Treatment with Tumor Necrosis Factor Blockers Is Associated with a Lower Incidence of First Cardiovascular Events in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To investigate the risk of cardiovascular disease (CVD) in patients with rheumatoid arthritis (RA) treated with tumor necrosis factor (TNF) inhibitors, compared to a standard RA population.
Methods. Patients were recruited from a regional register, which includes over 90% of patients with RA started on TNF blockers in 1999 or later, and a local community based cohort of RA patients, established in 1997. Of a total of 983 patients in the combined cohort, 531 received treatment with etanercept or infliximab during the study period. The total cohort (n = 983) was linked with national registers for inpatient care and cause of death through December 31, 2001. CVD was defined as the first inpatient care or death from CVD without inpatient care for CVD prior to study entry. First CVD events in those treated versus not treated with TNF blockers were estimated, using age and sex adjusted incidence density computations with treatment and disease severity markers as time-dependent covariates.
Results. In the anti-TNF-treated patients, the age-sex adjusted incidence rate of first CVD event was 14.0/1000 person-years at risk (95% CI 5.7–22.4), compared with 35.4/1000 person-years (95% CI 16.5–54.4) in those not treated. Controlling for disability, the age-sex adjusted rate ratio was 0.46 (95% CI 0.25–0.85, p = 0.013) in anti-TNF-treated versus not treated.
Conclusion. These findings suggest that the risk of developing CVD is lower in patients with RA treated with TNF blockers. This is compatible with the hypothesis that inflammation contributes to the development of cardiovascular events. (J Rheumatol 2005;32:1213–8)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
TUMOR NECROSIS FACTOR
CARDIOVASCULAR DISEASE
TREATMENT

Rheumatoid arthritis (RA) is a chronic inflammatory disease resulting in substantial disability and also an increased mortality compared to the general population[1]. The major cause of excess mortality in patients with RA is cardiovascular disease (CVD)[2,3], and recently several studies have also reported an increased cardiovascular morbidity in RA[4,5]. The mechanisms underlying this increased comorbidity have not been defined in detail, but it is clear from other studies that vulnerable atherosclerotic plaques are histologically characterized by inflammatory infiltrates[6], and it has been postulated that this may play a role in plaque rupture[6]. The importance of inflammatory mechanisms for the development of vascular events is further supported by findings of circulating markers of inflammation as major predictors of CVD events[7,8].

Tumor necrosis factor-α (TNF-α) is an important proinflammatory cytokine, abundantly expressed in synovitis in patients with RA[9] as well as in atherosclerotic lesions[10]. Randomized controlled trials with the TNF-α blockers etanercept[11] and infliximab[12] have shown efficacy in reducing inflammation and joint destruction in RA. On the other hand there have been concerns about potential side effects, including comorbidities. Given the observed worsening of a subgroup of patients with severe congestive heart failure (CHF) in clinical trials with infliximab[13], the onset of heart failure in some RA patients treated with TNF inhibitors has been interpreted as a possible negative effect of these drugs on CHF and CVD in patients with RA[14].

Our aim was to estimate the relative risk for first CVD events in patients with RA treated with anti-TNF therapy compared to untreated patients, with adjustment for disease related confounders. We also compared these rates of CVD events to that of the background population.

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Supported by Lund University and the Swedish Rheumatism Association.

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Accepted for publication February 3, 2005.

MATERIALS AND METHODS

Study design. Our study was based on estimation of CVD risk in a community based register of patients treated with TNF blockers and in a community based comparison cohort of patients within the same geographical area, who largely were at risk during the 2 years before the introduction of anti-TNF therapy. In these analyses the 2 cohorts were treated as one, and the effect of TNF blockers was evaluated in a time-dependent fashion; that is, if subjects changed from one stratum to another [for example, not anti-TNF-treated to TNF-treated or one Health Assessment Questionnaire (HAQ) level to another] during the course of the study, the person-years of risk were computed within the appropriate category. Information on events was obtained from national registers for this combined cohort as well as for the background population in Malmö, Sweden. The study was approved by the ethics committee at the Medical Faculty at Lund University.

