REVIEW ARTICLE

Relationship between Tumor Necrosis Factor-α Inhibitors and Cardiovascular Disease in Psoriasis: A Review

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Abstract

Psoriasis, a cutaneous disease that is increasingly recognized as a systemic inflammatory process, is associated with an increased risk for the development of cardiovascular disease. Although use of tumor necrosis factor-α inhibitors for the treatment of psoriasis has also been associated with decreased incidence of major adverse cardiac events, the precise mechanism by which these agents lower cardiovascular risk remains uncertain. Speculated mechanisms include the suppression of systemic inflammation or improvement of cardiovascular risk factors. Here we review the evidence in support of the beneficial effects of tumor necrosis factor-α inhibitors on cardiovascular health. Larger, future studies of patients treated with biologic agents will provide data to more definitively quantify the risk reduction of these agents on major adverse cardiac events.

Introduction

Psoriasis is one of the most prevalent chronic inflammatory diseases, affecting approximately 2% or 3% of the population and more than 125 million patients worldwide.[1,2] Study findings have linked autoimmune diseases, including rheumatoid arthritis (RA) and psoriasis, with chronic systemic inflammation and a subsequent increase in cardiovascular risk.[3-7] Psoriatic arthritis, which has a prevalence rate of 7% to 26%[8,9] in patients with psoriasis, shows an elevated cardiovascular risk similar to that experienced by patients with RA.[10] It follows that anti-inflammatory treatment may theoretically reduce the incidence of cardiovascular risk factors and thus ultimately reduce patients' eventual risk of cardiovascular disease-related mortality.[11,12]

However, the degree to which psoriasis, with its wide range of severity, is associated with major adverse cardiac events (a composite endpoint of myocardial infarction (MI), stroke, or cardiovascular death) has not been well defined. A case-control study of 3600 patients with severe psoriasis and 14,300 healthy subjects demonstrated a 53% increased incidence of major adverse cardiac events in the presence of severe psoriasis.[13] A diagnosis of severe psoriasis was shown to confer an additional 6.2% 10-year risk of major adverse cardiac events.[13] A limitation of this study was the focus on only severe psoriasis. Equivalent data about cardiovascular mortality in patients with mild psoriasis were not available at that time. Previous work has suggested only modest increased risk of cardiovascular events, including MI and stroke, in patients with mild psoriasis.[14-16] Therefore, the 10-year risk of major adverse cardiac events attributed to mild psoriasis was anticipated to be small and unlikely to meaningfully affect 10-year risk estimates in the setting of severe disease.[14,16]

The effects of tumor necrosis factor (TNF)-α inhibitors on cardiovascular disease are potentially multifaceted because these drugs may promote heart failure and decrease heart compliance while controlling inflammation and decreasing risk for plaque formation.[17] Because these agents were approved by the US Food and Drug Administration to treat rheumatologic diseases as a first indication, the safety data from most TNF-α inhibitors originate from clinical trials in rheumatology. Infliximab has been shown to improve endothelial function, specifically flow-mediated vasodilation, in RA after 12 weeks of therapy.[18] However, values returned to baseline 4 weeks after the infusion in patients followed for 1 year.[19] In addition to providing at least a temporary improvement in endothelial cell function during treatment, infliximab also induces a transient increase in flow-mediated dilation.[20] The beneficial effect of drug-induced dilation is countered by its association with vasoconstriction, increased wall shear stress, and deleterious effects on high-density lipoprotein.[20] Despite these mixed effects on vessel wall remodeling, TNF-α inhibitor therapy may improve other risk factors for accelerated atherosclerosis, including decreased insulin resistance,[21] decreased C-reactive protein and interleukin (IL)-6 levels, and increased high-density lipoprotein levels.[17]

Methods

This review was performed by searching MEDLINE and PubMed for articles published between 2000 and 2013 with English abstracts containing the following key terms: psoriasis; psoriatic arthritis; major adverse cardiac events; myocardial infarction; stroke; cardiovascular death; and diabetes. Manual searches of the bibliographies of selected articles were performed to identify additional studies.

