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TITLE PAGE

Anti-inflammatory therapy with tumor necrosis factor inhibitors is associated with reduced risk of major adverse cardiovascular events in psoriasis

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ABSTRACT

Background: Psoriasis is a systemic chronic inflammatory condition associated with increased risk of cardiovascular disease. Data demonstrating that decreased skin inflammation reduces cardiovascular events in psoriasis patients may be generalizable to other chronic inflammatory states with heightened cardiovascular risk.

Objective: To determine whether tumor necrosis factor inhibitor (TNFi) therapy is associated with decreased major adverse cardiovascular events (MACE) in psoriasis patients.

Methods: In this retrospective cohort study using the KPSC health plan, patients had at least 3 ICD-9 codes for psoriasis and no antecedent MACE codes. Propensity score-adjusted multivariable cox regression assessed hazard ratios (HR) of MACE associated with TNFi use.

Results: After adjusting for cardiovascular risk factors, the TNFi cohort had significantly lower MACE HR compared with the topical cohort (HR, 0.80; 95% CI, 0.66-0.98). The oral/phototherapy cohort had similar MACE HR compared with the topical cohort (HR, 1.19 (95% CI, 0.99-1.42).

Conclusions: We observed significantly lower MACE risk in psoriasis patients receiving TNFi compared to topical or oral/phototherapy agents. TNFi therapy may have benefits beyond skin disease in mitigating cardiovascular event risk.

INTRODUCTION

Inflammation is the cornerstone in the pathogenesis of atherosclerosis[1]. Psoriasis is an immune-mediated chronic inflammatory skin disease that affects 2-3% of the world population.[2] Patients with severe skin disease are at increased risk for cardiovascular[3-11] and cardiometabolic diseases[3,5,12-15]. As psoriasis is associated with increased systemic and vascular inflammation[16], and with increased risk for cardiovascular events as well as mortality[11], it provides an ideal clinical model to assess the impact of anti-inflammatory therapies on skin disease and, in turn, on cardiovascular event risk.

With the progress in our understanding of the role of inflammation in atherogenesis, we have understood that control of inflammation may quell prospective cardiovascular risk[17-19]. In line with this finding, we have reported previously from population-derived cohorts that use of anti-

inflammatory therapies such as TNF inhibitors (TNFis) was associated with a 50% reduction in myocardial infarction risk in patients with psoriasis and psoriatic arthritis[20] and a 54% reduction in major adverse cardiovascular events (MACE, i.e., myocardial infarction, stroke, and cardiovascular death) compared to reference groups.[21] However, a systematic comparison of MACE in psoriasis patients treated with TNFis to those treated with other therapies over a longer duration follow-up on a population level is yet to be performed.

In this study, we sought to investigate the incidence rate of MACE in patients treated with TNFis compared to those treated with topical or oral/phototherapy. Utilizing a retrospective cohort study design, we assessed whether treatment with TNFis in psoriasis patients had beneficial impact on cardiovascular risk in terms of incidence rate of MACE compared to psoriasis patients who received only topical therapy or oral/phototherapy. We hypothesized that patients treated with TNFis would have lower MACE incidence compared to those not treated with any biologic agent.

MATERIALS AND METHODS

Design Overview

This was a retrospective cohort study conducted within the Kaiser Permanente Southern California (KPSC) Health Plan, a large integrated health maintenance organization that has served approximately 3-4 million members during each of the past 12 years. Membership attrition averages 10% per year. The membership of KPSC comprises approximately 20% of the region's population. Membership demographics, racial/ethnic composition, and socioeconomic status are representative of California.[22,23] Health plan members receive the majority of their health care at KPSC-owned facilities. More than 92% of members obtain their prescription medication from a KPSC pharmacy. All the data were extracted from HealthConnect, the electronic databases of KPSC.

The study protocol was approved by the local Institutional Review Board at KPSC. This study was conducted and reporting was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[24] statement and the Declaration of Helsinki.