The case cohort. The South Swedish Arthritis Treatment Group (SSATG) register has been described[15]. The catchment area for the register is about 1,300,000 inhabitants. The SSATG register includes RA patients treated with leflunomide, anti-TNF drugs, anti-interleukin 1, and other new disease modifying antirheumatic drugs (DMARD) at rheumatology units. A total of 8 rheumatology centers report to the SSATG, of which 6 are in the Skåne region in southern Sweden (1,100,000 inhabitants). The register has been compared to pharmaceutical sales data and found to cover over 90% of anti-TNF treated patients in the area (P. Geborek, unpublished results). Patients with RA according to a rheumatologist who were treated with etanercept or infliximab and included in the SSATG register between February 1, 1999, and December 31, 2001, and with no previous hospital discharge due to CVD according to the event definition used in the study (see below), were identified and included in our analyses (n = 531). Patient and disease characteristics including age, sex, disease duration, HAQ score[16], visual analog scale (VAS) result for patient global assessment of disease severity (VAS global assessment) and pain (VAS pain), and data on previous DMARD medication had been registered at inclusion and were retrieved from the register for this analysis. Followup of these patients began when anti-TNF treatment was first initiated (after February 1, 1999).

Comparison cohort. In 1997, a register of all known patients with RA in Malmö (the major city of Skåne region) was established. Inclusion was based on a clinical diagnosis of RA by a rheumatologist and fulfillment of the 1987 American College of Rheumatology criteria for RA[17]. Patients were recruited from the rheumatology outpatient clinic of Malmö University Hospital, which is the only hospital serving the city, and from the 4 rheumatologists in private practice in Malmö[18]. Subsequent surveys using the diagnostic index of primary care centers and questionnaires sent to other physicians in the area indicate that > 90% of all patients with diagnosed RA in the city have been seen by a rheumatologist and thus are included in the register[18]. In the 1997 survey, a total of 1016 patients with RA were identified, corresponding to a prevalence of patients with RA currently under active care of 0.49% in the adult population — close to a recent prevalence estimate from Oslo, Norway[19]. In July 1997 these patients were sent a questionnaire, which was answered by 70% (n = 730), of whom 543 later were found to have had no previous hospital discharge due to CVD according to the event definition used in the study (see below). The questionnaire was used to obtain data on time of onset of RA, present and previous treatment with DMARD and prednisolone, HAQ, VAS global, and VAS pain. Followup of this subset began July 1, 1997.

Event definition and statistical analysis. Data on cardiovascular events were retrieved from the Swedish National Hospital Discharge Register and the Causes of Death Register[20,21]. These registers are both administered by the Swedish National Board of Health and Welfare. The hospital discharge register is based on reports from local registers and has nationwide coverage from 1987. It includes information on age, sex, and place of residence for each individual, as well as the time of hospitalization and discharge, and discharge diagnoses classified according to the *International Classification of Diseases*, 9th and 10th Revision (ICD-9, ICD-10)[22,23] for each inpatient episode. The proportion of hospital discharges not reported to the register has been estimated to be 1–2%[21]. In evaluations of the accuracy of registered diagnoses conducted in 1987 and 1995, 86% of episodes classified as being due to acute myocardial infarction (MI) fulfilled predefined criteria for definite acute MI, whereas 9% were considered to have had possible acute MI[21]. The Causes of Death Register is based on compulsory reporting of underlying and contributing causes of death, and contains information on age, sex, place of residence, and date of death. In 1996, the register was estimated to include data on 99.42% of all deaths[20]. Validation studies of death certification for MI have reported confirmation rates of 92–96%[24].

Data on all hospital episodes with a registered diagnosis of CVD (ICD-9 401-448, ICD-10 I110-I798) were collected between 1987 (start of the Hospital Discharge Register) and the close of the study (December 31, 2001). An event was defined as the first (since 1987) discharge or death without such previous discharge during the study period, due to CVD defined by these ICD codes. Using the same Hospital Discharge Register, comorbidity in diabetes or chronic obstructive pulmonary disease (COPD) was defined as previous inpatient care for any of these diagnoses after 1987.

From the same sources, and using the same event definition, events during the study period were identified for residents of Malmö and used for computations of the standard morbidity ratios (SMR) for those treated and not treated with TNF blockers.

The age range was restricted to age 20 through 79 years, due to the low number of person-years at risk over the age of 80 in patients exposed to anti-TNF treatment. Age-adjusted mortality rates[25] and age-adjusted mortality rate ratios[26] with 95% confidence intervals[27] were computed as described. For those in the comparison cohort the period of risk began at the time of the response to the questionnaire (July 1, 1997) and for those in the case cohort as they started taking etanercept or infliximab for the first time (after February 1, 1999, when these drugs became available in Sweden) and were included in the SSATG register. Subjects were followed at the occurrence of a CVD event until death, or the close of the study (December 31, 2001), whichever occurred first. Stratified incidence data were used for these computations. Age group, sex, exposure to anti-TNF treatment (yes or no), markers of disease severity (disease duration, HAQ, VAS pain, VAS patient global assessment), number of DMARD (all dichotomized by their median value), present prednisolone treatment (yes or no), and presence of diabetes or COPD were then used as covariates in a time-dependent manner. That is, if subjects changed from one stratum to another during the course of the study, patient-years were computed within the appropriate category. Of the total 983 patients with RA (Table 1) in the combined cohort, 531 were part of the SSATG cohort and 543 part of the comparison cohort. Thus, 91 patients from Malmö were started on anti-TNF treatment and included in the SSATG. These were included in both cohorts and contributed with person-years at risk to both those exposed and those not exposed to anti-TNF treatment.

