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Risk of Malignancy Associated with Pediatric Use of Tumor Necrosis Factor Inhibitors

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Details of contributors: Dr. Beukelman conceptualized and designed the study, acquired the data, interpreted the results, drafted the initial manuscript, and reviewed and revised the manuscript. Mr. Xie analyzed the data and critically reviewed the manuscript. Dr. Chen acquired the data, analyzed the data, and critically reviewed the manuscript. Drs. Horton, Mamtani, and Mannion interpreted the results and critically reviewed the manuscript. Dr. Lewis conceptualized and designed the study, interpreted the results, and critically reviewed the manuscript. Dr. Saag acquired the data, interpreted the results, and critically reviewed the manuscript. Dr. Curtis conceptualized and designed the study, acquired the data, interpreted the results, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Ethics approval: We obtained ethics approval from the Institutional Review Board of the University of Alabama at Birmingham, protocol number X140507011. A waiver of informed consent was granted.

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Abstract

Objective: To determine whether tumor necrosis factor inhibitor (TNFi) use is associated with an increased rate of incident malignancy compared to no TNFi use in the treatment of juvenile idiopathic arthritis (JIA), pediatric inflammatory bowel disease (pIBD), and pediatric plaque psoriasis (pPsO).

Methods: We performed a retrospective cohort study of administrative claims data from the United States from 2000–2014. Exposure to TNFi was considered permanent from the first observed exposure onward. The malignancy outcome was defined by diagnosis codes with evidence of cancer treatment. We calculated standardized incidence ratios (SIR) comparing the observed number of malignancies to the expected numbers according to cancer surveillance data. We used multivariable Cox proportional hazard models to estimate adjusted hazard ratios (aHR) for incident malignancy.

Results: We identified 15,598 children with TNFi use and 73,839 children with no TNFi use (30,703 and 121,801 person-years of follow-up, respectively). We identified 15 malignancies among children with TNFi use (SIR 2.9 [1.6–4.9]) and 42 malignancies among children without TNFi use (SIR 2.1 [1.5–2.9]). The aHR was 1.58 [0.88–2.85] for TNFi use versus no TNFi use. In pIBD, TNFi use with thiopurine use was associated with a higher SIR (6.0 [1.2–17.5]) compared to TNFi use without thiopurine use (2.5 [0.7–6.4]).

Conclusion: Children diagnosed with JIA, pIBD, and pPsO had an increased rate of malignancy compared to the general population, but treatment with TNFi did not appear to significantly further increase the risk compared to no TNFi use. More data are needed about the long-term risks of TNFi use.

Keywords

juvenile idiopathic arthritis; anti-TNF; epidemiology; treatment

INTRODUCTION

Tumor necrosis factor inhibitors (TNFi) are highly effective for the treatment of juvenile idiopathic arthritis (JIA) (1, 2); pediatric inflammatory bowel disease (pIBD), including Crohn's disease (3, 4) and ulcerative colitis (5); and pediatric plaque psoriasis (pPsO) (6). Indeed, the advent of TNFi began the era of treatment with biologic agents, which has greatly improved expected outcomes in these chronic conditions.

Nevertheless, there is significant worry about the potentially increased rate of malignancy associated with pediatric use of TNFi compared to the rate in the general population, as first reported by the United States Food and Drug Administration (FDA) in 2009 (7). This initial report had many limitations, including failure to account for a possible increased risk of malignancy associated with the underlying conditions being treated with TNFi (i.e., increased background risk of malignancy) or for a possible increased risk associated with other immunosuppressive medications, such as the thiopurines (8).

To date, the very low incidence of pediatric malignancy and the relatively small number of children exposed to TNFi have limited attempts to definitively prove or disprove an independent association between pediatric TNFi use and subsequent malignancy. In this study, we used administrative claims data from the United States (U.S.) to determine the comparative rates of malignancy among children with JIA, pIBD, and pPsO who were and were not treated with TNFi.

METHODS

Data Source.

