ORIGINAL ARTICLES

Tumor necrosis factor-α blockade, cardiovascular outcomes, and survival in rheumatoid arthritis

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The effect of TNF-α blockade on the risk of cardiovascular outcomes and long-term survival in patients with rheumatoid arthritis (RA) is not known. We assembled a cohort of 20,811 (75,329 person-years) U.S. veterans who were diagnosed with RA between October 1998 and September 2005, and who were treated with a disease-modifying anti-rheumatic drug (DMARD). Cox survival models were built to examine the effect of TNF-α antagonists on the risk of a composite endpoint of cardiovascular outcomes defined as the occurrence of atherosclerotic heart disease, congestive heart failure, peripheral artery disease, or cerebrovascular disease, and on the risk of death. Treatment with TNF-α antagonists was not associated with a significant effect on the composite endpoint of cardiovascular outcomes. When each outcome was examined separately, the use TNF-α antagonists was not associated with an increased risk of atherosclerotic heart disease, congestive heart failure, or peripheral artery disease, but it was associated with decreased risk of cerebrovascular disease (hazard ratio (HR) = 0.83; confidence interval (CI) = 0.70–0.98). The use of TNF-α antagonists did not affect the risk of death (HR = 0.99; CI = 0.87–1.14). In subgroup analyses, the use TNF-α antagonists was associated with a reduced risk of cardiovascular outcomes (HR = 0.90, CI = 0.83–0.98) in patients younger than the median age of our cohort (63 years). The use TNF-α antagonists was not associated with a change in the risk of death in any other subgroup. These results show that the risk of cardiovascular events and survival in patients who receive TNF-α antagonists is not different than those who receive other DMARDs. (Translational Research 2011;157:10–18)

Abbreviations: BIRLS = Beneficiary Identification and Records Locator Subsystem; CPT = current procedural terminology; DMARD = disease-modifying anti-rheumatic drug; PBM = Pharmacy Benefits Management; RA = rheumatoid arthritis; TNF-α = tumor necrosis factor-α; VA = Veterans Administration

Rheumatoid arthritis (RA) is a chronic inflammatory disease that causes disability, deformity, and increased cardiovascular morbidity and mortality. Patients with RA have increased serum levels of tumor necrosis factor (TNF)-α. These patients have been traditionally treated with anti-inflammatory medications as well as disease modifying anti-rheumatic drugs (DMARDs). These drugs help to prevent the

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Supported by a Department of Veterans Affairs (VISN 15) Career Development Award (to Z. A.A.).

Submitted for publication August 2, 2010; revision submitted September 21, 2010; accepted for publication September 22, 2010.

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1931-5244/$ - see front matter

Published by Mosby, Inc.

doi:10.1016/j.trsl.2010.09.005

AT A GLANCE COMMENTARY

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Background

Animal studies suggest that TNF-α plays a pivotal role in chronic inflammation-associated disturbances in glucose and insulin metabolism, lipid homeostasis, endothelial dysfunction, and accelerated atherosclerosis. Gain-of-function and loss-of-function experiments support a major role for TNF-α in vascular calcification, a vascular condition that is associated with an increased risk of death in humans.

Translational Significance

The effect of TNF-α blockade on cardiovascular outcomes and survival is not clear. This study builds on the findings in the basic science literature and examines the effect of TNF-α blockade on cardiovascular outcomes and death in humans.

disability and deformity associated with RA. Since 1998, several new biologic DMARDs have been approved by the Federal Drug Administration for the treatment of RA. Three of these, which include etanercept, infliximab, and adalimumab, work by antagonizing TNF-α. Several controlled clinical trials have unequivocally established the effectiveness of these agents in slowing the clinical and radiographic progression in RA.[1,2]

Chronic inflammatory conditions are associated with increased cardiovascular morbidity and mortality.[3,4] Traditional risk factors such as hypertension, diabetes mellitus, hyperlipidemia, obesity, and smoking do not fully explain the increased morbidity and mortality in this patient population. Recent evidence suggests that this gap between the expected and observed cardiovascular morbidity, as well as cardiovascular and all-cause mortality, may be explained by chronic inflammation.[4-6] Chronic inflammation is now recognized as a novel nontraditional risk factor for cardiovascular morbidity and mortality.

The chronic inflammatory state in RA is characterized by increased levels of pro-inflammatory cytokines such as TNF-α.[7] Animal studies and some data from human studies suggest that TNF-α plays a pivotal role in chronic inflammation-associated disturbances in glucose and insulin metabolism, lipid homeostasis, endothelial dysfunction, and accelerated atherosclerosis.[7,8] All of these factors are recognized as contributors to vascular injury. Furthermore, evidence from the epidemiologic literature suggests that blockade of TNF-α may ameliorate cardiovascular morbidity and mortality in patients with chronic inflammatory conditions.[3,8,9] However, beyond its role in RA, TNF-α has numerous other pleiotropic effects.[7,10] TNF-α levels correlate with increased aortic pulse velocity in RA patients, and anti-TNF-α therapy in patients with RA has been shown to reduce aortic stiffness to a level comparable with that of healthy individuals.[9] Similarly, studies have shown that measures of vascular endothelial function improved with anti–TNF-α treatment.[11] TNF-α might also contribute to the dysregulated coagulation system in patients with RA.[9]

Although the pleiotropic effects of TNF-α noted previously could improve survival, multiple studies have shown an increased risk of infection, congestive heart failure, and malignancies in RA patients treated with TNF-α antagonists. As a result of these competing effects of TNF-α on cardiovascular outcomes and survival, it is unknown whether TNF-α blockade has any significant effect on long-term survival.[12] The clinical trials demonstrating the safety and efficacy of these biologic agents have a short follow-up time that does not allow the detection of any significant effect on long-term outcomes such as cardiovascular events or all-cause mortality.[11,12] The Department of Veterans Affairs national health care databases provide an ideal opportunity to investigate the associations between medication use and long-term outcomes.[13] Our objective in this work is to examine the effect of TNF-α blockade on cardiovascular outcomes and long-term survival in U.S. veterans with RA.

PATIENTS AND METHODS

Study population. We built a cohort of 20,811 U.S. veterans who were diagnosed with RA between October 1998 and September 2005. Patients were included in the cohort if they had an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code for RA during the study period and who, after ≥4-month history of receiving medications from the Veterans Administration (VA) during the study period, subsequently received a first prescription of DMARD. Prior experience demonstrates that combining the RA diagnosis with DMARD results in a cohort of patients with a greater than 90% chance of having RA.[14] Additional inclusion criteria required that patients (1) have age and sex recorded and (2) have at least 2 separate outpatient or inpatient clinical encounters during the study period. These criteria will ensure that included subjects have significant contact with the VA health care system and are new DMARD recipients, thus lending validity to time zero in the survival analyses.