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Tumor Necrosis Factor Alpha Inhibitor Therapy and Cancer Risk In Chronic Immune Mediated Diseases

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Abstract

Background—We compared the incidence of cancer following tumor necrosis factor alpha antagonists (TNF-I) therapy to that with commonly used alternative therapies across multiple immune mediated diseases.

Methods—The Safety Assessment of Biologic thERapy (SABER) study used data from national Medicaid & Medicare, Kaiser Permanente Northern California, TennCare, and pharmacy benefits plans for Medicare beneficiaries in New Jersey and Pennsylvania. Propensity score adjusted hazard ratios (HR) and 95% confidence intervals (CI) were computed to estimate the relative rates of cancer, comparing TNF-I users to alternative disease modifying therapies. The cancer finding algorithm had a positive predictive value ranging from 31% for any leukemia to 89% for female breast cancer.

Results—We included 29,555 patients with rheumatoid arthritis (13,102 person-years), 6,357 patients with inflammatory bowel disease (1,508 person-years), 1,298 patients with psoriasis (371 person-years), and 2,498 patients with psoriatic arthritis (618 person-years). The incidence of any solid cancer was not elevated in rheumatoid arthritis (HR 0.80, CI 0.59-1.08), inflammatory bowel disease (HR 1.42, CI 0.47-4.26), psoriasis (HR 0.58, CI 0.10-3.31) or psoriatic arthritis (HR 0.74, CI 0.20-2.76) during TNF-I therapy compared to disease specific alternative therapy. Among patients with rheumatoid arthritis, the incidence of any of the ten most common cancers in the

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United States and nonmelanoma skin cancer was not increased with TNF-I therapy compared to methotrexate failure.

Conclusions—Short-term cancer risk was not elevated among patients treated with TNF-I therapy relative to commonly used therapies for immune mediated chronic inflammatory diseases in this study.

Keywords

rheumatoid arthritis; inflammatory bowel disease; psoriasis; psoriatic arthritis; ankylosing spondylitis; tumor necrosis factor alpha

Introduction

Medications designed to inhibit the effects of tumor necrosis factor alpha (TNF-I) have become important components of the treatment of multiple chronic inflammatory disorders, including rheumatoid arthritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), psoriasis, psoriatic arthritis, and ankylosing spondylitis. During the premarketing trials of infliximab, adalimumab and etanercept, the incidence of lymphoma was higher in the patients treated with these TNF-Is than was expected based on rates in the general population. However, interpretation of these data is complicated by higher reported risk of lymphoma among patients with rheumatoid arthritis, particularly those with more severe disease¹⁻³.

In 2006, a systematic review and meta-analysis by Bongartz et al. reported a higher incidence of cancer, including lymphoma and non-melanoma skin cancer (NMSC) among patients treated with infliximab or adalimumab in placebo controlled trials⁴. A subsequent meta-analysis demonstrated a higher, but not statistically significant, incidence of malignancy with etanercept versus comparison therapies⁵. Thus, these studies suggested a possible increased risk of cancer among TNF-I treated patients with short-term therapy. In contrast, a meta-analysis of randomized trials of TNF-I for Crohn's disease found no increased risk of cancer with TNF-I therapy⁶. Similarly, a recent meta-analysis of 74 randomized trials of infliximab, adalimumab, or etanercept for a variety of conditions demonstrated no significant increased risk of cancers other than NMSC, but a 2-fold higher incidence of NMSC with TNF-I. In that study, there was some evidence that relative risks may vary between specific TNF-I medications⁷. Finally, a meta-analysis of patients with early rheumatoid arthritis treated with TNF-I or placebo found no increased risk of cancer with TNF-I therapy⁸.

Because clinical care generally entails a choice between alternative active treatments, we designed the Safety Assessment of Biologic thERapy (SABER) study as a comparative safety analysis of TNF-I and disease specific alternative treatment strategies⁹. One component of SABER assessed whether the risk of the most common cancers in the United States was higher among patients treated with TNF-I than among those receiving disease specific alternative therapies. Here we report that the incidence of these common cancers was not significantly higher in patients receiving TNF-I.

Methods

SABER is a retrospective cohort study that combines data from four data sources: 1) *National Medicaid and Medicare databases* (Medicaid Analytic eXtract, 2000–2005, excluding Tennessee; Medicare, 2000–2006; and Medicare Part D, 2006); 2) *Tennessee Medicaid (TennCare, 1998–2005)*; 3) *The New Jersey's Pharmaceutical Assistance to the Aged and Disabled, and the Pennsylvania's Pharmaceutical Assistance Contract for the*

Elderly (PAAD/PACE, 1998–2006); and, 4) Kaiser Permanente Northern California (KPNC, 1998–2007). A common programming algorithm was used to identify patients with autoimmune diseases who were initiating TNF-I and comparator drugs.

Exposure definitions

The SABER methods of cohort assembly and definitions of new users of TNF-I and comparator therapies have been previously reported⁹. In brief, we first identified patients with rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, or ankylosing spondylitis on the basis of ICD-9 diagnostic codes and medical therapies. We limited the cohort to new users of TNF-I and/or the comparative therapy, where new use required that patients have one full year of data prior to the first prescription that defined a new course of therapy and no use of TNF-I therapy in all available data within the database. The comparator therapies differed according to the disease being treated: rheumatoid arthritis – initiation of hydroxychloroquine, sulfasalazine or leflunomide following therapy with methotrexate; inflammatory bowel disease – initiation of azathioprine or mercaptopurine; psoriasis – initiation of retinoids, high potency topical steroids, or phototherapy following treatment with methotrexate; psoriatic arthritis and ankylosing spondylitis – initiation of methotrexate or sulfasalazine.

