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Tumor necrosis factor- α antagonist use and heart failure in elderly patients with rheumatoid arthritis

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Abstract

Background—Clinical trials have shown that tumor necrosis factor- α antagonists (TNFAs) confer little benefit, and some may cause potential harm in advanced heart failure (HF). Although TNFAs had significant benefits in treating rheumatoid arthritis (RA), little is known whether the drugs pose an increased risk of HF in older patients with RA.

Methods—A cohort study was conducted using data from Medicare and drug benefit programs in 2 states (1994–2004). We identified patients with RA aged ≥ 65 who received TNFA or methotrexate (MTX). The cohort was divided into patients with and without previous HF. We considered demographic variables, cardiovascular risk factors, RA severity-related measures, and other comorbidities. The primary end point was hospitalization with HF. We used stratified Cox proportional hazards regression to estimate the adjusted effect of TNFAs on HF hospitalization.

Results—The cohort consisted of 1,002 TNFA users and 5,593 MTX users. There were 59 HF admissions during 1,680 person-years of TNFA use and 227 HF admissions during 10,623 person-years of MTX use. Comparing TNFA with MTX users, the adjusted hazard ratio for HF hospitalization was 1.70 (95% confidence interval 1.07–2.69). We found similar results in patients with and without previous HF. Among patients with previous HF, the adjusted hazard ratio for death was 4.19 (95% confidence interval 1.48–11.89).

Conclusions—TNFAs may increase the risk of both first hospitalization and exacerbation of HF in elderly patients with RA. The potential for residual confounding in our study cannot be ruled out; larger and more detailed studies are needed to confirm the findings.

Inflammatory mediators such as tumor necrosis factor (TNF)- α play an important role in the pathogenesis of heart failure (HF), contributing to cardiac remodeling and peripheral vascular disturbances.^{1,2} The strong association between elevated TNF- α levels and an increased risk and poor prognosis of HF^{3,4} led to speculation that pharmacologic TNF- α inhibition may be an effective treatment of HF. However, clinical trials found no benefit or potential harm of TNF- α antagonists (TNFAs) on mortality and rehospitalization in patients with symptomatic HF.^{5,6} In response to the results of these studies, a warning for TNFAs about HF was distributed to health care professionals.⁷

TNFAs have significant benefit in treating the pain and functional disability of rheumatoid arthritis (RA) and have been used increasingly in these patients. A few epidemiologic studies have suggested that the risk of HF may be increased in patients with RA as compared with the general population.^{8,9} The increased risk of HF does not seem to be explained by an increase in the prevalence of conventional risk factors for HF among patients with RA, suggesting that the chronic formation of inflammatory cytokines in RA may contribute to myocardial dysfunction.¹⁰ In addition, a few observational studies suggest that the risk of HF may be reduced in patients with RA treated with TNFAs as compared with patients with RA treated with other medications.^{9,11} However, these studies were conducted in relatively young patients with RA, and TNFA might have a differential effect in elderly patients with higher prevalence of cardiovascular comorbidities. Furthermore, little is known about the effect of TNFAs in patients with RA with a previous history of HF. Using a large database with linked pharmacy and health care records, we estimated the risk of HF hospitalization in TNFA users among elderly patients with RA with and without previous HF.

Patients and methods

Study patients and data sources

We conducted a retrospective cohort study pooling health care utilization databases from 2 states: (1) Medicare beneficiaries enrolled in the Pharmaceutical Assistance Contract for the Elderly in Pennsylvania from January 1, 1994, to December 31, 2004; and (2) Medicare beneficiaries enrolled in the Pharmaceutical Assistance to the Aged and Disabled or in Medicaid in the state of New Jersey from January 1, 1994, to December 31, 2004. Both drug benefit programs in Pennsylvania and New Jersey provide comprehensive pharmacy coverage with a small or no copayment. Patients are eligible if their income is greater than the Medicaid annual income threshold, but less than approximately \$35,000, thus including primarily lower middle-class elderly. The linked Medicare/state drug benefit program data provide basic demographic, coded diagnostic, and procedural information as well as pharmacy dispensing information with high accuracy.^{12,13} The Institutional Review Board of the Brigham and Women's Hospital (Boston, MA) approved this study, and data use agreements were established. All potentially traceable personal identifiers were removed from the data before analyses to protect patients' privacy.