After obtaining Institutional Review Board approval, we performed this study using national U.S. Medicaid Analytic eXtract files (MAX) (from government-provided health insurance for low income families) from 2000 through 2010 and national U.S. Truven MarketScan® files (from commercial health insurance via employers) from 2010 through 30 September 2014. Race and ethnicity data were not available in MarketScan. We used all of the data available to us at the time of the study.

Study Populations.

We identified cohorts of children with the most common disease indications for TNFi. Criteria for study inclusion were: (a) the first physician diagnosis code for pPsO, JIA, or pIBD prior to age 18 years old; (b) at least 2 physician diagnosis codes for pPsO, JIA, or pIBD that were >7 and <183 days apart OR any 1 physician diagnosis code for pPsO, JIA, or pIBD that was followed by a prescription claim for immunosuppressant medications typically used to treat pPsO, JIA, or pIBD (e.g., methotrexate, azathioprine, TNFi) within 183 days. Patients were excluded for diagnosis codes of pPsO, JIA, or IBD prior to 6 months of age and for any diagnosis codes for organ transplantation, human immunodeficiency virus infection (HIV), or systemic lupus erythematosus and related rheumatologic conditions (SLE) prior to the start of follow-up. Follow-up for each patient began 183 days after the first diagnosis code of the codes that satisfied criterion (b) above in order to exclude prevalent or misdiagnosed malignancy. Patients were excluded for any diagnosis codes for malignancy or any claims for cancer chemotherapy prior to the start of follow-up. Patients were assigned to disease cohorts using a hierarchy (pPsO < JIA < pIBD) and could change during the course of the study (e.g., a patient's diagnosis could change from JIA to pIBD, but not the reverse).

We used the same approach to identify a cohort of children diagnosed with attention-deficit hyperactivity disorder (ADHD) to evaluate the performance of our malignancy outcome algorithm, described below. In addition to the exclusions above, children were excluded from the ADHD cohort for any diagnoses of pPsO, JIA, or IBD or any exposure to any of the medications of interest at any time.

Medication Exposures.

We identified exposure to any of the 5 commercially available TNFi (adalimumab, certolizumab, etanercept, golimumab, infliximab) using pharmacy and infusion claims, and all TNFi were considered together as a single exposure group. For patients with pIBD,

exposure to thiopurines (azathioprine and mercaptopurine) was also assessed. For both TNFi and thiopurines, patients were considered permanently exposed from the first observed exposure onward, including exposures prior to the start of study follow-up. Exposure categories were binary, and patients could contribute follow-up time to more than one medication exposure group sequentially throughout the study according to their treatment course (e.g., a patient could begin follow-up in the no TNFi use group and switch to the TNFi group upon first observed exposure). We classified new TNFi users as defined by >6 months of observation without any TNFi exposure prior to the first observed TNFi exposure.

Malignancy Outcome.

We used an adapted version of a malignancy-finding algorithm that was previously validated in adults (9, 10). Incident malignancy was defined by at least 1 physician diagnosis code for malignancy accompanied by claims evidence of treatment for malignancy (i.e., chemotherapy, radiation therapy, or surgical excision). Diagnoses of non-melanoma skin cancer (NMSC) were ignored because they could not be sufficiently substantiated.

Study Follow-up.

Follow-up for all patients continued until one of the following events occurred: end of study period, malignancy outcome, loss of observability in the data (i.e., loss of healthcare coverage benefits), or any diagnosis codes for organ transplantation, HIV, or SLE.

Analysis.

We determined the malignancy rates for the disease cohorts stratified by exposure to TNFi. We then combined results across diseases. We used Surveillance Epidemiology and End Results (SEER) data to calculate the expected number of malignancies according to the age, sex, and race distributions of follow-up time in each cohort. We calculated standardized incidence ratios (SIR) with 95% confidence intervals comparing the observed number of malignancies to the expected numbers according to SEER. We separately evaluated lymphomas because of particular concern about this malignancy type (7).

