Association Between Tumor Necrosis Factor Inhibitor Therapy and Myocardial Infarction Risk in Patients With Psoriasis

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Objective: To assess whether patients with psoriasis treated with tumor necrosis factor (TNF) inhibitors have a decreased risk of myocardial infarction (MI) compared with those not treated with TNF inhibitors.

Design: Retrospective cohort study.

Setting: Kaiser Permanente Southern California health plan.

Patients: Patients with at least 3 International Classification of Diseases, Ninth Revision, Clinical Modification, codes for psoriasis (696.1) or psoriatic arthritis (696.0) (without antecedent MI) between January 1, 2004, and November 30, 2010.

Main Outcome Measure: Incident MI.

Results: Of 8845 patients included, 1673 received a TNF inhibitor for at least 2 months (TNF inhibitor cohort), 2097 were TNF inhibitor naive and received other systemic agents or phototherapy (oral/phototherapy cohort), and 5075 were not treated with TNF inhibitors, other systemic therapies, or phototherapy (topical cohort). The median duration of follow-up was 4.3 years (interquartile range, 2.9, 5.5 years), and the median duration of TNF inhibitor therapy was 685 days (interquartile range, 215, 1312 days). After adjusting for MI risk factors, the TNF inhibitor cohort had a significantly lower hazard of MI compared with the topical cohort (adjusted hazard ratio, 0.50; 95% CI, 0.32-0.79). The incidence of MI in the TNF inhibitor, oral/phototherapy, and topical cohorts were 3.05, 3.85, and 6.73 per 1000 patient-years, respectively.

Conclusions: Use of TNF inhibitors for psoriasis was associated with a significant reduction in MI risk and incident rate compared with treatment with topical agents. Use of TNF inhibitors for psoriasis was associated with a non–statistically significant lower MI incident rate compared with treatment with oral agents/phototherapy.


Psoriasis is a chronic skin condition that affects approximately 2% to 3% of the population.1,2 Beyond cutaneous manifestations, psoriasis is a systemic inflammatory state that is associated with an increased risk of cardiovascular diseases, including obesity,3,4 type 2 diabetes mellitus,5,6 hypertension,5,7 dyslipidemia,3,7 metabolic syndrome,7,8 peripheral vascular disease,6 atherosclerosis,6,9 coronary artery calcification,10 myocardial infarction (MD),7,11 stroke,7,14 and cardiac death.15,16 Psoriasis is also associated with behaviors that worsen cardiovascular risk, such as smoking17,18 and alcohol intake.24

The effect of systemic treatment for psoriasis on cardiovascular disease has been largely unexplored. It has been suggested that therapeutic use of methotrexate, probably owing to its anti-inflammatory properties, may reduce vascular disease in patients with psoriasis.19 It is not well described whether treatment with etanercept,20 infliximab,21 or adalimumab22 affects the risk of cardiovascular disease in patients with psoriasis. Abuabara et al23 recently reported that there does not seem to be a reduced risk of MI in patients with psoriasis receiving systemic therapy (including tumor necrosis factor [TNF] inhibitors) compared with a group undergoing phototherapy. However, there are possible flaws in the study design, such as grouping all systemic therapies, that put the conclusion into question.24

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The primary objective of this study was to assess whether patients with psoriasis treated with TNF inhibitors have a decreased risk of MI compared with those not treated with TNF inhibitors (ie, those who received oral agents/phototherapy or topical agents).

**METHODS**

**DESIGN OVERVIEW**

This is a retrospective cohort study conducted in the Kaiser Permanente Southern California (KPSC) health plan, a large integrated health maintenance organization that has served approximately 3.2 million members during each of the past 10 years. Membership attrition averages 10% per year. The membership of KPSC composes approximately 15% of the region's population. Its membership demographic, socioeconomic, and racial/ethnic composition are representative of California.25,26 Health maintenance organization members receive most of their health care at KPSC-owned facilities, including medical centers and offices. However, the health plan is also financially responsible for KPSC members' emergency medical care received at facilities outside the health plan. More than 92% of members have prescription drug benefits and obtain their prescription medications from a KPSC pharmacy. All the patients have blood chemistry and other laboratory test benefits. All the data were extracted from HealthConnect, the electronic databases of KPSC clinic and hospital systems. The study protocol was approved by the local institutional review board at KPSC.