Results and Discussion

There have been preliminary reports of an excess number of major adverse cardiac events in randomized controlled trials in patients with psoriasis treated with anti-IL-12/23 agents, and a small number of events reported from studies of anti-TNF-α agents for the treatment of psoriasis. Twenty-two randomized controlled trials of monotherapy comprising 10,183 patients

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(with safety outcomes data for major adverse cardiac events) of anti-IL-12/23 agents (ustekinumab and briakinumab) and anti-TNF-α agents (adalimumab, etanercept, and infliximab) in adults were studied to evaluate a possible association between biologic therapies for chronic plaque psoriasis and major adverse cardiac events.[22] The primary outcome measured was a major adverse cardiac event during the placebo-controlled phase of treatment in patients receiving at least 1 dose of study agent or placebo. During the placebo-controlled phases of the anti-IL-12/23 studies, 10 of the 3179 patients treated with these therapies had a major adverse cardiac event compared with no events in the 1474 patients treated with placebo. In studies of anti-TNF-α agents, 1 of the 3858 patients receiving these agents had a major adverse cardiac event compared with 1 of the 1812 treated with placebo. This meta-analysis did not show a significant increase in the risk of major adverse cardiac events associated with the use of anti-IL-12/23 agents or anti-TNF-α agents.[22] However, this study may have been underpowered to identify a significant difference. Although some preliminary reports have indicated an increased risk of major adverse cardiac events with the use of certain biologic therapies to treat chronic plaque psoriasis, an analysis of the previous 22 studies found no significant difference in the rate of these events among patients who received these medications compared with patients who received placebo. However, in a recent reevaluation of the results of this meta-analysis study, which excluded studies of psoriatic arthritis, there was a possible higher risk of major adverse cardiac events in those patients treated with IL-12/23 agents compared with placebo (odds ratio [OR] = 4.23; 95% confidence interval [CI] = 1.07-16.75).[23]

A specific major adverse cardiac event, risk of MI, has been shown to be elevated in a robust cohort study from the US. On the basis of administrative and pharmacy claims data from a large US insurer, this study compared 25,554 patients with psoriasis who received either systemic treatment (methotrexate, cyclosporine, alefacept, efalizumab, adalimumab, etanercept, and infliximab) or phototherapy.[24] The study showed a trend toward an increased risk of MI in the systemic treatment group but not a significant difference in overall MI risk (hazard ratio [HR] = 1.33; 95% CI = 0.90-1.96). The relative risk varied by age, with patients aged 50 to 70 years appearing to have a higher MI risk (HR = 1.37; 95% CI = 0.79-2.38) compared with patients younger than age 50 years (HR = 0.65; 95% CI = 0.32-1.34). No difference in risk of MI between patients receiving traditional systemic therapies and biologic therapies was identified.[24] Notable concerns raised regarding this study were the grouping of all systemic therapies together and comparing them against phototherapy, as well as the exclusion of patients receiving only psoralen and ultraviolet A therapy or acitretin.[25]

The biologic agents available in the study by Suissa et al[26] involving patients with RA included infliximab, etanercept, and anakinra. In this case-control study, 42 of the 558 patients receiving these agents had an acute MI compared with 324 of the 5580 subjects in the control group.[26] The investigators concluded that use of biologic agents was not associated with a reduction in MI risk in patients with RA.

In a study that included 121,280 patients with RA or psoriasis from North America between January 1996 and June 2008, nearly 14,000 patients were receiving a variety of disease-modifying antirheumatic drugs (DMARDs).[27] The use of TNF-α inhibitors lowered the risk of diabetes (multivariate adjusted HR = 0.62; 95% CI = 0.42-0.91).[27]

Another study showed that patients with inflammatory arthropathies receiving anti-TNF-α therapy had reduced aortic stiffness at 3 months.[28] Furthermore, TNF-α blockade leads to a partial reappearance of $CD4^+CD28^+$ T cells.[29] Peripheral blood expansion of $CD4^+CD28^-$ T cells has been hypothesized to contribute to early atherosclerotic damage predisposing patients with RA to the development of more aggressive disease. However, the beneficial effects of anti-TNF-α agents on endothelial function do not appear to be sustained and are absent in the case of diabetic patients treated with etanercept.[19,30] Furthermore, two case-control studies showed no reduction of cardiovascular events in RA with TNF-α inhibitor treatment.[26,31] Other reports from large databases show discordant results of cardiovascular disease incidence in TNF-α inhibitors users vs nonusers.[32,33]