To assess the performance of the malignancy outcome algorithm, we determined the rate of malignancy in the ADHD cohort and computed age, sex, and race-adjusted SIR. The ADHD cohort is expected to have a rate of malignancy comparable to the general population.

We used Cox proportional hazard models to determine the hazard ratio for incident malignancy for TNFi use compared to no TNFi use. We assessed for confounding using bivariate models including age, sex, race, and data source and included variables that altered the hazard ratio for TNFi use by approximately 10% or more. Because individual patients could contribute sequentially to both cohorts, a sandwich variance estimator was applied to account for additional correlations in the data (11). Analyses were performed using SAS 9.4 (SAS Institute).

RESULTS

We identified 28,005 patients with JIA, 24,035 patients with pIBD, and 31,438 patients with PsO, including 7,419/6,808/1,371 TNFi users, respectively (Table 1). The proportion of TNFi users was much greater among JIA (26%) and pIBD (28%) compared to PsO (4%). The proportion of TNFi users was higher among patients in MarketScan (27%) compared to MAX (13%). The median duration of follow-up after first TNFi exposure was 1.4 years, and 25% of TNFi users had at least 2.8 years of follow-up after TNFi exposure. The approximate distribution of TNFi use overall was etanercept 37%, infliximab 34%, adalimumab 29%, certolizumab 2%, and golimumab 1%.

Table 2 shows the incident malignancy rates and corresponding SIR compared to age, sex, and race adjusted SEER estimates. The incidence of malignancies in the ADHD cohort was highly consistent with that predicted by SEER, with a resultant SIR of 0.97 [0.91–1.05].

In total, there were 15 incident malignancies identified during 30,703 person-years of follow-up after TNFi use and 42 malignancies in 121,801 person-years of follow-up among those without TNFi use. The 15 malignancies following TNFi use included 6 lymphoma, 3 brain, 2 leukemia, 2 malignant melanoma, 1 bone, and 1 liver. The SIR associated with no TNFi use for JIA, pIBD, and pPsO were nearly identical (2.1 [1.1–3.5], 2.1 [1.1–3.6], and 2.1 [1.1–3.5], respectively). The SIR associated with TNFi use in JIA and pIBD was very similar (3.1 [1.3–6.1] and 3.3 [1.3–6.9], respectively), and there were no malignancies identified following TNFi use among those with pPsO (SIR 0 [0–9.2]). When the results for all 3 indications for TNFi were combined, the SIR associated with TNFi use was 2.9 [1.6–4.9] and the SIR associated with no TNFi use was 2.1 [1.5–2.9].

Table 3 shows the incident lymphoma rates and corresponding SIR. The incidence of lymphomas in the ADHD cohort was highly consistent with that predicted by SEER (SIR 1.05 [0.89–1.24]). In total, there were 6 lymphomas identified following TNFi use (3 each for JIA and pIBD) and 9 lymphomas among those without TNFi use (3 for pIBD and 6 for pPsO). When all 3 indications for TNFi were combined, the SIR associated with TNFi use was 6.0 [2.4–14.5] and the SIR associated with no TNFi use was 2.7 [1.2–5.2].

Table 4 shows the results from Cox proportional hazard ratio models. The unadjusted HR for TNFi use versus no TNFi use was 1.45 [0.80–2.62]. In bivariate models, this estimate was not confounded by age, sex, or race. Adjusting for data source, the HR was 1.58 [0.88–2.85] for TNFi use versus no TNFi use. The HR for lymphoma was 2.64 [0.93–7.51] for TNFi use versus no TNFi use.

Of the 15,598 TNFi users, 9,744 (62%) met the definition of new users and had 20,149 person-years (median 1.6 years) of follow-up after TNFi use. Among the TNFi new users, we observed 9 incident malignancies. The median duration of time from new TNFi use to malignancy diagnosis was 343 days (range 38 to 1159), and 3 malignancies were diagnosed within 6 months of starting TNFi.

