RA control groups were identified through a computer generated random number list to select patients from a rheumatology clinic and primary care clinic, respectively. Patients who had received any one of the TNF-α antagonists were excluded from the RA control group and patients with a diagnosis of RA were excluded from the non-RA control group.

All patient charts were reviewed for a documented ICD-9 code for systolic heart failure, signs and symptoms of CHF, including development of shortness of breath, and discharge summaries documenting CHF exacerbations. Risk factors for CHF were ascertained and included smoking history, coronary artery disease, diabetes mellitus, hypertension, and the use of drugs associated with worsening CHF (doxazosin, pioglitazone, rosiglitazone, itraconazole, doxorubicin, and daunorubicin). All cause mortality was also ascertained for each group. These methods were reviewed and approved by our Institutional Review Board.

Baseline characteristics were analyzed using a Pearson chi square analysis for K independent variables or a Fisher's exact test where appropriate. These methods were also employed to determine any difference between the three groups regarding history of CHF, CHF exacerbation, and mortality. Continuous data were analyzed using an ANOVA with a bonferroni correction. All analyses were two sided with an $\alpha = 0.05$. Statistical analyses were analyzed using SPSS software 11.0 for Windows (Chicago, IL).

Results

Baseline characteristics did not differ significantly between the three groups (Table 1). The frequency of the three individual TNF agents is represented in Table 2. There was no difference in the number of CHF admissions between the three groups; TNF = 7, RA control = 8, Non-RA control = 7 ($P = 0.940$). Mortality also did not differ significantly ($P = 0.147$) between the groups (Table 3).

Of the seven patients in the TNF-α group who had a hospital admission for CHF, four were receiving or had received infliximab (5 mg/kg), and three were receiving or had received etanercept. There were no patients in this group who had received adalimumab. Six of these seven patients had a prior history of CHF. The one patient who did not have a prior history had previously received both etanercept and infliximab. This patient

Table 1 Baseline characteristics

Characteristics	TNF-α ($n = 103$)	RA control ($n = 100$)	Non-RA control ($n = 100$)	P value
Age (mean ± SD)	58.7 ± 11.7	67.6 ± 10.2	59.25 ± 13.1	0.725
Males	92	93	86	0.273
Hypertension	58	58	70	0.094
Diabetes	22	18	27	0.301
CAD	20	22	21	0.901
Smokers	30	27	39	0.150
History of CHF	13	14	12	0.911
Dose of infliximab ($n = 28$)				
3 mg/kg	9			
5 mg/kg	18			
10 mg/kg[a]	1			

[a] Used for a Crohn's disease patient

Table 2 Frequency of TNF-α agents

TNF-α agent	Frequency	Mean (± SD) duration of treatment in months	Percent
Infliximab	28	22.0 ± 11	27.2
Etanercept[a]	62	16.3 ± 13.6	60.2
Adalimumab[b]	13	6.3 ± 2.3	12.6
Total	103		

[a] Etanercept 25 mg SC twice a week

[b] Adalimumab 40 mg SC every other week

Table 3 All cause mortality

Group	Number
TNF-α	4
RA control	7
Control	11

$P = 0.147$

developed CHF after 13 infusions of infliximab. None of these exacerbations were associated with any of the previously identified drugs known to be associated with worsening CHF. One patient receiving infliximab had to discontinue therapy due to the development of shortness of breath.

There were four patients in the TNF-α group who died, two had received infliximab (5 mg/kg) and two had received etanercept. One of the infliximab patients died of sepsis secondary to immunosuppression, the other died of a myocardial infarction (40 days after last infusion). The two patients in the etanercept group died of undocumented causes.

Discussion

Our retrospective study showed no difference between the three groups in either CHF exacerbation or mortality. In fact, patients receiving TNF-α antagonists appeared to have a trend towards a lower mortality as compared to the two control groups. However, this was not evident in CHF exacerbations. Our results are in agreement with similar conclusions of a recently published report on heart failure in RA and anti-TNF-α use [11]. This was a retrospective study that evaluated over 13,000 subjects with RA and over 2,500 patients with osteoarthritis (OA) over a 2-year period. The authors reported that CHF was more common in patients with RA than in patients with OA (3.9 and 2.3%, respectively), and that heart failure was less common in patients being treated with TNF-α antagonists (either infliximab or etanercept) than patients on other regimens (3.1 and 3.8%, respectively; $P < 0.05$).

We encountered a wide range of therapy duration in our study (represented in Table 2). However, the reported therapy duration was also wide in the WedWatch report, ranging from 24 h to 20 months prior to the adverse event [8].

As with any retrospective study, there are limitations. Such limitations include inability to control for all factors between the groups and insufficient sample size and follow up time. Though not conclusively proven, it is plausible that the development of CHF or the worsening of CHF may not be a real adverse drug event or may occur at such a low rate that a very large sample size would be needed to detect such a difference. Another limitation of our study is the lack of data from outside facilities that our subjects may have utilized. Ventricular remodeling or shortness of breath could have also gone unnoticed or undocumented in our patient charts. We only looked at ICD 9 codes for systolic heart failure, it is possible that patients that developed shortness of breath only could have been found under other codes. It is important to note that although not statistically significant, the RA patients who had never received a TNF-α antagonist were generally older than those patients in the TNF-α group, and therefore, not an ideal control group when looking at CHF. This could also indicate that TNF-α antagonists are reserved for younger, less frail patients, and

those with fewer risk factors for CHF in our institution, suggesting confounding by indication. The individual TNF-α antagonists were not equally represented in our study, the small number of patients on adalimumab is attributed to the fact that it had not been made available on the market to prescribers as long as the other two agents. Other limitations of this study was the inability to record severity of CHF since it was not consistently documented in those patients with a prior history, and that patients were not contacted for personal interviews, which could have provided further insight to their medical course. However, given the comparative incidence of CHF exacerbations we have reported here, and recent evidence with similar findings, it seems unlikely that appropriately dosed TNF-α antagonists were associated with the development or worsening of CHF.

It is widely speculated that TNF-α plays a role in heart failure progression through induction of other inflammatory cytokines, which cause an inflammatory response in the myocardium, changes in myocyte size and subsequently changes in left ventricular contractility [12–16]. Published trials have shown that as the levels of circulating TNF-α rise, short and long-term prognosis worsens [1, 17, 18]. It is thus intriguing that previous trials with anti-TNF-α in class III and IV heart failure have failed to show the expected benefit. An alternative explanation is that TNF-α and other cytokines may not be as detrimental in CHF as previously thought and may actually play an important role in cardiac homeostasis. [19, 20] Furthermore, some studies have found that TNF-α may induce nitric oxide production and decrease peripheral vascular resistance. [21, 22] Lastly, it has also been proposed that in heart failure, which is associated with a large network of cytokines, TNF-α blockade alone may not be sufficient to show any benefit. [7, 23] Because of conflicting results of clinical trials and the intriguing association between heart failure and inflammatory cytokines, further research with anti-cytokine therapies is warranted.

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