Solomon et al,[31] a nested case-control study, examined the cardiovascular risk of glucocorticoids and cytotoxic agents other than methotrexate (leflunomide, cyclosporine, and azathioprine) compared with methotrexate and/or biologic agents among a group of older patients with RA. Hospital-based cardiovascular events were identified in 946 patients with RA from a Medicare cohort of 3501 patients with RA. There was no difference in cardiovascular events between patients receiving methotrexate monotherapy and those receiving biologic agents (OR = 1.0; 95% CI = 0.5-1.9), methotrexate plus biologic agents (OR = 0.8; 95% CI = 0.3-2.0), or biologic agents plus nonmethotrexate cytotoxic immunosuppressive agents (OR = 1.2; 95% CI = 0.7-2.2). A statistically significant increased risk of cardiovascular events was noted with glucocorticoid monotherapy (OR = 1.5; 95% CI = 1.1-2.1), glucocorticoid combination therapy (OR = 1.3; 95% CI = 0.8-2.0), and both monotherapy and combination therapy with nonmethotrexate cytotoxic immunosuppressive agents (OR = 1.8; 95% CI = 1.1-3.0). Noncytotoxic agents (gold, sulfasalazine, and hydroxychloroquine) did not increase the risk of cardiovascular events. Significant limitations to this observational study included the broad CIs on the risk estimates, the lack of information about out-of-hospital events and death, and the elderly patient cohort with increased comorbidity. The study findings suggest that methotrexate and/or biologic agents may be protective from a cardiovascular standpoint.

A team of Spanish researchers examining 4459 patients with RA treated with TNF-α antagonists provided evidence that all-cause mortality is 30% to 50% lower in patients treated with TNF-α antagonists.[32] The authors also found that cardiovascular mortality (0.58; 95% CI = 0.24-1.41), particularly in women, was notably reduced.[32] The rates of cardiovascular disease were 5 to 7 times higher in the patients with RA who were not treated with TNF-α inhibitors. The investigators acknowledged that the study's main limitation was that it was not an internal cohort and that patients in the non-TNF-α inhibitor

registry had milder disease activity as assessed by baseline disease activity score. Patients treated with TNF-α inhibitors were also an average of 2 years younger than their untreated counterparts, which could have influenced the difference in the cardiovascular outcomes measured.

The British Society for Rheumatology conducted a large prospective epidemiologic study comparing 8670 patients with RA who were receiving anti-TNF-α inhibitors and 2170 patients treated with traditional DMARDs. After adjusting for baseline cardiovascular risk, similar rates of MI in the 2 cohorts were demonstrated. Further stratification revealed, however, that the risk of MI was markedly reduced by up to 60% in those who responded to TNF-α inhibitors by 6 months compared with nonresponders, which supports the underlying role of inflammation in cardiovascular disease.[33] Different TNF-α inhibitors may have differential effects on endothelial and smooth-muscle cells and on vascular function.

An international team of researchers analyzed data from the QUEST-RA (Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis) study, including 4363 patients from 48 sites in 15 countries.[34] They examined the causes and effects of RA, as well as the potential benefits of various treatments. A lower risk of all major adverse cardiac events and MI was associated with a longer exposition-duration to TNF-α blockers (HR = 0.42; 95% CI = 0.21-0.81), although limited availability of biologics might have interfered with the results. Furthermore, patients with suspected cardiovascular disease may not have been prescribed biologic agents because of fear of possible side effects or drug interactions.

A study from Sweden[35] suggested that the risk for developing an initial major adverse cardiac event in RA is lower in patients treated with TNF-α inhibitors. The investigators recruited patients from a regional registry that included more than 90% of patients with RA started on a regimen of TNF-α blockers in 1999 or later. Of 983 patients in the combined cohort, 531 received treatment with etanercept or infliximab (but not adalimumab) during the study period. The total cohort was linked with national registries for inpatient care and cause of death. The researchers estimated the major adverse cardiac events in patients treated with TNF-α blockers vs those not treated, using age- and sex-adjusted incidence-density computations, with treatment and disease-severity markers as time-dependent covariates. This study did not control for most of the traditional and nontraditional risk factors, nonsteroidal anti-inflammatory drug use, or family history of MI. Furthermore, it was noted that patients starting anti-TNF-α inhibitor therapy had more severe disease and a higher level of disease activity compared with a community RA population. It is probable that patients who start anti-TNF-α inhibitor treatment usually have severe, refractory disease and are at a higher baseline risk of development of cardiovascular disease.