Inclusion and exclusion criteria

We identified all new users of either TNF-I or comparator therapies in the four datasets. We sought to exclude patients with a history of cancer defined as any code for cancer other than non-melanoma skin cancer (NMSC) by excluding those with at least one ICD-9 diagnosis code recorded in the year prior to the initiation of therapy. We also excluded patients with a history of organ transplant, HIV infection, or treatment with tacrolimus or cyclosporine during the one year look back period. These latter conditions were used as censoring events if they occurred after the start of follow-up.

We excluded patients who used another biologic medication from outside the TNF-I class in the 365 day period prior to exposure and censored people after cohort entry who initiated biologics from outside the TNF-I class. This was particularly important for rituximab, which can be used to treat lymphoma.

Outcome definitions

We identified incident cancers for patients in Kaiser Permanente using the Kaiser Permanente Northern California cancer registry. For each of the other data sources, incident cancers were identified using an adaption of the algorithm developed and validated by Setoguchi et al using Medicare data¹⁰ as we previously employed in assessing rates of malignancy in patients with juvenile idiopathic arthritis¹¹. For all disease groups, we examined the following outcomes: any lymphoma, any leukemia, any solid cancer, and NMSC. For patients with rheumatoid arthritis, we also studied the 10 most common cancers in the United States.

Because the Setoguchi algorithm was developed in an older population and for a limited number of cancers, we determined the sensitivity, specificity, and the positive predictive value (PPV) of our adaptation of Setoguchi's algorithm to identify incident cancers for each of the ten most common cancers in the United States. We tested our adaptation of the Setoguchi algorithm as applied to the electronic health record data in Kaiser Permanente using the Kaiser Permanente Northern California cancer registry as the gold standard. This cancer registry is one of several sites that submit data to the Surveillance, Epidemiology, and End Results (SEER) program, the largest cancer registry in the United States. SEER case ascertainment rates are documented to be greater than 98%. NMSC is not routinely captured

in SEER and therefore was not evaluated.¹² Details of the validation study are described further in the Appendix. The sensitivity of the algorithm exceeded 60% for all cancers other than melanoma (56%) and leukemia (28%) (Appendix Table 1). After employing a 1-year period prior to therapy initiation (look back) to exclude patients with cancer diagnosed prior to the start of therapy, the positive predictive value of the algorithm ranged from 31% (any leukemia) to 89% (female breast cancer). The low predictive values were due in part to cancer diagnoses that represented prevalent cancers not detected by the 1-year look back period, and ranged from 26% (any leukemia) to 61% (prostate cancer) (Appendix Table 1).

Baseline covariates

As described previously, the list of covariates was developed to capture variables believed to be potentially associated with the exposure of interest and the various outcomes included in SABER⁹. Baseline covariates included demographics: age, gender, race, residence (urban/rural), nursing home/community dwelling, area income, calendar year; generic markers of comorbidity: number of hospitalizations, outpatient and emergency room visits, number of different medication classes filled; surrogate markers of disease severity: extra-articular disease manifestations, number of intra-articular and orthopedic procedures, number of laboratory tests ordered for inflammatory markers, chronic obstructive pulmonary disease (COPD), diabetes and use of cancer screening tests (prostate specific antigen testing and mammography).

Statistical analysis

For each period of new use of a TNF-I or comparator drug, we calculated a propensity score to summarize the covariates recorded during the look back period. Propensity scores were computed using unconditional logistic regression with use of TNF-I as the dependent variable. Propensity scores were computed separately in each data set. We then examined the distribution of the propensity scores across each comparator group and excluded TNF-I treated patients with propensity scores in areas with no overlap with the comparator group and vice versa¹³.

Medication exposure was treated as a time updated variable such that patients could accrue follow-up time in one or both of the treatment arms sequentially and not simultaneously. However, once patients were treated with a TNF-I, they could not accrue follow-up time in the comparator cohort. In the primary as-treated analysis, follow-up continued until the earliest of the outcome of interest, the end of the available data or exposure to TNF-I or comparator drugs was discontinued. Our definition of discontinuation of therapy allowed for a grace period of 30 days between the expected end of a dispensing of drug and the next prescription. For patients treated with the comparator drugs, initiation of a TNF-I also marked the end of follow-up in the comparator cohort and the beginning of follow-up in the TNF-I cohort. We also conducted a first exposure carried forward analysis in which patients who discontinued the comparator treatment continued to contribute follow-up time to that cohort until they initiated TNF-I therapy or experienced the outcome of interest; patients treated with TNF-I contributed follow-up time to that cohort until the end of the available data or the date that they experienced the outcome of interest. Thus, the first analysis examined only outcomes that occurred while patients were receiving therapy, and the secondary analysis allowed for an indefinite lag between discontinuation of therapy and the onset of cancer.