**SETTING AND PARTICIPANTS**

The study cohort was drawn from KPSC patients with at least 3 recorded diagnosis codes for psoriasis (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 696.0) or psoriatic arthritis (ICD-9-CM code 696.0) between January 1, 2004, and November 30, 2010. To qualify for study inclusion, a patient must have been a KPSC member for at least 1 year to allow adequate time for comorbidity ascertainment/documentation and must have had at least 1 medical encounter per year to ensure that the patient was active in health management. The exclusion criterion was a history of MI (ICD-9-CM code 410.XX or 412) documented prior to the third psoriasis diagnosis code.

Each patient was assigned to 1 of 3 mutually exclusive cohorts. Patients with psoriasis who received etanercept, infliximab, or adalimumab for at least 2 consecutive months during the study were analyzed as the TNF inhibitor cohort, regardless of changes in treatment regimen, discontinuation or restarting TNF inhibitor use, or use combined with an oral agent or phototherapy. The TNF inhibitor–naive patients who received oral agents (ie, cyclosporine, acitretin, and methotrexate) or phototherapy (broad-band UV-B, narrow-band UV-B, or psoralen–UV-A) formed the oral/phototherapy cohort. These patients were grouped together since the amount of psoriasis was severe enough to justify more aggressive therapy than topical agents and dermatologists generally consider oral therapy or phototherapy as the next step up before prescribing a TNF inhibitor. Patients who were not treated with TNF inhibitors, oral agents, or phototherapy but were treated with topical agents formed the topical cohort. We define severe disease as the use of any systemic therapy or phototherapy and mild disease as the use of topical agents and the nonuse of systemic therapy or phototherapy.7,13–16

**COVARIATE ASCERTAINMENT**

Age was calculated from date of birth until the third psoriasis ICD-9-CM code and was measured as a continuous variable. Common MI risk factors were identified using ICD-9-CM codes and KPSC electronic medical records and included adult-onset diabetes mellitus (code 250.X), hypertension (codes 401.0, 401.01, 401.09, 401.1, 401.11, 401.19, 401.9, 401.91, and 401.99), dyslipidemia (codes 272.0–272.4 and 272.9), active/current smoking, and obesity (defined as a body mass index >30 [calculated as weight in kilograms divided by height in meters squared]). These risk factors were identified at any time during the study. Prescription drugs that may affect incident MI risk were identified using the KPSC pharmacy database and included statins and β-blockers. Treatment with methotrexate has previously been suggested to possibly lower MI risk in patients with psoriasis.19 However, in the univariable analysis of this cohort, methotrexate use (n=1983) was not associated with MI risk (hazard ratio [HR], 0.89; 95% CI, 0.64–1.23) and was not further analyzed. Also in the univariable analysis of this cohort, obesity (n=8464; HR, 0.86; 95% CI, 0.63–1.14) and smoking (1104; 0.87; 0.56–1.34) were not associated with MI risk and were not further analyzed. The diagnostic accuracy of ICD-9-CM codes for diabetes mellitus and hypertension in the KPSC administrative database has been previously validated by manual medical record review to have a κ of 0.82 to 0.94.27,28 The numbers of psoriasis diagnoses or medical encounters, considered in this study as a proxy for health care resource use, were also entered into the models as covariates.