In the databases, we identified a cohort of subjects aged ≥ 65 years who had at least one recorded diagnosis of RA and filled at least one prescription of any TNFA or methotrexate (MTX) after the first RA diagnosis during the study period. All patients were required to have at least one filled prescription and at least one clinical service during each of 4 consecutive 6-month periods before the use of disease-modifying antirheumatic drugs (DMARDs) to ensure their eligibility and to assess prior comorbid conditions. Therefore, the earliest observation included in the analyses was January 1, 1996. We then divided the cohort into patients with and without previous HF. Previous HF was defined by the presence of an HF diagnosis at any position in a hospital discharge summary during the 2 years before filling prescription for MTX or TNFA. This definition of prevalent HF was previously shown to have positive predictive value of 97% when compared with physicians' diagnosis of HF in medical records.¹⁴ Patients 'without previous HF' had no HF diagnosis recorded in any hospital discharge summary or outpatient claim during the 2 years before filling prescription for MTX or TNFA. We excluded patients who had a diagnosis of HF in an outpatient file but no HF noted in a hospital discharge summary ($n = 339$).

Study exposure and potential confounders

We defined TNFA exposure as filling at least one prescription of a TNFA (etanercept, infliximab, and adalimumab). We chose MTX users as a comparison group because their RA severity was expected to be more similar to that of TNFA users than other DMARD users. Cohort follow-up started at the first prescription of TNFA or MTX during the study period. Some patients contributed person-time to multiple exposure categories. Patients who were on both TNFA and MTX at the same time were categorized as TNFA users.

Potential confounders were measured during the 24 months before the exposure to TNFA or MTX using diagnosis and procedure codes and/or prescription information in the data, including demographic variables, risk factors for cardiovascular disease, previous HF hospitalizations (shown to predict mortality for HF patients¹⁵), factors associated with severity of RA including use of oral steroids, nonsteroidal anti-inflammatory drug and other DMARDs, and other major comorbid conditions (see Table I for a list of potential confounders).

Study end points

Subjects were censored at (1) the last use of TNFA or MTX, (2) death, (3) end of the study period, or (4) occurrence of HF hospitalization. The last use of TNFA or MTX was defined as the last date of prescription plus the number of days supply by the prescription, plus a 14-day grace period to account for the time lag between filling the prescription and the actual intake of the medication. This censoring criterion was used to test whether TNFA increases the risk of developing/worsening HF assessed as HF hospitalizations while patients are on the drug. HF hospitalization was defined as hospitalization in an acute care facility with HF as the primary diagnosis listed in the discharge summary. This definition of HF hospitalization was shown to have a positive predictive value of 94% when compared to the Framingham criteria of HF.¹⁶

Death from all causes is the most uncontroversial end point for a clinical trial to assess the achievement for therapeutic intervention in patients with HF. In subjects with previous HF, we also assessed deaths as a secondary outcome.

Data analysis

We used Cox proportional hazards regression to estimate the unadjusted and age- and sex-adjusted effects of TNFA on HF hospitalization. The hazard ratios (HRs) adjusted for all possible confounders were calculated from a multivariate Cox proportional hazard model. Patients from 2 states were combined and analyzed in stratified Cox proportional hazard regression allowing different baseline incidence of HF hospitalization between the 2 regions. We first analyzed patients with and without previous HF separately to allow for a potentially differential effect of TNFA between the 2 groups. Then, we combined the 2 groups in a multivariate model to test for an interaction between TNFA and prior HF history. When we did not see the evidence for differential effects, we combined the 2 groups into one cohort and repeated the same analyses.