For each outcome, we computed hazard ratios using Cox regression stratified by data set. Because patients could accrue follow-up time in both the TNF-I and comparator cohorts, we used the Huber-White “sandwich” variance estimator to calculate robust standard errors for all estimates¹⁴. The only independent variables in the model were the exposure group (TNF-

I vs. comparator drugs), use of corticosteroids at baseline, and the propensity score which was categorized in quintiles. Separate analyses were performed for the outcomes of any lymphoma, any hematologic cancer, any solid cancer other than NMSC, and NMSC, defined as squamous cell or basal cell, across diseases for which TNF-I was indicated. Because the number of cancer diagnoses among patients with diseases other than rheumatoid arthritis were relatively small, analysis of specific cancers was limited to patients with rheumatoid arthritis. We elected only to report hazard ratios when there were at least 5 patients with the outcome of interest and at least one patient with the outcome in each of the treatment arms.

A sensitivity analysis was conducted to estimate the potential impact of prevalent cancers being misdiagnosed as incident cancers. Under the assumption of an observed null association between TNF-I use and cancer risk, we varied the distribution of observed cancers that were prevalent rather than incident and the distribution of these cancers across the treatment groups to estimate the potential magnitude of bias that may have resulted from this misclassification. See Appendix for additional details.

Results

From the entire SABER cohort, we included 29,555 patients with rheumatoid arthritis (19,750 TNF-I; 9805 comparator drug), 6,357 patients with inflammatory bowel disease (2,657 TNF-I; 3,700 comparator drug), 1,298 patients with psoriasis (563 TNF-I; 735 comparator drug), 2,498 patients with psoriatic arthritis (1,036 TNF-I; 1,462 comparator drug), and 1,486 patients with ankylosing spondylitis (783 TNF-I; 703 comparator drug). The characteristics of the TNF-I treated patients and the comparator groups were generally similar (Table 1). In the rheumatoid arthritis cohort, follow-up time was 13,102 person-years [median 0.5 years (IQR 0.2–1.1) for TNF-I and 0.3 years (IQR 0.2–0.6) for the comparator group] in the analysis limited to follow-up time while patients were receiving the drug. This increased to 33,203 person-years [median 1.5 years (IQR 0.7–2.8) for TNF-I and 1.4 years (IQR 0.6–3.0) for the comparator group] in the first exposure carried forward analysis for rheumatoid arthritis (Table 1). Among the 9805 patients with rheumatoid arthritis in the comparator group, 2400 (24%) were subsequently treated with a TNF-I. Median follow-up for this subgroup in the first exposure carried forward analysis was 0.9 years (IQR 0.4–1.9) with the comparator drug and 1.4 years (IQR 0.6–2.6) with a TNF-I. For the propensity-score adjusted analysis the proportion of patients with non-overlapping propensity scores in the RA solid tumor analysis was 1.5%.

Consistent with the size of the cohorts, the greatest number of cancer diagnoses occurred in the rheumatoid arthritis cohort (Table 2). The cancer incidence rates were similar in the primary and the secondary analyses, although the number of events was 2 to 3 fold higher in the secondary analysis.

In the primary analysis, rates of solid cancers were not significantly higher in the TNF-I group than in the comparator group across all immune mediated diseases (Table 3) and as shown in Kaplan-Meier curves for RA (Figure 1). For all diseases and cancer types where there were a sufficient number of events to estimate hazard ratios, no significant increase risk was observed for any lymphoma, any leukemia or lymphoma, or NMSC in both the primary and secondary analyses (Table 3).

We examined the relative hazard of the ten most common cancers in the United States in the cohort with rheumatoid arthritis (Table 4). Patients treated with TNF-I did not have a significantly increased risk for any of these cancers. The largest hazard ratio was observed for colorectal cancer in the primary analysis (HR= 1.75, 95% CI 0.65 – 4.68).

To assess the impact of prevalent cancers being identified as incident cancers, we computed the potential magnitude of bias that could result across a range of assumptions for the following variables: the proportion of false positive cancer diagnoses that were prevalent cancers and the distribution of these false positive prevalent cancers between the TNF-I and comparator group. For an observed relative risk of 1.0, the true relative risk could be elevated as high as 2.0 if the proportion of falsely identified incident cancers that were prevalent cancers was 50% and 100% of these were in the comparator group (Table 5).

Discussion

Previous evaluations of the relative risk of cancer associated with TNF-I have come to differing conclusions, with some but not all meta-analyses of clinical trial data suggesting that TNF-I may increase the risk of cancer, particularly among patients with rheumatoid arthritis. Observational studies are potentially able to overcome the sample size and short follow-up limitations of clinical trials but can be biased by channeling and residual confounding. Several observational studies have come to differing conclusions about the risk of cancer with TNF-I therapy^{15–21}. For example, within a Crohn's disease center of excellence, patients treated with TNF-I appeared to have an increased incidence of cancer¹⁵. Several studies suggest a possible increased risk of skin cancers among patients with rheumatoid arthritis who are treated with TNF-I, particularly when used with concomitant immunosuppressant medications.^{17, 21} Previous studies^{17–20} did not observe a higher incidence of any solid cancer or lymphoma among rheumatoid arthritis treated with TNF-I. In this large retrospective cohort study that included a broad spectrum of patients from multiple health plans throughout the United States, we did not observe evidence of an increased risk of cancer associated with TNF-I therapy in either an analysis limited to the period of current therapy or in an analysis that continued follow-up after the patient discontinued therapy.