**OUTCOMES AND FOLLOW-UP**

For patients in the TNF inhibitor cohort, treatment onset was defined by the date of the patient’s first TNF inhibitor dispensation after the third psoriasis ICD-9-CM code. For the oral/phototherapy cohort, follow-up began on the date of the first dispensation of any non–TNF inhibitor systemic agent or the first day of phototherapy after the third psoriasis ICD-9-CM code. For patients in the topical cohort, follow-up began on the date of the third psoriasis ICD-9-CM code. Follow-up ended (was censored) with the first occurrence of any of the following: (1) fatal or nonfatal MI, (2) death during the study, (3) disenrollment from KPSC, or (4) October 28, 2011 (the end of the study). Cause of death was obtained from California state death certificates. The mortality file consolidates information from KPSC hospital deaths and California state death records. Death records are linked to patients based on linkage weight calculated using a probabilistic method based on demographic information. For patients who did not experience any of these events, the last visit before the end of the study was used as that patient’s end date to minimize information bias.

**STATISTICAL ANALYSIS**

Demographic and clinical characteristics of patients were summarized by frequency (percentage) for categorical variables and mean (SD) for continuous variables; χ² and unpaired t tests, respectively, were used to compare their association with the outcome variable. The primary analyses were conducted using Cox proportional hazards regression. Univariate Cox proportional hazards regression was used to screen for potential significant association between each covariate and the outcome. Covariates with P < .15 were selected for multivariable model building using the backward selection method until the most parsimonious model was reached. To further examine the association between the outcome and the covariates, we performed subset analyses using...
Cox proportional hazards regression, adjusting for each of the individual cardiac risk factors and medications that are known to reduce MI risk in addition to age, sex, and person-years among the cohorts.

Poisson regression was used to examine the incidence rate of MI in each treatment group. The incidence rates of MI in the 3 cohorts (TNF inhibitors, oral/phototherapy, and topical) were first compared using unadjusted Poisson regression. The rates were then adjusted for age, sex, and person-years of observation and were compared with yield incidence rate ratios. All the statistical analyses were performed using a commercially available software program (SAS Enterprise Guide, version 4.3; SAS Institute, Inc).

### RESULTS

Between January 1, 2004, and November 30, 2010, there was a cohort of 8845 patients with psoriasis (Figure). Of 3217376 KPSC members in 2008, 18726 (0.58%) had a diagnosis of psoriasis, 1759 (0.06%) had a diagnosis of psoriatic arthritis, 1170 (0.04%) had both, and 19315 (0.60%) had a diagnosis of any psoriatic disease. The cohort mean age was 52.8 years, and 50.0% were men (Table 1). In this cohort, 5073 (57.4%) were not treated with any systemic therapy or phototherapy and were assigned to the topical cohort. Of the remaining patients, 1673 (18.9%) were treated with TNF inhibitors for at least 2 consecutive months, and 2097 (23.7%) were treated with oral systemic agents or phototherapy.

The cohort was observed for a median of 4.3 years (interquartile range, 2.9, 5.5 years), resulting in 42424 patient-years of follow-up. The data for 8624 patients (97.5%) were censored: 402 (4.5%) for death and 1818 (20.6%) for membership discontinuation, and 6404 (72.4%) were observed to the end of the study. The overall cohort experienced 221 episodes (2.5%) of incident MI, for an overall rate of 5.21 per 1000 patient-years. The incident rates of MI for the TNF inhibitor, oral/phototherapy, and topical cohorts were 3.05, 3.85, and 6.73 per 1000 patient-years, respectively (P < .001) (Table 2).

In pairwise comparisons of the 3 cohorts, the TNF inhibitor cohort had a statistically significant 55% reduction in MI incidence compared with the topical cohort (Table 3). The oral/phototherapy cohort had a statistically significant 43% reduction in MI incidence compared with the topical cohort. The TNF inhibitor cohort...
had a nonsignificant 21% reduction in MI incidence compared with the oral/phototherapy cohort.