A study analyzed data from 10,156 patients with RA enrolled in the Consortium of Rheumatology Researchers of North America (CORRONA) RA Registry between October 2001 and December 2006.[36] The researchers found that TNF-α inhibitor treatment was associated with a reduced risk of any cardiovascular event (HR = 0.39, 95% CI = 0.19-0.82) compared with nonbiologic DMARDs other than methotrexate.[36] The primary outcome was major adverse cardiac events. During the study period, there were 88 events, including 45 strokes or transient ischemic attacks, 26 MIs, and 17 deaths. Risks for cardiovascular events were adjusted for multiple possible confounders, including age, sex, smoking, and concomitant disease such as diabetes and hypertension, as well as previous MI or stroke. These data indicate that TNF-α inhibitors may represent a therapeutic strategy to attenuate the heightened cardiovascular risk experienced by patients with RA and psoriasis. Strengths of the study included the size of the cohort and the availability of detailed data on drug exposure and potential confounders. However, as with all observational studies, there were limitations, such as potential confounding by indication and selection bias, as well as the small number of cardiovascular events that limited the study's statistical power for secondary outcomes.

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In a Danish database study over a 3-year period from 2007 to 2009, Ahlehoff et al[37] identified 2400 patients whose severe psoriasis was treated with phototherapy or systemic agents (including biologic agents in 693 patients and methotrexate in 799).[37] In the biologic agents group, 80% received TNF-α inhibitors and approximately 20% received anti-IL-12/23. The incidence rates of major adverse cardiac event were reduced with the use of biologic agents (HR = 0.28; 95% CI = 0.12-0.64) and methotrexate (HR = 0.65; 95% CI = 0.42-1.00) compared with other therapies.

In a recent retrospective study analyzing a database of approximately 3.2 million patients in the Kaiser Permanente Southern California Health Plan, researchers found 8845 patients who received a diagnosis of psoriasis between 2004 and 2010.[38] This cohort included 1673 patients treated with TNF-α inhibitors for at least 2 months, an "oral/phototherapy" (other systemic agents or phototherapy) cohort of 2097 patients who had not received TNF-α inhibitors, and a topical therapy cohort of 5075 patients. The median duration of TNF inhibitor therapy was 685 days (interquartile range, 215-1312 days). The HR of major adverse cardiac event was significantly lower in the TNF inhibitor cohort vs the topical cohort after adjustment for MI risk factors (adjusted HR = 0.50; 95% CI = 0.32-0.79). Incidence rates of major adverse cardiac event per 1000 patient-years were 3.05 in the TNF inhibitor cohort, 3.85 in the oral/phototherapy cohort, and 6.73 in the topical therapy cohort.

Conclusion

In the past decade, TNF-α inhibitors have revolutionized the treatment of psoriasis. It is well documented that psoriasis increases the risk of cardiovascular disease, and although there appears to be some reduction in the risk of major adverse cardiac events, it remains unclear whether TNF-α inhibitors significantly reduce that risk across the spectrum of psoriasis. Precisely how TNF-α inhibitors may lower cardiovascular

Table 1. Summary of studies on use of tumor necrosis factor (TNF)-α inhibitors in psoriasis and rheumatoid arthritis (RA)