We then repeated the analyses using propensity score methods.¹⁷ To estimate propensity scores, we also included covariates not included in the final multivariate models; use of cardiovascular and noncardiovascular drugs, health service, and screening procedures. We also conducted sensitivity analyses by restricting TNFA exposure to the period before October 2001, before the Food and Drug Administration (FDA) issued a warning on the use of TNFA in patients with class III or IV HF.⁷ This was done to assess the effect of potential bias due to surveillance (physicians diagnosing HF more readily in TNFA users) and/or bias due to physicians avoiding TNFAs on patients with HF after the warning.

Finally, in our primary analyses, we included prevalent users of TNFA and MTX. In theory, including prevalent users can underestimate the true effect of the exposure by missing events that might have occurred soon after the first exposure and by leaving those who were less susceptible to the events.¹⁸ We also conducted analyses by restricting both TNFA and MTX users to new users (defined by no prior use of TNFA or MTX during 2 years before the index exposure).

Results

Study patients and their characteristics

We identified 5,593 patients with RA who used TNFA and/or MTX. Of 1,002 TNFA users (704 [70%] with etanercept, 298 [30%] with infliximab), 565 (56%) had used MTX previously and 433 (43%) received MTX after TNFA initiation. The characteristics of the study population measured during the 2-year period before exposure to either a TNFA or MTX are shown in Table I. The characteristics of subjects who were originally identified as MTX users but later started on a TNFA were measured twice, once before MTX use and again before TNFA use. The median durations of use in TNFA and MTX users were 1.2 and 1.6 years with 55% and 61% using the drug for >2 years, respectively. TNFA users generally had more severe RA than MTX users, as indicated by the percentage of subjects who had RA surgery, extra-articular manifestations, C-reactive protein (CRP) test ordered, arthrocentesis, and other cytotoxic DMARDs used. The prevalence of cardiovascular comorbidities was slightly but not substantially more frequent in TNFA users. Previous myocardial infarction (MI), hypertension, and other comorbidities except for cancer were more frequent in TNF users. Although there is heterogeneity in the characteristics between those with and without previous HF, there was minimal heterogeneity within the same groups across the 2 states.

Incidence rates of HF hospitalization

Table II shows the number of HF hospitalization, person-years of follow-up, and incidence rate of HF hospitalization in the combined cohort from both states. As expected, the incidence of HF hospitalization is 5 times higher in the group of patients with previous history of HF. In both groups (with and without previous HF), the incidence of HF hospitalization is increased in TNFA users (crude rate ratio of 1.43 for the group without history of HF and 1.39 for the group with previous HF).

Risk of TNFA on HF hospitalization

In the multivariate Cox proportional hazard models after adjusting for potential confounders, we found similarly increased risk of TNFA use on HF hospitalization in patients with and without a history of HF (Table III). In the combined group of patients with and without previous HF, a significant increase was observed in the risk of HF hospitalization in TNFA users (HR 1.70, 95% confidence interval [CI] 1.07–2.69). We also measured prior use of cardiovascular drugs (loop diuretics, potassium-sparing diuretics, thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β -blockers, calcium-channel blockers, and digoxin) and included these factors in the multivariate model. This yielded very similar results to the main analyses and the risk of HF hospitalization among TNFA users of 1.72 (95% CI 1.08–2.74).

Propensity score analyses yielded similar results to the multivariate analyses with a propensity score-adjusted HR for the risk of HF hospitalization among TNFA users of 1.61 (95% CI 1.08–2.39). The 95% CI from the propensity score analyses were somewhat narrower showing the advantage of using propensity score method when the number of outcome was relatively small to the number of potential confounders.

When we restricted the exposure and follow-up to the period before the FDA warning on TNFA and HF, the point estimates for the risk did not change meaningfully, but the 95% CIs became wider due to the smaller number of the exposures and outcomes (Table III). We finally conducted analyses by restricting both TNFA and MTX users to new users. As we expected, we found that the HRs were somewhat larger compared with those from the primary analyses (fully adjusted HR 3.1; 95% CI 1.17–8.23 for patients with previous HF and HR 3.52, 95% CI 1.42–8.73 for those without previous HF).

Risk of death among patients with previous HF

We also assessed the risk of death among patients with previous HF. We observed 22 deaths in TNFA users and 85 deaths in MTX users. After adjusting potential confounders, we found that the TNFA users had a 4.2-fold increase in the risk of death compared with MTX users (95% CI 1.48–11.89).