Setting, Participants, and Follow-up

The study cohort was drawn from KPSC patients with at least 3 recorded diagnosis codes of psoriasis or psoriatic arthritis (International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) code 696.1x or 696.0x) between January 1, 2004 and December 31, 2014. To qualify for study inclusion, a patient must have been a KPSC member for at least 1 year prior to study entry (with up to a 45-day gap in membership coverage allowed) to allow adequate time for co-morbidity ascertainment/documentation, have had a basic prescription drug benefit, and be at least 18 years of age or older at diagnosis. Exclusion criteria were a history of antecedent MACE (ICD-9: 410, 434.91, 436.0, 434.11, 430, 431, 432.0-432.9, 434.01; and after October 1, 2015, ICD-10 I00–I78, H34.1, I60.x, I61.x, I63.x, I64.x) documented prior to January 1, 2004 and since ustekinumab was not on formulary at KPSC during the study period, patients who received ustekinumab during follow-up were also excluded.

Each patient was assigned to one of three mutually exclusive cohorts. Patients with psoriasis who received at least 2 consecutive months of adalimumab, etanercept, or infliximab during the study period were analyzed as the "TNFi" cohort, regardless of changes in treatment regimen, discontinuation and/or restarting TNFi, or use in combination with an oral agent or phototherapy. TNFi-naïve patients who received oral agents (i.e., acitretin, apremilast, cyclosporine, methotrexate) or phototherapy (broad-band ultraviolet light B (BB-UVB), narrow-band ultraviolet light B (NB-UVB), or psoralen and ultraviolet A light (PUVA)) formed the "oral/phototherapy" cohort.

Patients not treated with TNFis, oral therapies, or phototherapy formed the "topical" cohort. The index date of follow-up was defined by the date of the patient's first systemic therapy dispensation or the first day of phototherapy after the third psoriasis ICD9 code. For patients in the topical cohort, follow-up began on the date of the first psoriasis ICD9 code. Follow-up ended (censored) with the first occurrence of any of the following: (a) fatal or nonfatal MACE, (b) death during the study period, (c) disenrollment from KPSC for more than 45 days, or (d) end of study on December 31, 2014.

Covariate Ascertainment

Age was calculated as a continuous variable, and defined as the time from date of birth until the index date. Common MACE risk factors were identified using ICD-9 and ICD-10 codes and KPSC electronic health records as described earlier.[20,25] Prescription drugs that may affect incident MACE risk, including statins and beta-blockers, were identified using the KPSC pharmacy database.

Outcomes

The following outcomes were assessed: fatal or nonfatal MACE. Diagnosis codes were not restricted to outpatient or inpatient setting, primary diagnosis only, nor required more than 1 diagnosis code. Cause of death was obtained from California State Death Certificates.

Statistical analysis

Summary statistics were generated and reported as mean± standard deviation for continuous variables, and as frequencies for categorical variables. Standardized differences were estimated between TNFis and topical and oral/phototherapy and topical treatments to compare demographic, comorbid, and concurrent treatment characteristics between the two cohorts. Multinomial logistic regression estimated confounder-adjusted propensity scores for treatment and propensity score-adjusted multivariable Cox regression assessed differences in MACE incidence rates. The multivariable regression models were adjusted for age at psoriasis diagnosis, sex, race/ethnicity, history of smoking or alcohol use, use of clopidogrel, antihypertensive agents, antihyperlipidemics, or anticoagulants (coumarins, factor Xa inhibitors, heparin and derivative substances, direct thrombin inhibitors).

Hypothesizing a 10% prevalence of TNFi use in the population, we required a total of about 430-1125 events to assess a hazard-ratio of 0.6-0.7 in the group treated with TNFis to achieve >90% power over the stated follow-up period of the study. All analyses were conducted using SAS Enterprise Guide version 5.1 (SAS Institute, Cary, North Carolina).

RESULTS

Demographics

Of 18,154 patients included, 1,463 received treatment with a TNFi for at least 2 months, 3,579 received oral agents or phototherapy, and 13,112 had received topical therapy (Table 1). Eighty-five patients given ustekinumab were excluded from the study. The mean duration of follow-up for the TNFi, oral/phototherapy, and topical cohorts were 3.3, 3.1, and 5.2 years, respectively;

average follow-up across the entire cohort was 4.7 years. The risk factors for MACE were similar between TNFis and topical therapy cohorts except for higher mean body mass index (BMI), higher rates of male sex, obesity, and current alcohol use or smoking; and lower age, and lower rates of dyslipidemia, coronary artery disease, and peripheral artery disease in the TNFi cohort. The risk factors for MACE were similar between oral/phototherapy and topical therapy cohorts except for higher mean BMI and higher rates of current alcohol use or smoking in the oral/phototherapy cohort.