Authors, year	Type of study	Number	Results	Degree of benefit
Ryan et al,[22] 2011	Psoriasis: meta-analysis of randomized controlled trials	3858	In the anti-TNF-α trials, only 1 of 3858 patients receiving anti-TNF-α agents experienced a MACE compared with 1 of 1812 patients receiving placebo.	No difference in rate of MACEs
Abuabara et al,[24] 2011	Psoriasis: cohort study	25,554	There did not appear to be a reduced risk of MI in patients with psoriasis receiving systemic therapy compared with a group undergoing phototherapy. The risk of MI may vary by age.	No reduction in rate of MACEs
Suissa et al,[26] 2006	RA: nested case-control analysis	107,908	The use of infliximab, etanercept, and anakinra did not show a reduction in MI risk in patients with RA.	No change in MACE risk factors
Solomon et al,[31] 2006	RA: nested case-control study	3501	No difference was observed in CV events between patients receiving methotrexate monotherapy and those receiving biologic agents.	No change in MACE risk factors
Dominguez et al,[30] 2005	Obese patients: open-label randomized trial	20	No improvement of vascular or metabolic insulin sensitivity was observed, although short-term etanercept treatment had a significant beneficial effect on systemic inflammatory markers.	Confounding effects noted
Hürlimann et al,[18] 2002	RA: prospective study	11	Infliximab showed improvement in endothelial function in RA.	May improve MACE risk factors
Gonzalez-Juanatey et al,[19] 2004	RA: prospective study	7	Infliximab showed an active but transient effect on endothelial function.	May improve MACE risk factors
Irace et al,[20] 2004	RA: prospective study	In vitro	Infliximab induced vasoconstriction and an increase of wall shear stress. HDL-cholesterol was reduced but did not seem to influence flow-mediated vasodilatation.	May worsen MACE risk factors
Kiortsis et al,[21] 2005	RA and ankylosing spondylitis: prospective study	45	Infliximab may have beneficial effects on insulin sensitivity in the most insulin-resistant patients with RA and ankylosing spondylitis.	May improve MACE risk factors
Popa et al,[17] 2005	RA: double-blind clinical trial	33	Patients receiving anti-TNF-α showed increased HDL-cholesterol levels and decreased CRP and IL-6 levels after 2 weeks.	May improve MACE risk factors
Jacobsson et al,[35] 2005	RA: cohort study	983	The risk of developing the first cardiovascular event was lower in patients treated with TNF-α inhibitors.	May improve MACE risk factors
Carmona et al,[32] 2007	RA: cohort study	4459	Mortality from all causes was 30% to 50% lower in the TNF-α inhibitors group, including CV mortality.	May improve MACE risk factors
Dixon et al,[33] 2007	RA: cohort study	8670	No reduction in the incidence of MI. However, risk of MI was markedly reduced by up to 60% in those who responded to TNF-α inhibitors by 6 months compared with nonresponders.	No change, and possible improvement, in MACE risk factors in early responders
Sokka et al,[34] 2007	RA: cross-sectional study	4363	A lower risk of all CV events and MI was seen with longer exposure to TNF-α inhibitors.	May improve MACE risk factors
Angel et al,[28] 2010	Inflammatory arthropathies: case-control study	60	Anti-TNF-α therapy improved aortic stiffness in patients with inflammatory arthropathies.	May improve MACE risk factors
Greenberg et al,[36] 2011	RA: cohort study	10,156	MACEs were reduced in the TNF-α inhibitor treatment group.	May improve MACE risk factors
Solomon et al,[27] 2011	RA and psoriasis: retrospective cohort study	13,905	Adjusted risk of diabetes mellitus was lower for individuals starting treatment with TNF-α inhibitors compared with initiation of other nonbiologic DMARDs.	May improve MACE risk factors
Ahlehoff et al,[37] 2013	Psoriasis: cohort study	2400	Incidence rates of MACE were reduced with use of biologic agents and methotrexate compared with other therapies.	May improve MACE risk factors
Wu et al,[38] 2012	Psoriasis: retrospective cohort study	8845	There was a reduction in MI risk and incident rate compared with treatment with topical agents and a nonstatistically significant lower MI incident rate compared with treatment with oral agents/phototherapy.	May improve MACE risk factors

CRP = C-reactive protein; CV = cardiovascular; DMARDs = disease-modifying antirheumatic drugs; HDL = high-density lipoprotein; IL = interleukin; MACE = major adverse cardiac event; MI = myocardial infarction.

risk is uncertain, but some research has suggested that they may help prevent plaque rupture and improve endothelial function. Overall, studies of their effects on cardiovascular risk show mixed results.[26,31-33] We must take into account that patients receiving TNF-α inhibitors may be at higher overall cardiovascular risk. Patients receiving other medications may be at lower cardiovascular risk. Limitations of clinical trial safety data, including sample size, heterogeneity, and limited follow-up durations, have made postmarketing registries an invaluable source of safety information.

This article reviewed some of the major published data about the relationship between TNF-α inhibitors and cardiovascular disease in psoriasis (Table 1). Whereas some trials indicate no increased risk of major adverse cardiac events, there are increasing indications that the use of TNF-α inhibitors may decrease the risk of major adverse cardiac events. As more patients receiving TNF-α inhibitor therapy are enrolled in postmarketing registries, more long-term data will help elucidate whether these agents may benefit the risk reduction for major adverse cardiac events. ❖

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Proceeding From The Heart

All the veins and arteries proceed from the heart; and the reason is that the maximum thickness that is found in the veins and arteries is at the junction that they make with the heart; and the farther away they are from the heart the thinner they become and they are divided into more minute ramifications.

—*Dell' Anatonia,* Vol I Ch III, Leonardo da Vinci, 1452-1519, Italian Renaissance polymath: painter, sculptor, architect, musician, mathematician, engineer, inventor, anatomist, geologist, cartographer, botanist, and writer