Sensitivity analyses on unmeasured confounders

One study found that the risk for HF was 2.6-fold in patients with RA with positive rheumatoid factor (RF), whereas the risk was 1.3 for RF-negative patients as compared with the non-RA population. Assuming a 2-fold increase in the risk for HF for RF-positivity⁸ and that the prevalence of RF positivity 75% for MTX users (similar to the general RA population), we calculated the true HR estimating the risk of HF hospitalization for TNFA users compared with MTX users. If we assume that the prevalence of RF-positive patients in TNFA users was about the same as in the general RA population (60%–100%), the corresponding range of HR would be 1.49 to 1.86.

We also conducted analyses to assess how an unmeasured confounder has to be imbalanced and strong to explain the observed risk of TNFA on HF hospitalization (Figure 1). This plot indicates that a highly imbalanced strong confounder ($OR_{EC} > 2$ and RR_{CD} of >3) would be needed to explain the risk of TNFA use observed in this study solely on the basis of unmeasured confounding.

Discussion

We estimated the risk of HF hospitalization among users of TNFA versus MTX in an elderly RA population and found a 70% increase in the risk of HF hospitalization among users of TNFA compared with users of MTX, regardless of history of previous HF. We also found a 4.2-fold increase in the risk of death among patients with previous HF. As suggested by the new user analyses, our main results are likely to underestimate the true risk of TNFA on HF. The strengths of our study include the use of a large data set representing a high-risk elderly population with high prevalence of comorbidities, who are generally underrepresented in clinical trials. The large number of patients was also necessary to identify sufficient numbers of TNFA users and patients in each subgroup. We used an internal comparison group with RA to minimize confounding by indication and compared TNFA users with MTX users because RA severity in patients treated with these drugs is more similar than for those treated with other DMARDs.

Wolfe and Michaud⁹ assessed the rate of HF in 13,171 patients with RA and 2,568 patients with osteoarthritis and found that HF was more common in patients with RA than patients with osteoarthritis. They also found that HF was significantly less common in anti-TNF-treated patients than the nontreated patients with RA, concluding that anti-TNF therapies may ameliorate the risk of HF in RA population.⁹ However, these conclusions were based on patient self-reports with or without validation, and the accuracy of patient-self report of HF diagnosis is unknown. More recently, Bernatsky et al¹¹ conducted a nested case-control

study in 41,885 patients with RA without previous history of HF using 2 North America insurance claims databases. They found a reduced risk of HF hospitalizations in those with current DMARD use (relative risk [RR] 0.7, 95% CI 0.6–0.9), and the reduction was greatest in users of TNFAs (RR 0.5, 95% CI 0.2–0.9). Another study by Cole et al¹⁹ failed to show a significant difference in the risk of developing new-onset or worsening HF among patients using TNFAs, those with RA without use of TNFAs, and those with no RA or TNFA use.¹⁹ However, the incidence was lower in those treated with TNFA.

Our results do not rule out the hypothesis that blocking TNF- α may reduce the risk of HF in younger patients with RA. The apparent discrepancy between our study and previous studies may be explained by the difference in the study population and a possible differential effect of TNF- α in patients with and without cardiovascular conditions. Previous studies examined the effect of TNF- α in much younger populations, most of whom had no history of HF and/or significant cardiovascular comorbidities. In our study, almost 30% of RA patients without a previous history of HF had conditions suggestive of structural heart diseases. One of the hypotheses that could explain these findings is that TNF- α might mediate the process of myocardial dysfunction in early stage but have a protective effect later in the disease.²⁰