Medications can increase the incidence of cancer by initiating the cancer process, by promoting progression of precancerous states to invasive cancer, or both. Relatively limited data are available on time since initiation of therapy and the risk of cancer. Askling recently reported that there was no increased risk of cancer among a cohort of patients with rheumatoid arthritis newly starting TNF-I therapy in Sweden and that risk did not increase with greater time since initiation²². In our study, we used two different definitions of exposure. In the primary analysis, follow-up was censored when the drug was discontinued, whereas the secondary analysis continued to follow these patients in their original exposure group, regardless of changes in treatment. The two analyses produced similar hazard ratios. Furthermore, the Kaplan Meier curves did not suggest an increasing relative risk with longer follow-up time although the number of patients with long duration of follow-up was relatively small. Of note, the absolute incidence rates in our cohort were remarkably similar to that in Askling's cohort²².

A unique aspect of SABER was the ability to address the same question in different disease states using the same methodology. Patients with rheumatoid arthritis have an increased risk of lymphoma that is associated with the underlying inflammation^{1–3} while there is little if any increased risk of lymphoma among patients with inflammatory bowel disease in the absence of immunosuppression.^{23, 24} The hazard ratios for any solid cancer were similar in the rheumatoid arthritis and inflammatory bowel disease cohorts. In our analysis of any lymphoma or leukemia, there was no significant increased risk in either population. In the inflammatory bowel disease cohort, the TNF-I therapy was non-significantly associated with a lower lymphoma or leukemia incidence (HR=0.41) whereas in the rheumatoid arthritis cohort the hazard ratio was 0.99. This apparent difference may be due to the choice of comparator therapy for the analysis of inflammatory bowel disease, since thiopurines are

associated with an increased incidence of lymphoma.^{24, 25} Similar patterns were seen for NMSC which has also been associated with thiopurine therapy.^{26, 27}

Major strengths of the SABER initiative include the large sample sizes, the diverse patient population, the comparison of TNF-I therapy to the relevant alternative therapy, and the ability to examine the association of TNF-I therapy with various adverse events across several different diseases for which these therapies are indicated and widely used. Our study is broadly generalizable to the US population given the data resources included low income Medicaid beneficiaries, those with private health insurance in Northern California, and a low income elderly population from the Northeast. However, there are several limitations to this study that should be considered when interpreting the results.

We had limited power to assess the association among some of the disease subgroups and for rare outcomes. This may have been due in part to the timing of FDA approval of TNF-I therapy for these indications. Adalimumab, the second TNF-I to be FDA approved for use in Crohn's disease received formal approval in February 2007. Likewise, infliximab and adalimumab did not receive approval for psoriasis until 2006 and 2008, respectively.

Studies that rely on previously collected electronic data must consider the accuracy of the methods used to identify the exposures and the outcomes. For medications, we utilized data on filled prescriptions. For our outcome assessment, we used two different methods. We were able to utilize cancer registry information to assign outcomes for the patients from Kaiser Permanente Northern California and we relied on a validated algorithm to identify cancer outcomes in claims data.¹⁰ We replicated the work of Setoguchi et al¹⁰ who tested a claims data-based definition for selected cancers in Medicare beneficiaries. Our results showed similar results with respect to sensitivity and positive predictive value in a health plan with computerized data, Kaiser Permanente Northern California. We extended the validation work to other solid cancers and report generally similar test characteristics across most of the cancers. Given the similar results in Medicare and Kaiser Permanente, it is likely that the algorithm performs comparably in Medicaid and TennCare data.

As is typical of observational studies using administrative and electronic health record data, the algorithm for identifying incident cancers was imperfect. Setoguchi previously demonstrated that the magnitude of bias toward the null expected based on the performance characteristics of the cancer finding algorithm is small when the misclassification is non-differential¹⁰. We further estimated that approximately 40% to 70% of the false positive incident cancers were actually prevalent cancers, but that approximately half of these were identified as prevalent and excluded from our cohort study by using the 1-year look back period. Therapy with TNF-I may be selectively avoided in patients with a history of cancer and such channeling may bias observational studies against finding an association between TNF-I therapy and cancer risk. Our sensitivity analysis, included as supplementary material, suggests that our observed relative risk estimates of approximately 1 could reflect true relative risk estimates of up to 2.0 due to such misclassification if one assumed that all prevalent cancers were in the comparator group. However, we further explored the distribution of prevalent cancer among the false positive cancer diagnoses in our validation study and found no difference between the exposure groups (data not shown). Thus, the magnitude of such bias in our study is likely smaller than we estimate in our sensitivity analysis. Similarly, patients with a history of cancer may be more likely to develop a second cancer, but in general, this represents a small proportion of all patients with an incident cancer²⁸ and as such should have a much smaller effect on the observed results. Because of the imperfect nature of the algorithm and the potential for channeling TNF-I to patients without a history of cancer, the lack of association observed in this study should be interpreted cautiously. While the results suggest that a strong association between TNF-I and

cancer risk is unlikely, our sensitivity analysis demonstrates that we cannot rule out small to modest associations. Whether such increased risk is clinically important depends on the clinical situation.^{29, 30}

We elected to combine multiple cancers together in our outcomes of any solid cancer or any lymphoma or leukemia. One advantage of this is that the larger numbers of events increases statistical precision. The composite measure also accounts for the possibility that the therapy could increase the incidence of one cancer while decreasing the incidence of another, thus helping physicians and patients to make decisions that account for each of these effects. However, a disadvantage is that the effect of specific cancer incidence rates can be obscured in analysis of the composite measure. For this reason we performed additional analyses of the 10 most common cancers in the United States. While these results were generally consistent with the analysis of the composite measure, it is possible that TNF-I could increase or decrease the incidence of less common cancers. Extremely large studies would be required to assess this.