RESULTS

The median age, sex distribution, and disease characteristics for the whole unified cohort are given in Table 1. In addition, similar information is given for those exposed and not exposed to anti-TNF therapy, as they first started their followup in the respective groups (Table 1). Patients treated with anti-TNF drugs tended to have higher markers of disease severity and a more extensive history of treatment with DMARD and prednisolone. Comorbidities (COPD or diabetes) tended to be more frequent in the anti-TNF-treated group. Of the markers for disease severity, the level of disability (HAQ), patient's assessment of disease severity (VAS global assessment), and the total number of previous and present DMARD used all were significant predictors of CVD events (Table 2).

Table 1. Patient characteristics at study entry for all subjects and when first entering as exposed to anti-TNF and not exposed. After inclusion, subjects (n = 91) were allowed to change exposure group depending on actual present exposure to anti-TNF treatment. These 91 subjects contribute with person-years at risk as both exposed and not exposed to treatment (see Materials and Methods). All values are median (interquartile range) unless otherwise stated.

	All, n = 983	At First Entry to Study	
		Anti-TNF Exposed, n = 531	Not Anti-TNF Exposed, n = 543
Age, yrs	58 (49–68)	55 (46–63)	61 (51–69)
Female, n (%)	747 (76)	415 (78)	409 (75)
HAQ, score limit 0–3	1.25 (0.75–1.75)	1.50 (1.13–1.88)	1.13 (0.50–1.63)
VAS patient global assessment	53 (31.5–74)	69 (50–80)	48 (25–70)
VAS pain	56 (31.5–75)	67 (51–81)	50 (24–72)
Disease duration, yrs	11 (5–20)	12 (6–20)	11 (5–21)
Present prednisolone treatment, n (%)	473 (48)	398 (75)	117 (22)
Previous DMARD treatment, no. of drugs	2 (1–4)	4 (2–5)	2 (1–4)
Comorbidity (COPD/diabetes), n (%)	45 (4.6)	31 (5.8)	19 (3.5)

HAQ: Health Assessment Questionnaire, VAS: visual analog scale, DMARD: disease modifying antirheumatic drug, COPD: chronic obstructive pulmonary disease.

Table 2. Relative risk (RR) for cardiovascular disease events for different markers of disease severity and comorbidities adjusted for age and sex.

Disease Severity Marker	RR (95% CI)	p
HAQ* (≥ 1.38 vs < 1.38)	2.06 (1.36–3.13)	< 0.001
VAS patient global assessment* (≥ 52 vs < 52)	1.65 (1.1–2.45)	0.012
Previous DMARD treatment (no. of drugs; ≥ 3 vs < 3)	1.76 (1.18–2.63)	0.0054
Presently taking prednisolone (yes vs no)	1.11 (0.74–1.67)	0.616
Disease duration* (≥ 12 vs < 12 yrs)	1.11 (0.74–1.66)	0.618
Comorbidity (COPD/diabetes; present vs absent)	1.56 (0.69–3.52)	0.281

*Stratified by median value. HAQ: Health Assessment Questionnaire, VAS: visual analog scale, DMARD: disease modifying antirheumatic drug, COPD: chronic obstructive pulmonary disease.

There was a total of 13 events in those exposed to anti-TNF treatment (acute MI, n = 6; cerebrovascular disease, n = 4; other, n = 3) in 656 person-years at risk; and in the unexposed there were 85 events (acute MI, n = 33; cerebrovascular disease, n = 15; CHF, n = 12; ruptured aortic aneurysm, n = 2; other, n = 23) in 2056 patient-years. The age-sex adjusted incidence rates were 14 and 35.4 events per 1000 patient-years, respectively, corresponding to a relative risk (RR) of 0.62 (95% CI 0.34–1.12, p = 0.111; Table 3).

Adjusting the age-sex adjusted RR in those treated compared to those not treated further, using one marker of disease severity at a time, revealed significant risk reduction in those treated, ranging from 0.4 to 0.6 (Table 4). Computing the SMR for those treated and not treated with TNF blockers (Figure 1) revealed a significantly increased risk of new onset CVD in those not treated with TNF blockers in relation to the background population of Malmö (SMR = 228, 95% CI 179–277). In those treated, the risk of new CVD was lower, as shown, with confidence intervals enclosing unity with the background population (SMR = 157, 95% CI 72–242).