The present study has several limitations. First, our findings might be susceptible to bias due to differential detection of HF outcomes because physicians might be more likely to admit patients with suspected HF if the patients are on TNFAs. The bias is likely to be more significant after the FDA's warning on TNFA use in patients with HF in 2001. Therefore, we restricted our analyses before the warning and found no significant difference from the main results. It is also possible that physicians may be more likely to admit patients to a hospital to confirm or rule out diagnosis of HF when patients are on TNFA. However, such rule-out hospitalizations tend to have shorter lengths of stay than the usual hospitalization for exacerbation of HF. When we compared the length of stay for HF hospitalizations between TNFA users and MTX users, we found that the mean length of stay for HF hospitalization was 8.6 for TNFA users and 7.7 for MTX users. The percentage of HF hospitalization with length of stay ≤ 2 days was 2% for TNFA users and 10% for MTX users, suggesting that HF hospitalization in TNF users is no shorter than those in MTX users. Second, our data set does not have precise information on HF. It is possible that severity of HF in patients with RA on TNFAs might differ from that in patients on MTX. However, all patients had a 2-year period to assess their comorbidity including number of previous HF hospitalizations, an independent predictor of mortality in HF patients.¹⁵ Finally, we lacked clinical information on RA severity, and we cannot rule out the potential for residual confounding. However, our sensitivity analyses showed that the expected imbalance of RF factor is unlikely to explain the observed findings and that a single unmeasured factor has to be very imbalanced among TNFA and MTX users and strongly associated with HF hospitalization to make the observed HR (1.7) to be the null. Furthermore, little is known whether other factors characterizing RA activity and severity such as CRP, number of inflamed joints, disease activity score, and functional status are associated with HF. Nonetheless, we chose MTX users for comparison because we expect the severity of RA to be similar in the TNF and MTX groups. We also adjusted for multiple factors related to RA severity in the analyses.

Clinical implication of our results may be better presented using a measure like number needed to harm (NNH). Although our analytic approach does not allow direct estimation of the measure, assuming a constant hazard over time, we could use the crude incidence rate for MTX users as the baseline event rates and calculate rate differences (therefore NNH) using the HR estimated from the Cox model. Using this method, NNH for HF hospitalizations will be approximately 19 for patients with prior HF and 105 for those

without prior HF. For the risk of death, NNH for death will be approximately 5 for patients with prior HF.

Our data indicate that TNFA use may pose a greater risk of HF hospitalization in elderly patients with RA compared with MTX use. TNFAs use may also pose a greater risk of death in those with previous HF. Our analyses likely underestimate the true risk of TNFA on HF as suggested in the new user analysis. However, more precise data with clinical information on RA and HF will be needed to confirm the hypothesis suggested by our findings and to assess the risk-benefit of TNFA in elderly patients with RA.

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Figure 1.

The sensitivity analysis shows how imbalanced a confounding factor needs to be imbalanced and strongly associated with HF hospitalization to account for the observed increased risk for TNFA use solely on the basis of confounding. Each line splits the area into 2: the upper right area represents all parameter combinations of OR_E and RR_{CD} that would create confounding by an unmeasured factor strong enough to move the point estimate of the observed HR ($HR = 1.7$) to the null ($HR = 1.0$) or even lower, that is, make the association go away. Conversely, the area to the lower left represents all parameter combinations that would not be able to move the observed HR to the null. We assumed a prevalence of the confounder of 0.2. (A prevalence of 0.2 for the confounder was chosen because this level minimized the magnitude of the odds ratios needed to elevate the apparent risk.) To elevate the HR of TNFA from 1.0 to the observed value of 1.7, a highly imbalanced factor between TNFA users and MTX that is strongly associated with HF hospitalization has to be unmeasured in our data.

Table I

Characteristics of TNFA or MTX users with age ≥ 65 (Medicare and Pharmacy Assistance Program in Pennsylvania and New Jersey combined; 1996–2004)