Despite combining data from 4 different data sources, given that cancer is rare, the sample sizes and follow-up time were still relatively small for some of the outcome measures and resulted in the imprecision of the risk assessment in non-RA cohorts. However, for several of these non-RA disease cohorts of patients our study is among the largest to date. Furthermore, the duration of TNF-I therapy was short and limits our ability to detect cancers that may occur later in the course of therapy, however our use patterns were consistent with known rates of loss of response during maintenance therapy^{31–35}. However, the hazard ratios measured in this study do not suggest an important increase in the risk of any of the cancers under study during the first several years of initiating treatment.

We elected to compare TNF-I treated patients to other patients with the same underlying disease process but who were treated with other non-biologic therapies. While this generally reflects the treatment decision facing clinicians and patients, this does not directly test the hypothesis of whether TNF-I therapies increase the risk of cancer (such as compared to no therapy or to placebo). Some of the comparator drugs that we studied have been strongly associated with selected cancers. Particularly well established is the association between thiopurine therapy and the risk of lymphoma.^{24, 25} Such therapies may also increase the risk of skin cancer and cervical cancer.^{26, 27, 36–38} To the extent that the comparator drugs increase the risk of the cancer, our new user comparative safety design may obscure a true biological effect of TNF-I. In contrast, previous or concurrent treatment thiopurines among the TNF-I cohort could potentially result in attribution of cancer risk to the TNF-I when in fact it was the thiopurine that led to the cancer. Additionally, our choice of comparators may still be subject to some unadjusted confounding, such as related to duration of the underlying disease, despite the propensity score methods. While there is no perfect study design to disentangle this issue, our design closely reflects the treatment decisions made every day in clinical practice.

We did not address cancer-related mortality in this study as cause of death can be difficult to determine in administrative data. Results of the association of TNF-I with all-cause mortality will be reported elsewhere.

In conclusion, we did not observe an increased incidence of cancer early in the course of treatment among patients treated with TNF-I in this large cohort study across multiple patient populations. Similarly, among patients with rheumatoid arthritis, the incidence of the 10 most common cancers was not higher among patients treated with TNF-I therapy. However, the potential for channeling of comparator therapies to patients with a history of cancer or other risk factor for cancer could have biased the results in a manner that would

obscure a small to modest association between TNF-I and cancer. Similarly, the outcomes of long term therapy will require further study in these or other cohorts.

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Abbreviations

Sens	sensitivity of the cancer algorithm
PPV	positive predictive value of the cancer algorithm
FP	false positive cancer diagnosis based on the cancer algorithm
OC	observed cancer
OC_{TNF}	observed cancers in TNF-I group; subscript notation is the same for all variables
OC_{COMP}	observed cancers in comparator group; subscript notation is the same for all variables
PC	observed cancers that are actually prevalent cancers
NPFP	false positive cancer diagnoses based on the cancer algorithm that are not prevalent cancers
OIC	observed cancers that are true incident cancers
UC	unobserved true cancers (i.e. incident cancers missed by the algorithm)
PFPP	proportion of false positive cancers that are prevalent (i.e. $PC/((1-PPV)*OC)$)
PPCG	proportion of prevalent cancers that are in the comparator group

To compute the “true” relative risk under this assumption, we used the following calculations

PC	$OC * (1 - PPV) * PFPP$
NPFP	$OC * (1 - PPV - ((1-PPV)*PFPP))$
OC_{TNF}	$OC*0.5$
PC_{TNF}	$(1-PPCG)*PC$
NPFP_{TNF}	$NPFP * 0.5$
OIC_{TNF}	$OC_{TNF} - PC_{TNF} - NPFP_{TNF}$
UC_{TNF}	$(OIC_{TNF}/Sens) - OIC_{TNF}$

OC_{COMP}	$OC - OC_{TNF}$
PC_{COMP}	$PPCG * PC$
$NPFP_{COMP}$	$NPFP * 0.5$
OIC_{COMP}	$OC_{COMP} - PC_{COMP} - NPFP_{COMP}$
UC_{COMP}	$(OIC_{COMP}/Sens) - OIC_{COMP}$
True RR	$(OIC_{TNF} + UC_{TNF}) / (OIC_{COMP} + UC_{COMP})$