MACE incidence and risk

The incidence rate of MACE in the TNFi, oral/phototherapy, and topical cohorts were 9.25, 14.19, and 12.79 per 1,000 patient-years, respectively (Table 2). The TNFi cohort had a significantly lower risk of MACE compared with the topical cohort (propensity score-adjusted hazard ratio (HR), 0.80; 95% CI, 0.66-0.98) (Table 2). Despite the higher incidence rate, we did not have enough evidence to show the risk of MACE as being statistically significantly higher in the oral/phototherapy cohort compared with the topical cohort (HR, 1.13; 95% CI, 1.00-1.28).

In a sensitivity analysis that excluded phototherapy and non-methotrexate oral therapy, HRs for TNFi, methotrexate, and topical cohorts were 0.80 (95% CI, 0.65-0.98); 1.19 (95% CI, 0.99-1.42); and 1.00 (reference), respectively (Table 3). Similarly, exclusion of oral therapies yielded HRs of 0.81 (95% CI, 0.66-0.99); 1.13 (95% CI, 0.95-1.35); and 1.00 (reference), for TNFi, phototherapy, and topical cohorts respectively (Table 4).

DISCUSSION

Major findings demonstrated in this study are: (1) a significantly lower risk of MACE in psoriasis patients treated with TNFis compared to those treated with topical agents, over a long duration follow-up; (2) sensitivity analyses comparing various treatments in the oral therapy/phototherapy cohort to the TNFi cohort showed no significant differences with the primary analysis, and revealed a lower MACE risk for those treated with TNFis. Collectively, our study demonstrated a favorable cardiovascular risk profile for psoriasis patients treated with TNFis compared to those treated only with oral therapy/phototherapy or topical therapy. The original epidemiologic study investigating risk of myocardial infarction showed a 50% reduction in risk in the TNFi cohort compared to the topical cohort (adjusted HR, 0.50; 95% CI, 0.32-0.79).[20] Our current study, conducted on a population level (18,154 patients vs. 8,845 patients in the original study) showed a 20% reduction in the risk of all MACE (not limited to myocardial infarction) in the TNFi cohort compared to the topical cohort.

In recent years, it has become increasingly evident that psoriasis associates with an increased cardiovascular disease risk, and increased prevalence of diabetes, obesity, and metabolic syndrome[26]. Furthermore, psoriasis is also associated with higher incidence of cardiovascular and cerebrovascular events[27,28], greater cardiovascular mortality[26] and an elevated burden of overall mortality.[29] These associations were stronger in patients with severe psoriasis[11,30]. With elevated insulin resistance[31], impaired HDL function[32] and increased systemic as well as vascular inflammation[16,33] psoriasis provides a clinical human model to study the role of inflammation in the pathophysiology of atherogenesis. However, whether treatment of psoriasis skin disease leads to an improvement in cardiovascular disease is not well known.

Psoriasis is a chronic inflammatory skin disease involving inflammatory biomarkers in its pathogenesis[34], which are also associated with the severity of skin disease[35]. Furthermore, psoriasis is associated with increased vascular inflammation by 18-fluorodeoxyglucose positron emission tomography computed tomography, and with inflammation in the skin plaques[34]. Recent studies incriminate chronic low-grade inflammation as the main culprit promoting vascular disease in psoriasis[36,37]. Additionally, chronic low-grade inflammation is also implicated in cardiovascular disease progression in healthy individuals, and has been shown to be associated with prospective cardiovascular events[38,39]. Despite the elevated risk in psoriasis patients, this population remains poorly-treated in general[40]. As such, we hypothesized that reduction in skin inflammation may have beneficial impact on systemic inflammation, and may subsequently reduce cardiovascular events. We demonstrated that anti-inflammatory therapy with TNFis was associated with a lower risk of MACE independent of traditional cardiovascular risk factors suggesting an important role of controlling inflammation in cardiovascular risk mitigation.