The median duration of TNF inhibitor therapy was 685 days (interquartile range, 215, 1312 days). Adjusting for common characteristics and medications that may affect MI risk, use of TNF inhibitors was associated with a 50% lower hazard of incident MI (HR, 0.50; 95% CI, 0.32-0.79) compared with the topical cohort (Table 4). Patients in the oral/phototherapy cohort had a 46% lower risk of MI compared with the topical cohort (HR, 0.54; 95% CI, 0.38-0.77). Increasing age, male sex, and the classic MI risk factors were strongly associated with a greater risk of MI in this cohort of patients with psoriasis, whereas statin use was protective. β-Blockers did not confer statistically significant results. Psoriatic arthritis was associated with a 63% increased risk of MI compared with psoriatic patients without arthritis. In sensitivity analyses restricted to having at least 3 ICD-9-CM codes with a time-dependency analysis comparing TNF inhibitor use, methotrexate use, and topical agent use, the results were similar (Table 5).

In a multivariable model with an age stratification of patients 60 years and younger, the TNF inhibitor cohort had a statistically significant 54% lower hazard of incident MI (HR, 0.46; 95% CI, 0.25-0.88) compared with the topical cohort, and the oral/phototherapy cohort had a nonsignificant 40% lower risk of MI compared with the topical cohort (0.60; 0.34-1.03) (Table 6). In the group older than 60 years, the TNF inhibitor cohort had a significant 68% lower hazard of incident MI (HR, 0.32; 95% CI, 0.14-0.73) compared with the topical cohort, and the oral/phototherapy cohort had a significant 65% lower risk of MI compared with the topical cohort (0.35; 0.21-0.59) (Table 6).

When using the median duration of TNF inhibitor therapy of 685 days as the cutoff point and 685 days and less as the reference group (n = 840), there was a nonsignificant trend that longer duration of TNF inhibitor therapy (n = 833) was associated with a higher MI risk (HR, 1.36; 95% CI, 0.64-2.90; P = .43) compared with shorter duration.

In the multivariable model that included the 3 cohorts, the use of TNF inhibitors and oral agents/phototherapy for psoriasis was associated with statistically significant reductions (50% and 46%, respectively) in MI risk compared with patients treated with topical agents. It seems that controlling psoriasis with aggressive therapy and, thus, lowering inflammation leads to a reduction in MI risk. When making head-to-head comparisons, there is a trend that the use of TNF inhibitors is associated with a non–statistically significant lower MI incident rate compared with psoriatic patients treated with oral agents/phototherapy. The results of this study confirmed that psoriasis is associated with an increased risk of diabetes,5,6 hypertension,3,7 and dyslipidemia.3,7 As can be expected, a large proportion (49.4%) of patients in the TNF inhibitor cohort had psoriatic arthritis.

In the age-stratified multivariable model, it seems that treatment with TNF inhibitors and oral agents/phototherapy may have stronger protective effects in the group older than 60 years compared with the group 60 years and younger. One reason for this is that older patients are more likely to have type 2 diabetes mellitus, and the benefits of TNF inhibitor use may be mediated through improving risk of type 2 diabetes mellitus. Solomon et al28 recently reported that in those with psoriasis...
or rheumatoid arthritis treated with a TNF inhibitor or hydroxychloroquine (but not methotrexate), the adjusted risk of incident diabetes mellitus was lower than that in those treated with nonbiological disease-modifying antirheumatic drugs. As some studies have shown that TNF inhibition therapy improves insulin metabolism, this class of therapy may affect atherosclerotic risk via this mechanism as well.

An elevated level of C-reactive protein (CRP), a marker for inflammation, is associated with an increased risk of MI. Lowering CRP levels with statin therapy is associated with significantly lower incidences of MI, stroke, and other major cardiovascular events. Strober et al examined the effect of etanercept therapy on high-sensitivity CRP in patients with psoriasis. Psoriatic patients with and without psoriatic arthritis were noted to have elevated baseline high-sensitivity CRP levels. After 12 weeks of etanercept therapy, high-sensitivity CRP levels were significantly reduced regardless of concomitant statin therapy.