Appendix

Because the Setoguchi algorithm was developed in an older population and for a limited number of cancers, we determined the sensitivity, specificity, and the positive predictive value (PPV) of our adaptation of Setoguchi's algorithm to identify incident cancers for each of the ten most common cancers in the United States. We tested our adaption of the Setoguchi algorithm as applied to the electronic health record data in Kaiser Permanente using the Kaiser Permanente Northern California cancer registry as the gold standard. This cancer registry is one of several sites that submit data to the Surveillance, Epidemiology, and End Results (SEER) program, the largest cancer registry in the United States. SEER case ascertainment rates are documented to be greater than 98% however NMSC is not routinely captured in SEER and therefore was not evaluated.¹² For the validation study, we used all cancers recorded in the registry in the period from 180 days following start of enrollment in SABER to 180 days before the end of enrollment in SABER. We then looked for a computerized health-care-record-based definition in the computerized healthcare data during the period from 180 days before to 180 days after the tumor registry entry to determine sensitivity and specificity. Correspondingly we looked for a tumor registry record in the 180 days before or after the claims-based definition to determine the positive predictive value of the claims algorithm. Thus a true positive was defined as an incident diagnosis of the cancer in the computerized healthcare data and in the cancer registry within 180 days of each other. Additionally, we used the cancer registry to estimate the proportion of incident cancer diagnoses based on the algorithm that had been diagnosed more than 180 days prior to the date identified by the algorithm (i.e. prevalent cancers). We next determined the proportion of the prevalent cancers that would be detected by excluding patients with cancer during the 1 year look back period. This was used to compute the final positive predictive value of the algorithm and the proportion of false positives that were prevalent cancers that were missed by the 1 year look back period.

The sensitivity of the algorithm exceeded 60% for all cancers other than melanoma (56%) and leukemia (28%) (Appendix Table 1). After employing a 1 year look back period to exclude patients with cancer diagnosed prior to the start of therapy, the positive predictive value of the algorithm ranged from 31% (any leukemia) to 89% (female breast cancer). The proportion of false positive cancer diagnoses that were prevalent cancers not detected by the 1 year look back period ranged from 26% (any leukemia) to 61% (prostate cancer).

Sensitivity analysis to detect the impact of prevalent cancers on the observed relative risk estimates

A sensitivity analysis was conducted to assess the impact of the proportion of falsely identified incident cancers that were actually prevalent cancers and the distribution of these prevalent cancers between the TNF-I and comparator group. In the sensitivity analysis, we assumed an observed relative risk of cancer of 1.0 and equal follow-up time between the

TNF-I and comparator group. We also assumed that falsely identified incident cancers that were not prevalent cancers were evenly distributed between the study groups. We varied the proportion of false positive observed cancers that were prevalent cancers and the distribution of these between the TNF-I and comparator groups.

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Figure 1.

Kaplan-Meier curves for patients with rheumatoid arthritis (RA), comparing rates of solid cancers in the tumor necrosis factor inhibitor(TNF-I)–treated group with rates of solid cancers in the comparator-treated group. **A**, Results from the primary analysis. **B**, Results from thesecondary analysis. The primary analysis examined only outcomes that occurred while patients were receiving therapy, and the secondary analysisallowed for an indefinite lag between discontinuation of therapy and the onset of cancer (see Patients and Methods). The Kaplan-Meier curves didnot suggest an increasing relative risk with longer followup time.

Table 1

Characteristics of the immune mediated disease cohorts

	Rheumatoid arthritis		IBD		Psoriasis		Psoriatic Arthritis		Ankylosing spondylitis	
	TNF-I treated (n=19,750)	Comparator (n=9,805)	TNF-I treated (n=2,657)	Comparator (n=3,700)	TNF-I treated (n=563)	Comparator (n=735)	TNF-I treated (n=1,036)	Comparator (n=1,462)	TNF-I treated (n=783)	Comparator (n=703)
Person-time Primary	8,242.6	4,859.7	813.22	694.9	227.1	143.5	398.1	219.9	313.3	119.8
Person-time Secondary	17,850.6	15,352.1	2,865.3	2,290.2	485.3	481.1	779.0	642.5	657.9	462.3
Female (%)	85.1	85.8	66.9	65.9	65.2	59.6	63.3	63.0	30.8	39.0
Race (%)										
White	62.3	61.6	78.7	76.1	69.6	68.4	81.9	77.7	66.8	62.3
Black	16.3	15.9	15.7	15.0	8.7	8.6	3.19	4.5	7.7	10.5
Other	21.4	22.5	5.5	8.9	21.7	23.0	15.0	17.9	25.5	27.2
Age (%)										
<35	6.1	5.0	36.5	39.1	16.3	11.6	11.1	11.1	19.5	20.9
35–65	60.1	60.4	55.0	50.9	67.3	60.3	72.5	69.4	72.5	67.9
>65	33.9	34.6	8.6	9.9	16.4	28.2	16.4	19.5	7.8	11.3
Health plan (%)										
Medicaid	74.0	62.8	73.7	58.7	67.5	57.8	65.6	50.6	70.2	59.3
KPNC	13.6	21.5	14.1	26.7	22.2	29.0	26.1	39.1	22.9	28.6
TennCare	7.2	11.4	11.1	13.0	9.2	11.0	5.0	6.2	6.5	10.5
PACE/PAAD	5.2	4.3	1.1	1.6	1.1	2.2	3.3	4.1	0.4	1.6
Charlson comorbidity score (%)*										
0	1.8	2.9	68.1	70.9	60.4	55.2	48.8	59.2	63.2	65.0
1	56.7	56.7	22.2	21.0	26.3	27.9	31.9	26.5	26.8	23.9
2+	41.4	40.5	9.7	8.0	13.3	16.9	19.4	14.3	10.0	11.1
COPD	20.0	20.7	18.1	16.6	17.4	17.7	14.9	14.0	11.4	12.7
Median household income (median, range)	36,230 (0–200,001)	36,763 (0–186,998)	37,426 (7,236–154,906)	39,150 (8,292–161,452)	37,063 (12,351–127,565)	38,565 (4,732–142,704)	40,208 (9,487–200,001)	43,256 (0–200,001)	40,105 (10,974–144,406)	40,694 (0–142,459)
Hospitalizations in the prior year (median, range)	0 (0–25)	0 (0–28)	1 (0–20)	0 (0–16)	0 (0–16)	0 (0–10)	0 (0–13)	0 (0–14)	0 (0–10)	0 (0–14)
Index therapy										