	Patients with heart failure (n = 1033)		Patients without HF (n = 4560)	
	TNFA	MTX	TNFA	MTX
Total population (n)	225	808	777	3783
Average follow-up, mean (SD), y	1.6 (1.5)	1.7 (1.9)	1.8 (1.6)	2.5 (2.4)
Demographic				
Age, mean (SD)	73 (6)	77 (7)	72 (6)	74 (6)
Male	11	16	10	11
White	88	92	89	91
RA severity-related covariates				
RA-related surgery	7	4	10	6
Extra-articular manifestations	39	34	28	23
Arthrocentesis	64	53	58	48
CRP order	30	21	31	21
Injection (joint, tendon, etc)	23	12	16	11
Corticosteroids	67	56	59	48
Other cytotoxic DMARDs	24	4	24	5
Noncytotoxic DMARDs	35	22	32	26
COX2 inhibitors	48	26	48	24
Cardiovascular comorbidities				
MI hospitalization	17	15	3	3
Ischemic heart disease	66	63	21	19
Valvular heart disease	45	39	20	16
Cardiomyopathy	18	19	5	5
Cardiac surgery	10	9	1	1
Prior HF hospitalization				
1 hospitalization	13	17	-	-
2 hospitalizations	5	2	-	-
3 hospitalizations	1	1	-	-
Vascular surgery	29	27	12	14
Ventricular arrhythmia/cardiac arrest	2	2	1	0
Atrial fibrillation	39	37	8	8
Other dysrhythmias	24	21	8	6
Intervention for arrhythmia	4	6	1	1
Cerebrovascular diseases	29	34	13	16
Hypertension	92	87	72	70
Other comorbidities				
Hyperlipidemia	64	53	58	46
Diabetes	48	47	31	27
Chronic kidney diseases	33	25	15	10

	Patients with heart failure (n = 1033)		Patients without HF (n = 4560)	
	TNFA	MTX	TNFA	MTX
Dialysis	1	0	0	0
Anemia	64	52	55	47
Hypothyroidism	17	17	12	11
Chronic airway diseases	60	53	34	29
Cancer	22	19	13	14
Anxiety or depression	55	48	43	35

Covariates were assessed during 2 years before exposure to TNF or MTX. Values are expressed as percentage unless otherwise indicated.

Other cytotoxic DMARDs: azathioprine, cyclosporine, and leflunomide.

Noncytotoxic DMARDs: sulfasalazine, hydroxychloroquine, auranofin, gold sodium thiomalate, D-penicillamine, and minocycline.

Table II

Number of HF admissions, person-years, and incidence rate of HF admission in study patients with and without previous history of HF (n = 5593)

	TNFA users			MTX users		
	No. of cases	Person-years	Incidence rate	No. of cases	Person-years	Incidence rate
Patients with previous HF (n = 1033)	33	304	108	101	1333	76
Patients with no HF (n = 4560)	26	1375	19	126	9290	14
2 groups combined	59	1680	35	227	10623	21

Incidence rates are per 1,000 person-years.

Table III

Effects of TNFAs compared to MTX on HF and/or death

	With previous HF (n = 1033)		Without previous HF (n = 4560)		2 groups combined (n = 5876)			
	HR	95% CI	HR	95% CI	HR	95% CI		
Unadjusted*	1.33	0.79	2.26	1.67	3.01	1.73	1.19	2.51
Sex, age, and race adjusted [†]	1.36	0.80	2.33	1.78	3.26	1.91	1.31	2.80
Fully adjusted [‡]	1.75	0.86	3.56	2.07	4.25	1.70	1.07	2.69
Fully adjusted [‡] with follow-up ending October 2001 (n = 3671)	1.50	0.41	4.79	3.41	16.05	1.61	0.75	3.49

* Stratified Cox proportional hazard model by year of exposure and state with study time as a time scale.

[†] Above plus age, sex, and race in the model.

[‡] Above plus cardiovascular comorbidities (history of MI, other coronary artery disease, atrial fibrillation, ventricular arrhythmia, valvular heart disease, cerebrovascular disease, peripheral vascular disease, hypertension, history of cardiac, and vascular surgery), RA severity-related measures (RA-related surgery, extra-articular manifestations, use of other DMARD and nonsteroidal anti-inflammatory drug, arthrocentesis, intra-articular injection, CRP order, erythrocyte sedimentation rate order), number of previous HF hospitalization, and other comorbidities (chronic kidney disease, chronic airway disease, diabetes, hyperlipidemia, cancer, depression/anxiety, hypothyroidism, osteoporosis, acute infections, and anemia).