Despite advances in biologic therapy options for psoriasis, TNFis have remained a cornerstone of psoriasis biological therapy[41]. These therapies have a positive impact on psoriasis inflammation by reducing TNF availability in pathogenic pathways. Furthermore, TNF alpha is also involved in inflammatory pathways responsible for pathogenesis of metabolic syndrome, diabetes and cardiovascular disease[1,42]. Together, these support the inflammatory hypothesis of atherosclerosis and suggest that alleviating the impact of TNF alpha may quell the overall cardiovascular risk, which is in accord with the findings we presented in this study.

A previous study in a longitudinal Danish nationwide cohort from 2007-2011 of psoriasis patients (n = 6902) evaluated the risk of MACE associated with various therapies used for psoriasis[21] and showed that the adjusted HR of MACE in patients with TNFis (n=959) was 0.46 (95% CI, 0.22-0.98) compared to other therapies (n=3961). Additionally, methotrexate was associated with significantly lower rates of cardiovascular events compared to patients treated with other antipsoriatic therapies. In comparison, our study represents a larger, more diverse population of psoriasis patients (n=18154) on TNFis (n = 1463) with a longer duration of follow-up. We did not find methotrexate to be associated with a decreased rate of MACE. Similar findings have been shown in the rheumatoid arthritis literature.[43-45] Previous observational studies have suggested that treatment of psoriasis is associated with improved CV outcomes and surrogate outcomes such as insulin resistance, endothelial dysfunction, and vascular inflammation[20,46-51] Based on findings from our study, treatment of psoriasis with TNFis reduced future risk of MACE. These findings suggest that reduction of skin disease reduces risk of vascular events via a decrease in systemic inflammation, however our study design precludes firm conclusions. These findings may impart knowledge beyond psoriasis, as other ongoing interventional studies of methotrexate and IL-1 beta inhibitors in patients with a history of myocardial infarction, viz. the CIRT (Cardiovascular Inflammation Reduction Trial, NCT01594333) and CANTOS (The Canakinumab Anti-inflammatory Thrombosis Outcomes Study, NCT01327846), will be completed by 2018 and inform further whether decrease in inflammation through use of methotrexate or inflammasome inhibition decreases subsequent vascular events. Furthermore, the VIP (Vascular Inflammation in Psoriasis, NCT01553058, NCT02187172, and NCT01866592) trials should all be available for results by 2020 and answer whether randomized allocation of biologic therapy in psoriasis patients reduces vascular inflammation after 1 year of skin disease clearance.

There are certain limitations to our study that warrant mention. While this epidemiologic study included a large number of patients with a long-term follow-up, the data were obtained with the use of electronic health records limiting our ability to validate exposure and outcome measures. Our utilization of data from a large health maintenance organization comprising people of varied backgrounds and ethnicities makes our findings generalizable on a population level, however, this may also lead to misclassification between groups as patients can receive multiple different treatments simultaneously. A time-dependent analysis to determine the time-varying nature of treatment was not performed.

We could not assess disease severity (such as with body surface area), so it is possible that TNFis were given for those with mild disease, but in a managed health care setting were costs are scrutinized, TNFis typically are prescribed only for those severe disease. Additionally, the lack of detailed information regarding disease severity may impact assessment of MACE incidence, given that severe psoriasis, and not mild psoriasis, is associated with an increased risk of MACE. Furthermore, the epidemiologic study design induces a significant healthy-user bias in the analyses, but the MACE risk factors were evenly balanced between the various study cohorts. Moreover, the study design precludes assessment of risk modification secondary to previous treatments, such as over the counter aspirin that patients may have received. There is an inadvertent selection bias in the study design in that patients treated with topical medications are followed from an earlier onset (first visit) as opposed to the TNFi cohort (third visit). We did not find a significantly reduced risk in the patients receiving methotrexate, which differs from some published literature that shows that methotrexate use was also associated with MI risk reduction.[49] A recent larger study using the MarketScan database with TNFi users (N = 9148) and methotrexate users (N = 8581) showed that TNFi users had overall lower cardiovascular events than methotrexate users (hazard ratio = 0.55; $P < .01$).[52] In comparison, this current study includes other oral agents (retinoids, cyclosporine), topical

therapies and phototherapy in the data analysis. While cyclosporine has been shown to elevate serum triglycerides and total cholesterol after 2 weeks of use in psoriasis patients,[53] etretinate did not show an increased risk of CV events in this patient population.[54]

Collectively, we observed a significantly lower risk of MACE in patients with psoriasis who were prescribed a TNFi compared to those who used topical agents or oral/phototherapy. The results support evidence that TNFi treatment may have benefit in reducing CV outcomes in patients with psoriasis. However, this association needs confirmation by large prospective randomized trials.