	Rheumatoid arthritis		IBD		Psoriasis		Psoriatic Arthritis		Ankylosing spondylitis	
	TNF-I treated (n=19,750)	Comparator (n=9,805)	TNF-I treated (n=2,657)	Comparator (n=3,700)	TNF-I treated (n=563)	Comparator (n=735)	TNF-I treated (n=1,036)	Comparator (n=1,462)	TNF-I treated (n=783)	Comparator (n=703)
Infliximab	34.7	N/A	96.8	N/A	3.6	N/A	21.7	N/A	25.9	N/A
Adalimumab	22.7	N/A	3.2	N/A	2.5	N/A	11.6	N/A	9.5	N/A
Etanercept	42.6	N/A	N/A	N/A	94.0	N/A	66.7	N/A	64.6	N/A
Hydroxychloroquine	N/A	48.9	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Leflunomide	N/A	37.4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Sulfasalazine	N/A	13.7	N/A	N/A	N/A	N/A	N/A	26.5	N/A	55.1
Methotrexate	N/A	N/A	N/A	N/A	N/A	N/A	N/A	73.5	N/A	45.0
Azathioprine/Mercaptopruine	N/A	N/A	N/A	100.0	N/A	N/A	N/A	N/A	N/A	N/A
UV light therapy	N/A	N/A	N/A	N/A	N/A	36.6	N/A	N/A	N/A	N/A
Topical steroids	N/A	N/A	N/A	N/A	N/A	20.3	N/A	N/A	N/A	N/A
Retinoid	N/A	N/A	N/A	N/A	N/A	43.1	N/A	N/A	N/A	N/A

Table 2
Cancer Incidence rates per 100 person-years in the study cohorts (Number of new cancer diagnoses)

	Rheumatoid Arthritis	Inflammatory bowel disease	Psoriasis	Psoriatic arthritis	Ankylosing Spondylitis
Primary analysis *					
Any lymphoma					
TNF-I	0.12 (22)	0.00 (0)	0.00 (0)	0.00 (0)	0.00 (0)
Comparator	0.13 (8)	0.05 (<5)	0.00 (0)	0.00 (0)	0.00 (0)
Any lymphoma or leukemia					
TNF-I	0.13 (23)	0.06 (<5)	0.00 (0)	0.00 (0)	0.00 (0)
Comparator	0.17 (10)	0.05 (<5)	0.00 (0)	0.00 (0)	0.00 (0)
Any solid cancer					
TNF-I	0.91 (160)	0.82 (13)	0.78 (<5)	0.77 (8)	0.44 (<5)
Comparator	1.10 (66)	0.41 (9)	1.21 (<5)	0.81 (7)	1.47 (<5)
NMSC					
TNF-I	0.31 (54)	0.25 (<5)	0.52 (<5)	0.29 (<5)	0.15 (<5)
Comparator	0.35 (21)	0.65 (14)	1.22 (<5)	0.34 (<5)	0.73 (<5)
Secondary analysis †					
Any lymphoma					
TNF-I	0.14 (52)	0.00 (0)	0.00 (0)	0.05 (<5)	0.00 (0)
Comparator	0.11 (22)	0.05 (<5)	0.00 (0)	0.06 (<5)	0.00 (0)
Any lymphoma or leukemia					
TNF-I	0.16 (61)	0.08 (<5)	0.00 (0)	0.05 (<5)	0.00 (0)
Comparator	0.16 (31)	0.06 (6)	0.00 (0)	0.06 (<5)	0.14 (<5)
Any solid cancer					
TNF-I	1.05 (394)	0.80 (43)	0.61 (5)	0.84 (17)	0.45 (6)
Comparator	1.14 (225)	0.63 (47)	1.07 (17)	0.84 (30)	0.79 (11)
NMSC					
TNF-I	0.35 (134)	0.26 (14)	0.49 (<5)	0.39 (8)	0.15 (<5)
Comparator	0.39 (77)	0.40 (30)	0.37 (6)	0.11 (<5)	0.43 (6)

Rates and counts of cases were computed prior to exclusion of patients at the extremes of the propensity score distributions