Since the observation periods of those exposed and not exposed to anti-TNF therapy do not completely overlap in calendar time, the age-sex adjusted relative risk was also computed for the period when such overlap did occur. The risk reduction for the anti-TNF-treated patients was 0.48 for the period February 1, 1999, to June 30, 2000, and 0.32 for the period July 1, 2000, to December 31, 2001.

Since the followup was longer in those not treated with TNF blockers, we also restricted the followup time in the 2 groups to 1 and 2 years, respectively, resulting in relative risks for CVD events in those treated of 0.35 (95% CI 0.15–0.83) and 0.34 (95% CI 0.17–0.65), respectively.

Similar point estimates were obtained when excluding vascular pulmonary disease and CHF from the event definition (RR = 0.50, 95% CI 0.27–0.95, for TNF vs not TNF-treated, adjusting for age, sex, and HAQ), although 95% CI overall were wider.

There were 3 deaths (2 CVD, one lymphoma) in the anti-TNF-treated group, and 29 deaths (12 CVD) in those not treated. Non-CVD causes of death in those not TNF-treated included malignancy (n = 7), suicide (n = 3), RA related (n = 4), and one each of liver cirrhosis, Alzheimer's disease, and infection.

Table 3. Age and sex-specific and adjusted incidence rates for cardiovascular disease events by anti-TNF treatment.

	Anti-TNF Treatment			
	Yes		No	
	Events	Person-yrs	Events	Person-yrs
Men, age group				
20–39	0	13.1	1	19.4
40–49	0	14.7	0	54.2
50–59	2	58.1	4	126.7
60–69	1	43.5	9	176.9
70–79	0	11.4	12	137.3
Women, age group				
20–39	0	89.9	1	136.4
40–49	1	102.1	1	235.6
50–59	3	165	14	402.8
60–69	3	97.5	19	406.5
70–79	3	60.5	24	370.9
Total	13	655.6	85	2066.7
Age-sex adjusted incidence/1000 person-yrs at risk (95% CI)	14.0 (5.7–22.4)		35.4 (16.5–54.4)	

Table 4. Relative risk (RR) for cardiovascular disease events in the whole combined cohort by anti-TNF treatment, adjusting for age, sex, and one marker of disease severity at a time.

Confounder Adjusted for	RR (95% CI)	p
HAQ* (≥ 1.38 vs < 1.38)	0.46 (0.25–0.85)	0.013
VAS patient global assessment* (≥ 52 vs < 52)	0.46 (0.24–0.87)	0.017
Previous DMARD treatment (no. of drugs; ≥ 3 vs < 3)	0.43 (0.24–0.77)	0.005
Presently taking prednisolone (yes vs no)	0.47 (0.25–0.89)	0.020
Disease duration* (≥ 12 vs < 12 yrs)	0.61 (0.34–1.08)	0.091
Comorbidity (COPD/diabetes; present vs absent)	0.60 (0.33–1.10)	0.097

*Stratified by median value. HAQ: Health Assessment Questionnaire, VAS: visual analog scale, DMARD: disease modifying antirheumatic drug, COPD: chronic obstructive pulmonary disease.

DISCUSSION

We found a decreased incidence and relative risk for the development of severe first-time CVD event when controlling for disease severity in patients with RA treated with TNF-blocking therapy. To our knowledge this is the first study evaluating the effect of TNF blockers on CVD events.

Premature mortality in RA occurs particularly in patients with severe extraarticular disease manifestations[1,28], and it has been shown that severe extraarticular RA[29] and persistently high disease activity[30] predispose to ischemic heart disease in patients with RA. In accord with this, we found increased disability and disease severity to be predictive of CVD in our study. Further, we observed that patients starting anti-TNF therapy had a more severe disease and higher level of disease activity compared to a community RA population. It is conceivable that patients who start anti-TNF treatment, who usually have severe, refractory disease, are at a higher baseline risk of developing CVD. We suggest that the excess risk of CVD in such patients is reduced by aggressive antirheumatic therapy. This is also supported by the findings of Choi and coworkers, who reported that treatment with methotrexate for RA was associated with a reduced risk of cardiovascular mortality in a large observational study[31]. Contradictory results have been published by other investigators[32], but response to methotrexate seems to be associated with improved survival[33].