Using data from the large CORRONA (Consortium of Rheumatology Researchers of North America) registry of patients with rheumatoid arthritis, another inflammatory disease associated with cardiovascular disease, the investigators found that treatment with TNF antagonists was associated with a reduced risk of cardiovascular events (HR, 0.39; 95% CI, 0.19-0.82), including nonfatal MI (0.24; 0.06-0.95), compared with nonbiological disease-modifying antirheumatic drugs. Methotrexate therapy had no effect on cardiovascular events (HR, 0.94; 95% CI, 0.49-1.80). The present study is consistent with these previous studies and adds support to the hypothesis that TNF inhibition may lower the risk of MI in patients with systemic inflammatory conditions, such as psoriasis.

This study has several strengths: KPSC has many patients with psoriasis, a stable membership, and accurate diagnosis coding of psoriasis, MI, and other medical comorbidities. This allowed a substantial collection of cumulative longitudinal follow-up (patient-years of follow-up), giving the study adequate power to capture relatively uncommon events, such as MI. Furthermore, prescription drug use in the study cohort was well documented since more than 90% of all the prescriptions of KPSC members are filled in a health plan pharmacy (internal records).

The study results are generalizable to other psoriatic patients who are from an insured and ethnically diverse population. Based on internal documentation for the KPSC database, the accuracy and completeness for all the variables (except smoking) were in the upper 90% range. We believe that there is minimal selection bias as to why some patients with severe psoriasis were treated with TNF inhibitors vs oral therapy or phototherapy. The presence of psoriatic arthritis could influence a dermatologist to more likely prescribe a TNF inhibitor. An older age may reduce the likelihood of that patient receiving a TNF inhibitor since Medicare patients have less coverage of prescription benefits for the costly TNF inhibitors and older patients are more likely to have a recent history of cancer, which is a contraindication for TNF inhibitor therapy. However, psoriatic arthritis and age are already adjusted for in the multivariable analysis. A history of MI, diabetes, hypertension, or dyslipidemia would not affect the prescribing habits for a TNF inhibitor.

However, there are some limitations to this study. Owing to the nature of the data obtained from community practice, severity of psoriasis as measured by the Psoriasis Area and Severity Index or body surface area is unavailable. Thus, it is possible that patients with severe psoriasis based on the Psoriasis Area and Severity Index or body surface area chose not to receive any systemic therapy and, thus, were placed in the topical cohort. We included all types of diabetes and did not limit to type 2

### Table 5. Multivariable Proportional Hazards Model Assessing Factors Associated With Incident Myocardial Infarction Comparing TNF Inhibitors vs Methotrexate vs Topical Agents

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF inhibitors</td>
<td>0.50 (0.32-0.81)</td>
<td>.004</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>0.52 (0.31-0.85)</td>
<td>.01</td>
</tr>
<tr>
<td>Topical agents</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>0.51 (0.38-0.68)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>0.45 (0.34-0.61)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>1.63 (1.12-2.38)</td>
<td>.01</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.22 (1.64-3.00)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>5.30 (3.08-9.12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8.38 (4.02-17.47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>1.06 (0.80-1.42)</td>
<td>.68</td>
</tr>
<tr>
<td>Statins</td>
<td>0.31 (0.22-0.42)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: TNF, tumor necrosis factor.