In the pIBD cohorts, children with thiopurine use and no TNFi use had 2 malignancies in 7,770 person-years with an SIR of 1.5 [0.2–5.6]. Children with TNFi use and no thiopurine

use had 4 malignancies in 8,913 person-years with an SIR of 2.5 [0.7–6.4]. Children with TNFi use and thiopurine use had 3 malignancies in 2,977 person-years with an SIR of 6.0 [1.2–17.5].

DISCUSSION

Despite nearly 20 years of use, there remains worry about the safety of TNFi, especially when used to treat children. This study using national administrative claims data from two sources in the U.S. assessed children with the 3 most common indications for TNFi and found no significant increased risk of overall malignancy associated with TNFi use compared to no TNFi use, although a 2 to 3-fold increase could not be excluded given the small number of observed malignancies. On the other hand, this study showed an approximate doubling of the incidence of malignancy associated JIA, pIBD, and pPsO in the absence of TNFi use compared to the general population. Taken together, these data suggest that, despite earlier reports to the contrary, TNFi use in childhood is not likely to substantially increase the overall risk of malignancy.

Our study confirmed previously published large studies showing an increased risk of malignancy associated with JIA in the absence of TNFi use. Large observational studies including those using linked national databases from Sweden (12) and Taiwan (13) and U.S. claims data from MAX (14) and commercial insurers (15) have consistently found a 2 to 4-fold increase in malignancies in children with JIA in the absence of TNFi use compared to the general population.

There are fewer studies about the background risk of malignancy in pIBD and pPsO. Our study found an increase in incident malignancy associated with pIBD without TNFi use that was comparable to results from recently published large prospective (16) and retrospective (17) cohort studies of pIBD. Numerous previously published studies of adult IBD have shown an increased risk of several malignancies, particularly gastrointestinal cancers (18). Our study found a similarly increased incidence of malignancy associated with pPsO without TNFi use, and several studies of adult PsO have shown an increased risk of malignancy (19, 20).

Our study adds to the growing evidence that TNFi use is likely not strongly associated with subsequent malignancy. In JIA, our preliminary prior study did not identify any incident malignancies in 2,922 person-years of follow-up after TNFi use (14). More recently, a report from the JIA German biologics registry did not observe an increase in the rate of malignancy following etanercept use compared to no TNFi use (21). The previously mentioned large prospective cohort of pIBD patients evaluated malignancy following any biologic use (>95% of which was TNFi use) (16). Biologic use without ever use of thiopurines was not associated with malignancy (SIR 1.11 [0.03–6.16]), while use of biologics with use of thiopurines was associated with malignancy (SIR 3.06 [1.32–6.04]). To our knowledge, there are no previously published large studies of the risk of malignancy associated with TNFi use in pPsO. In adults, large meta-analyses of clinical trials and large long-term observational studies have shown no increase in the risk of malignancy (aside from NMSC) following TNFi use in rheumatoid arthritis (22, 23), IBD (24), and PsO (25, 26).

One of the primary concerns in the initial FDA report was an increased incidence of lymphoma, up to 18 times the expected rate for children who received infliximab (7). Our study was limited by the few number of lymphomas identified. Nevertheless, the HR for lymphoma with TNFi use was much lower than the FDA's result while still suggesting a possible true association (2.64 [0.93–7.51]). We could not adjust for high disease activity and severity, and these factors are believed to increase risk of lymphoma in adults with RA up to 70-fold compared to those with low disease activity (27).

There are significant concerns about thiopurine use and malignancy, especially if TNFi are also used. Thiopurines alone have been shown to be associated with malignancy, particularly lymphoma, in adults with IBD (28, 29). TNFi and thiopurines together have been shown to be higher risk than TNFi alone in adults with IBD (30). As noted above, TNFi and thiopurine use in pIBD was reported to have an approximately 2.8-fold increase in the SIR compared to TNFi use alone (16). Our study showed a similar approximately 2.4-fold increase in the SIR for TNFi and thiopurine use compared to TNFi use alone. The small number of malignancies and the typical prescribing patterns for TNFi prevented extensive evaluation of co-medications (e.g., there were few children with JIA who received TNFi without having ever received methotrexate).