The mechanisms underlying vascular damage in RA are beginning to be characterized. CD4+ CD28-null T cells with cytotoxic capabilities have been found to be clonally expanded in peripheral blood in patients with RA[34] and in unstable angina[35,36], but not in stable angina[35]. The emergence of the CD4+ CD28-null T cell phenotype has been shown to be facilitated by TNF *in vitro*[37]. These and other immunopathologic mechanisms in RA may be involved in the development of acute coronary syndromes, and could be downregulated by blocking TNF. Our results underline the importance of further study of the role of proinflammatory cytokines in CVD.

Major strengths of our study include the completeness of the register of patients treated with TNF blockers in the catchment area as well as of the comparison cohort. They can both be considered community based, and thus largely

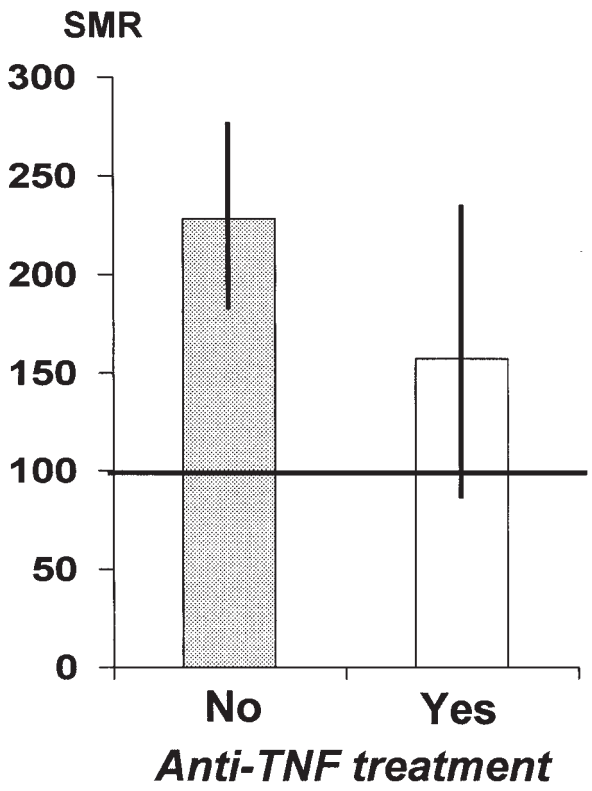

Figure 1. Standardized morbidity ratios (SMR) for those treated and not treated with TNF blockers, using the population of Malmö as the standard population.

represent estimates in the whole population of patients with RA. Further, the risk of recall or information bias was minimized as the exposure information was recorded prior to the occurrence of the outcome, as part of a structured process.

One limitation of the study is the sample size, which does not allow subgrouping of individual CVD events. It is possible that TNF inhibitors may have a differential effect on arterial thromboembolic events and CHF. In a study of infliximab for severe CHF, mortality was increased in patients treated with high dose infliximab (10 mg/kg)[13]. On the other hand, no increased mortality was seen in the 2 larger clinical trials that evaluated etanercept as treatment for severe to moderate CHF[38]. Data on CHF in RA are scarce, but in a recent observational study, the prevalence of CHF was lower in patients with RA treated with TNF blockers compared to non-TNF-treated patients[39]. In our study, exclusion of CHF from the event definition did not change the point estimates for relative risks.

Confounding by indication or channeling could affect results of this study, if patients with prevalent CVD at baseline were less likely to be treated with TNF blockers. However, as we excluded patients with registered CVD events between 1987 and study entry, the study was mainly limited to new-onset CVD. This decreases the likelihood that differences in baseline CVD risk would explain the results. As well, the severity (indicated by previous DMARD therapy and HAQ) and activity (patients' global assessment and HAQ) of the RA disease as well as the frequency of diabetes and COPD comorbidity all tended to be higher in those starting anti-TNF therapy. Statistical adjustment for these confounders somewhat strengthened the protective effect of anti-TNF therapy on CVD events.

Another limitation is the lack of information regarding exposure to traditional risk factors for CVD such as smoking, hyperlipidemia, and hypertension. Some of these possible confounders such as smoking[40] and insulin resistance[41] are clearly associated with severe RA, and would thus be expected to be overrepresented in the anti-TNF-treated patients. Confounding by smoking or insulin resistance would thus result in an underestimation of the protective effect of TNF blockers. It is, however, not possible to retrospectively establish if such factors were ever evaluated by the treating physicians, and how they affected the decision to initiate anti-TNF treatment.

Our investigation supports previous studies describing an increased risk for cardiovascular disease in patients with RA. Our data suggest that overall treatment with TNF blockers in RA is safe from a cardiovascular point of view, and appears to have a protective effect against CVD. These findings are also compatible with the hypothesis that inflammation is an important pathogenetic factor in the development of CVD events.

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