### Table 6. Multivariable Proportional Hazards Model Assessing Factors Associated With Incident Myocardial Infarction in Patients 60 Years and Younger vs Older Than 60 Years

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients ≤60 y (n = 6138)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF inhibitors</td>
<td>0.46 (0.25-0.88)</td>
<td>.02</td>
</tr>
<tr>
<td>Oral agents/phototherapy</td>
<td>0.60 (0.34-1.03)</td>
<td>.06</td>
</tr>
<tr>
<td>Topical agents (n = 3243)</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Female sex</td>
<td>0.51 (0.32-0.79)</td>
<td>.003</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>1.48 (0.86-2.53)</td>
<td>.16</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.41 (1.51-3.85)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>7.42 (3.08-17.87)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.18 (1.59-6.33)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>1.55 (1.00-2.41)</td>
<td>.052</td>
</tr>
<tr>
<td>Statins</td>
<td>0.52 (0.32-0.86)</td>
<td>.01</td>
</tr>
</tbody>
</table>

| Patients ≥60 y (n = 2707)   |                       |         |
| TNF inhibitors              | 0.32 (0.14-0.73)      | .006    |
| Oral agents/phototherapy    | 0.35 (0.21-0.65)      | <.001   |
| Topical agents (n = 1468)   | 1 [Reference]         |         |
| Female sex                  | 0.54 (0.38-0.76)      | <.001   |
| Psoriatic arthritis         | 1.57 (0.99-2.49)      | .055    |
| Diabetes mellitus           | 2.20 (1.53-3.17)      | <.001   |
| Dyslipidemia                | 5.90 (3.00-11.63)     | <.001   |
| Hypertension                | 25.12 (3.47-182.06)   | .001    |
| β-Blockers                  | 0.84 (0.59-1.18)      | .31     |
| Statins                     | 0.20 (0.13-0.28)      | <.001   |

Abbreviation: TNF, tumor necrosis factor.
diabetes mellitus. Data for smoking was 5% incomplete, which could explain why smoking was not found to be associated with increased MI risk. Waist measurement and not body mass index may be the best indicator of obesity-related diseases. Obtaining mortality data generally has a 1-year lag period, so the period between January 1, 2011, and October 28, 2011, captured only MI incidence and not any deaths caused by MI.

In the primary multivariable analysis, we assumed that medication effect remained until the end of follow-up. This is equivalent to an intent-to-treat analysis, which improves the rigor of the analysis. Furthermore, a time-dependency analysis was not used in the primary multivariable analysis since it would be difficult to separate effects of changing therapies and combinations of therapies, and it would not account for any postponed remodeling of atherosclerosis or other beneficial internal effects that the use of TNF inhibitors or oral agents/phototherapy may induce. However, a sensitivity analysis using a time-dependency analysis comparing TNF inhibitors, methotrexate, and topical agents resulted in a similar lower HR for MI risk in the TNF inhibitor cohort.

Not all the drugs that may affect an individual’s MI risk were entered into the models. In particular, over-the-counter nonsteroidal anti-inflammatory drugs, such as aspirin, may have been used differently in these psoriasis cohorts and could not be adjusted for. We also did not account for the duration and dosing of statins, β-blockers, or methotrexate. It is possible that this confounded the association of β-blockers or methotrexate with the risk of MI. We also did not account for the duration and dosing of the other therapies in the oral/phototherapy cohort. Almost 20.6% of the cohort dis-enrolled from the insurance plan, so there is a potential for not capturing outcomes. These were generally younger patients in the age range of 40 years. This group is more dynamic in terms of moving and also more at risk for unemployment and other significant life changes and, thus, their high disenrollment is to be expected in any database.

One study reported that patients having at least 3 ICD-9-CM codes for psoriasis in retrospective studies would have a high positive predictive value for psoriasis and that there is a potential for misclassification error that might occur with using only 1 psoriasis diagnostic code for the primary analysis. In the present study, the sensitivity analyses restricted to 1 ICD-9-CM code (n = 22,951) showed that the HR and incidence rates (analysis not shown) remained consistent with those of the primary analysis performed with 3 ICD-9-CM codes.

In conclusion, to our knowledge, this is the first large-scale retrospective cohort study to show that the use of TNF inhibitors for psoriasis is associated with a clinically and statistically significant reduction in MI risk and incident rate compared with the use of topical agents for psoriasis.

REFERENCES