The beginning and end of the potential risk window for malignancy following TNFi initiation and discontinuation are unknown. We assumed an immediate risk of infinite duration upon TNFi exposure to maximize the number of malignancies attributed to TNFi. When we restricted our analyses to new users of TNFi, we observed 3 of 9 malignancies occurred within 6 months of TNFi initiation, a time period that may be too short to be appropriately attributed to TNFi. If these 3 cases are excluded from the overall TNFi use cohort, then the resultant SIR is reduced to 2.4 [1.2–4.1]. The median time from initiation of TNFi to development of malignancy among the cases initially reported by the FDA was approximately 2.5 years (7). Greater than 25% of the TNFi users in this study had more than 2.5 years of observation after TNFi use, but overall long-term follow-up was limited.

A major challenge to the interpretation of studies of the association of TNFi and malignancy is confounding by indication. In studies of adults with RA (27) and IBD (31), high disease activity and severity are directly associated with an increased rate of malignancy irrespective of treatment. Because high disease activity and severity are the very indications for pediatric use of TNFi, all observational studies are susceptible to bias toward an increased risk of malignancy associated with TNFi use. Methotrexate or thiopurines are often used prior to TNFi and may impart additional risks of malignancy. If one completely ignores the contribution of disease activity and prior treatments and attributes all of the observed increased risk of malignancy causally to TNFi use, the absolute increased rate of malignancy is still very small. We observed an absolute crude increased rate of malignancy of 14.4 per 100,000 person-years with a corresponding number needed to harm of 6,944.

Our study had several important limitations. We did not have access to health care records to confirm the indications for TNFi or the diagnosis of malignancy. Over-diagnosis of the conditions commonly treated with TNFi among children without TNFi use would likely bias the study results against TNFi, given a background increased risk of malignancy associated

with these conditions compared to the general population. Our malignancy outcome identification algorithm produced results for the ADHD cohort that were highly correlated with expected rates for overall malignancy and lymphoma. Also reassuring is the similarity between our results and the results of a prospective pIBD cohort in which pathologic confirmation of malignancies was obtained (16). It is possible that some prevalent malignancies were misclassified as incident, but the use of a 6-month period to evaluate for prevalent malignancy prior to follow-up and the accuracy of our estimates for ADHD minimized this concern. Because NMSC is not reported to SEER, we could not evaluate the accuracy of that outcome and chose not to assess its incidence in our study. Owing to the few malignancy outcomes, we were unable to assess malignancy rates associated with individual TNFi. Because the rates of malignancy among children without TNFi use were so similar among the 3 diseases of interest, we chose to combine all patients into a single analysis to improve the precision of the estimates, but it is possible that there is effect modification by disease. We observed numerically different hazard ratios for malignancy in our 2 data sources, although this may possibly be attributable to few observed outcomes, as the estimates had overlapping 95% confidence intervals. Lastly, the amount of observable follow-up after TNFi exposure was limited, largely because of frequent changes in healthcare coverage in the U.S. A possible association between long-term TNFi use and malignancy could not be adequately evaluated. Many of these challenges may be partially addressed with long-term data from large prospective observational registries (16, 21, 32, 33).

In conclusion, our study demonstrates that being diagnosed with JIA, pIBD, or pPsO increases the risk of incident malignancy and that use of TNFi does not appear to significantly further increase this risk in the first few years after use, with the possible exception of lymphoma.

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Table 1.

Patient characteristics.

Characteristic	TNFi Use	No TNFi Use
Number of Patients	15,598	73,839
JIA	7,419 (48%)	23,116 (31%)
pIBD	6,808 (44%)	20,049 (27%)
pPsO	1,371 (9%)	30,674 (42%)
Female	57%	57%
Race		
White	21%	33%
Black	7%	10%
Other/Unknown	72%	57%
MAX data source (%)	41%	61%
Mean age in years at start of follow-up (SD)	13.4 (4.2)	11.6 (4.7)
Median age in years at start of follow-up (IQR)	14.0 (11.0, 17.0)	12.0 (8.0, 16.0)
Mean years of follow-up (SD)	2.0 (1.8)	1.7 (1.7)
Median years of follow-up (IQR)	1.4 (0.6–2.8)	1.1 (0.4–2.3)

5959 patients contributed to both no TNFi use and then subsequently the TNFi use cohorts.