* Follow-up is censored when the patient discontinues therapy

+ Follow-up continues even if the patient discontinues therapy

Table 3

Hazard ratio of incident cancer for TNF-I vs. the comparator therapy

	Rheumatoid Arthritis Hazard ratio (95% CI)	Inflammatory bowel disease Hazard ratio (95% CI)	Psoriatic arthritis Hazard ratio (95% CI)	Psoriasis Hazard ratio (95% CI)	Ankylosing Spondylitis Hazard ratio (95% CI)
Primary analysis*					
Any lymphoma	0.83 (0.33–2.05)	<5 events	<5 events	<5 events	<5 events
Any lymphoma or leukemia	0.65 (0.28–1.53)	<5 events	<5 events	<5 events	<5 events
Any solid cancer	0.80 (0.59–1.08)	1.42 (0.47–4.26)	0.74 (0.20–2.76)	0.58 (0.10–3.31)	0.03 (0.002–0.45)
NMSC	0.83 (0.49–1.42)	0.08 (0.01–0.82)	0.74 (0.06–8.72)	<5 events [†]	<5 events
Secondary analysis[‡]					
Any lymphoma	1.25 (0.71–2.20)	<5 events	<5 events	<5 events	<5 events
Any lymphoma or leukemia	0.99 (0.60–1.61)	0.41 (0.07–2.35)	<5 events	<5 events	<5 events
Any solid cancer	0.94 (0.79–1.12)	1.18 (0.66–2.09)	0.88 (0.39–1.98)	0.83 (0.23–3.02)	0.15 (0.03–0.76)
NMSC	1.07 (0.79–1.46)	0.37 (0.13–1.07)	2.65 (0.33–21.07)	0.35 (0.04–3.43)	0.57 (0.13–2.58)

* Follow-up is censored when the patient discontinues therapy

[†] Follow-up continues even if the patient discontinues therapy

[‡] Only two events remain after PS matching

Table 4

Relative hazards of the 10 most common cancers in the United States among patients with rheumatoid arthritis treated with TNF-I or the comparator therapies.

	TNF	Comp	Primary analysis [*]	TNF	Comp	Secondary analysis ⁺
Non-biologic DMARD person-years [‡]			6,000			19,699
TNF-I person-years [‡]			17,582			37,559
			Hazard Ratio[‡](95% CI)			Hazard Ratio[‡](95% CI)
Any lymphoma	13	8	0.83 (0.33 - 2.05)	31	19	1.25 (0.71, 2.20)
Any leukemia			<5 events	6	7	0.57 (0.21, 1.54)
Prostate	<5	<5	0.49 (0.14 - 1.71)	11	13	0.61 (0.31 - 1.22)
Female breast	10	11	0.60 (0.31 - 1.15)	30	33	0.90 (0.60 - 1.36)
Lung	13	14	0.77 (0.40 - 1.49)	46	49	1.03 (0.73, 1.46)
Colorectal	15	6	1.75 (0.65 - 4.68)	29	25	1.06 (0.62, 1.82)
Uterine			<5 events	<5	<5	0.80 (0.29 - 2.23)
Kidney/renal pelvis			<5 events	7	8	0.77 (0.33 - 1.77)
Bladder			<5 events	9	<5	1.30 (0.40 - 4.23)
Malignant melanoma			<5 events	<5	6	0.84 (0.32, 2.23)

^{*} Follow-up is censored when the patient discontinues therapy

⁺ Follow-up continues even if the patient discontinues therapy

[‡] Based on analysis of any solid cancer as an outcome.

[‡] Adjusted for propensity score and average steroid dose at baseline

In the secondary analysis, exposure continues until start of the alternative therapy even if the patient discontinues therapy

Table 5

Results of a sensitivity analysis to assess the impact of the proportion of falsely identified incident cancers that were truly prevalent cancers and the distribution of these prevalent cancers between the TNF-I and comparator group.

Proportion of falsely identified incident cancers that were truly prevalent cancers	Proportion of the false positive prevalent cancers that were in the comparator group	True relative risk
35%	100%	1.61
35%	75%	1.26
35%	67%	1.17
35%	50%	1.00
50%	100%	2.00
50%	75%	1.40
50%	67%	1.26
50%	50%	1.00
60%	100%	2.33
60%	75%	1.50
60%	67%	1.31
60%	50%	1.00

The analysis assumes an observed relative risk of 1.0, sensitivity 76%, positive predictive value of the algorithm of 60% and that falsely identified incident cancers that were not prevalent cancers were evenly distributed between the medication exposure groups.

Appendix Table 1

Sensitivity, specificity, and positive predictive value of claims-based definition of incident cancers* in Kaiser Permanente Northern California

	Sensitivity (%)	Positive predictive value without application of 1 year look back period(%)	Proportion of false positives that were prevalent cancers (%)	Proportion of prevalent cancers detected with 1 year look back period (%)	Positive Predictive Value of algorithm after applying 1 year look back period (%)	Proportion of false positives that were prevalent cancers after applying 1 year look back period (%)
Any lymphoma	76	52	48	27	60	35
Any leukemia	28	29	32	20	31	26
Prostate	62	52	86	29	70	61
Female breast	82	65	64	43	89	36
Lung	64	62	60	14	67	51
Colorectal	84	52	38	17	56	32
Uterine	74	61	56	20	69	45
Kidney/renal pelvis	86	70	55	17	77	46
Bladder	81	63	70	36	84	45
Melanoma	56	61	70	14	68	60

* Date of cancer incidence was based on the date that the cancer was recorded in the cancer registry