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ABBREVIATIONS:

TNFi = Tumor Necrosis Factor inhibitor

MACE = major adverse cardiovascular events

KPSC = Kaiser Permanente Southern California

STROBE = Strengthening the Reporting of Observational Studies in Epidemiology

ICD-9 = International Classification of Diseases, 9th Revision, Clinical Modification

HR = hazard ratio

BMI = body mass index

BB-UVB = broad-band ultraviolet light B

NB-UVB = narrow-band ultraviolet light B

PUVA = psoralen and ultraviolet A light

CIRT (Cardiovascular Inflammation Reduction Trial, NCT01594333)

CANTOS (The Canakinumab Anti-inflammatory Thrombosis Outcomes Study, NCT01327846)

VIP (Vascular Inflammation in Psoriasis, NCT01553058, NCT02187172, and NCT01866592) trials

Table 1. Cohort characteristics.

	TNF-Inhibitor	Oral/Phototherapy	Topical	Total	Standardized Difference	
	n = 1,463 (8.1)	n = 3,579 (19.7)	n = 13,112 (72.2)	n = 18,154	TNF inhibitors vs topical	Oral/photo vs topical
Male (%)	768 (52.5%)	1738 (48.6%)	6493 (49.5%)	8999 (49.6%)	-0.06	0.02
Age in years at index date, mean (SD)	46.1 (13.20)	51.1 (14.79)	51.8 (15.48)	51.2 (15.25)	-0.39	-0.04
Mean length of follow up in years (SD)	3.3 (2.47)	3.1 (2.52)	5.2 (3.16)	4.7 (3.14)	-0.69	-0.76
Race/ethnicity						
White, non-Hispanic	725 (49.6%)	1737 (48.5%)	6971 (53.2%)	9433 (52%)	-0.07	-0.09
Black, non-Hispanic	64 (4.4%)	163 (4.6%)	602 (4.6%)	829 (4.6%)	-0.01	0.00
Hispanic	375 (25.6%)	978 (27.3%)	3471 (26.5%)	4824 (26.6%)	-0.02	0.02
Asian, non-Hispanic	200 (13.7%)	449 (12.5%)	1384 (10.6%)	2033 (11.2%)	0.10	0.06
Other, non-Hispanic	99 (6.8%)	252 (7%)	684 (5.2%)	1035 (5.7%)	0.07	0.08
Body Mass Index (kg/m^2), mean (SD)	30.9 (6.95)	30.3 (6.73)	30.0 (6.82)	30.1 (6.81)	0.15	0.04
Risk factors for MACE						
Diabetes (%)	300 (20.5%)	854 (23.9%)	3354 (25.6%)	4508 (24.8%)	-0.12	-0.04
Dyslipidemia (%)	732 (50%)	2083 (58.2%)	8241 (62.9%)	11056 (60.9%)	-0.26	-0.10
Hypertension (%)	679 (46.4%)	1854 (51.8%)	7097 (54.1%)	9630 (53%)	-0.15	-0.05
Coronary artery disease (%)	52 (3.6%)	213 (6%)	1112 (8.5%)	1377 (7.6%)	-0.21	-0.10