TNFi = tumor necrosis factor inhibitor; JIA = juvenile idiopathic arthritis; pIBD = pediatric inflammatory bowel disease; pPsO = pediatric plaque psoriasis; MAX = Medicaid Analytic eXtract; SD = standard deviation; IQR = interquartile range

Table 2.

Incident malignancy rates and standardized incidence ratios.

Cohort	Incident Malignancies	Person-years of Follow-up	Rate per 100,000 person-years	Expected Malignancies according to SEER	SIR [95% CI]
JIA with TNFi use	8	16,272	49.2	2.6	3.1 [1.3–6.1]
JIA with No TNFi use	13	39,257	33.1	6.3	2.1 [1.1–3.5]
pIBD with TNFi use	7	12,189	57.4	2.1	3.3 [1.3–6.9]
pIBD with No TNFi use	13	35,615	36.5	6.1	2.1 [1.1–3.6]
pPsO with TNFi use	0	2,242	(0)	0.4	0 [0–9.2]
pPSO with No TNFi use	16	46,929	34.1	7.5	2.1 [1.2–3.5]
All Patients with TNFi use	15	30,703	48.9	5.1	2.9 [1.6–4.9]
All Patients with No TNFi use	42	121,801	34.5	19.9	2.1 [1.5–2.9]
ADHD	745	4,663,186	16.0	765.0	0.97 [0.91–1.05]

SEER = Surveillance, Epidemiology, and End Results; SIR = standardized incidence ratio; CI = confidence interval; TNFi = tumor necrosis factor inhibitor; ADHD = attention deficit hyperactivity disorder

Table 3.

Incident lymphoma rates and standardized incidence ratios.

Cohort	Incident Lymphomas	Person-years of Follow-up	Rate per 100,000 person-years	Expected Lymphomas according to SEER	SIR [95% CI]
JIA with TNFi use	3	16,272	18.4	0.4	7.5 [1.5–21.9]
JIA with No TNFi use	0	39,257	(0)	1.0	0 [0–3.7]
pIBD with TNFi use	3	12,189	24.6	0.4	7.5 [1.5–21.9]
pIBD with No TNFi use	3	35,615	8.4	1.1	2.7 [0.6–8.0]
pPsO with TNFi use	0	2,242	(0)	0.08	0 [0–45.9]
pPsO with No TNFi use	6	46,929	12.8	1.2	5.0 [1.8–10.9]
All Patients with TNFi use	6	30,703	19.5	0.9	6.0 [2.4–14.5]
All Patients with No TNFi use	9	121,801	7.4	3.3	2.7 [1.2–5.2]
ADHD	144	4,663,186	3.1	136.9	1.05 [0.89–1.24]

SEER = Surveillance, Epidemiology, and End Results; SIR = standardized incidence ratio; CI = confidence interval; TNFi = tumor necrosis factor inhibitor; ADHD = attention deficit hyperactivity disorder

Table 4.

Hazard ratios for the comparison of incident malignancy for TNFi use versus no TNFi use.

Comparison	Hazard Ratio [95% CI]
TNFi use vs No TNFi use (unadjusted)	1.45 [0.80–2.62]
TNFi use vs No TNFi use (adjusted for data source)	1.58 [0.88–2.85]
MarketScan vs MAX	0.56 [0.32–0.99]
TNFi use vs No TNFi use, restricted to MarketScan (unadjusted)	1.13 [0.49–2.58]
TNFi use vs No TNFi use, restricted to MAX (unadjusted)	2.61 [1.01–6.79]

TNFi = tumor necrosis factor inhibitor; CI = confidence interval; MAX = Medicaid Analytic eXtract