Peripheral artery disease (%)	30 (2.1%)	131 (3.7%)	669 (5.1%)	830 (4.6%)	-0.16	-0.07
Current smoker (%)	500 (40.1%)	1293 (42.3%)	2984 (36.1%)	4777 (38%)	0.26	0.30
Any alcohol use (%)	543 (40.6%)	1289 (39.4%)	3011 (32.9%)	4843 (35.2%)	0.31	0.29
Obesity (%)	682 (46.6%)	1522 (42.5%)	4496 (34.3%)	6700 (36.9%)	0.25	0.17
Concurrent Medications						
Anti-dyslipidemic use (%)	507 (34.7%)	1499 (41.9%)	5966 (45.5%)	7972 (43.9%)	-0.22	-0.07
Antihypertensive use (%)	536 (36.6%)	1460 (40.8%)	5579 (42.5%)	7575 (41.7%)	-0.12	-0.04
Anticoagulant use (%)	81 (5.5%)	252 (7%)	948 (7.2%)	1281 (7.1%)	-0.07	-0.01
Clopidogrel use (%)	27 (1.8%)	81 (2.3%)	420 (3.2%)	528 (2.9%)	-0.09	-0.06

1 - Pairwise comparisons were made using standardized differences between TNF inhibitors and topical cohorts; and oral/phototherapy and topical cohorts. Standardized difference is the difference in means or proportions divided by standard error; imbalance is defined as absolute value greater than 0.20 (small effect size).

Table 2. Incidence rates and relative risks of MACE in psoriasis patients treated with topical therapy vs. oral/phototherapy and TNF inhibitors.

Study Outcome	Treatment	Person-Years	Number of Events	Incidence Rate per 1,000 Person-Years	Unadjusted HR (95% CI)	Propensity Score-Adjusted HR (95% CI)[1]
MACE	Topical therapy	68,814	880	12.79	1.00 (Reference)	1.00 (Reference)
	Oral/phototherapy	10,923	155	14.19	1.18 (1.00, 1.41)	1.13 (1.00, 1.28)
	TNF inhibitor	4,755	44	9.25	0.78 (0.57, 1.05)	0.80 (0.66, 0.98)

1 - The propensity of receiving oral/phototherapy or TNF inhibitors was estimated using a multivariable logistic regression model that included age at psoriasis diagnosis, sex, race/ethnicity, history of smoking or alcohol use, and use of clopidogrel, antihypertensives, antidyslipidemics, or anticoagulants.

Table 3. Sensitivity analysis that excluded phototherapy and non-methotrexate oral therapy: incidence rates and relative risks of MACE in psoriasis patients treated with topical therapy vs. methotrexate and TNF inhibitors.

Study Outcome	Treatment	Person-Years	Number of Events	Incidence Rate per 1,000 Person-Years	Unadjusted HR (95% CI)	Propensity Score-Adjusted HR (95% CI)[1]
MACE	Topical therapy	68,814	880	12.79	1.00 (Reference)	1.00 (Reference)
	Methotrexate	4,080	63	15.44	1.27 (0.99, 1.65)	1.19 (0.99, 1.42)
	TNF inhibitor	4,755	44	9.25	0.77 (0.57, 1.05)	0.80 (0.65, 0.98)

1 - The propensity of receiving oral/phototherapy or TNF inhibitors was estimated using a multivariable logistic regression model that included age at psoriasis diagnosis, sex, race/ethnicity, history of smoking, alcohol use history, use of clopidogrel, antihypertensives, antidyslipidemics, or anticoagulants.

Table 4. Sensitivity analysis that excluded oral therapy: incidence rates and relative risks of MACE in psoriasis patients treated with topical therapy vs. phototherapy and TNF inhibitors.

Study Outcome	Treatment	Person-Years	Number of Events	Incidence Rate per 1,000 Person-Years	Unadjusted HR (95% CI)	Propensity Score-Adjusted HR (95% CI)[1]
MACE	Topical therapy	68,814	880	12.79	1.00 (Reference)	1.00 (Reference)
	Phototherapy	4,464	59	13.22	1.13 (0.87, 1.48)	1.13 (0.95, 1.35)
	TNF inhibitor	4,755	44	9.25	0.78 (0.57, 1.05)	0.81 (0.66, 0.99)

1 - The propensity of receiving oral/phototherapy or TNF inhibitors was estimated using a multivariable logistic regression model that included age at psoriasis diagnosis, sex, race/ethnicity, history of smoking, alcohol use history, use of clopidogrel, antihypertensives, antidyslipidemics, or anticoagulants.

Figure 1. Study population CONSORT.