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Rates of Malignancy Associated With Juvenile Idiopathic Arthritis and Its Treatment

Timothy Beukelman,[1] Kevin Haynes,[2] Jeffrey R. Curtis,[1] Fenglong Xie,[1] Lang Chen,[1] Christina J. Bemrich-Stolz,[1] Elizabeth Delzell,[1] Kenneth G. Saag,[1] Daniel H. Solomon,[3] and James D. Lewis,[2] on behalf of the Safety Assessment of Biological Therapeutics Collaboration

Objective. **To determine the relative rates of incident malignancy among children with juvenile idiopathic arthritis (JIA) with respect to treatment as compared to children without JIA.**

Methods. **Using national Medicaid data from 2000 through 2005, we identified cohorts of children with JIA and without JIA according to the diagnosis codes used by their physicians and the medication prescriptions that were dispensed. Study followup began after a 6-month lag period to exclude prevalent and misdiagnosed malignancies. Treatment with methotrexate (MTX) and tumor necrosis factor (TNF) inhibitors was categorized as ever exposed or never exposed. Malignancy outcomes were identified using an adapted version of a previously validated algorithm. Incident malignancies were categorized as possible, probable, or highly probable based on a comprehensive review of all claims. Malignancy rates were standardized to the age, sex, and race distribution of the overall JIA cohort. Standardized incidence ratios (SIRs) were calculated using children with attention deficit hyperactivity disorder (n = 321,821) (one of two comparator groups included) as the referent group.**

Results. **The JIA cohort included 7,812 children with a total followup time of 12,614 person-years; 1,484 of these children contributed 2,922 person-years of TNF inhibitor exposure. For all children with JIA versus children without JIA, the SIR was 4.4 (95% confidence interval [95% CI] 1.8–9.0) for probable and highly probable malignancies. For those taking MTX without TNF inhibitor use, the SIR was 3.9 (95% CI 0.4–14). Following any use of TNF inhibitors, no probable or highly probable malignancies were identified (SIR 0 [95% CI 0–9.7]).**

Conclusion. **Children with JIA appeared to have an increased rate of incident malignancy compared to children without JIA. The treatment for JIA, including TNF inhibitors, did not appear to be significantly associated with the development of malignancy.**

Tumor necrosis factor α (TNFα) inhibitors have been shown to be highly effective in the treatment of juvenile idiopathic arthritis (JIA) (1–7). However, questions persist about a possible increased risk of malignancy associated with their use (8), including reports of lymphoma among children with JIA who were treated with TNF inhibitors (9,10). In 2009, the US Food and

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[1]Timothy Beukelman, MD, MSCE, Jeffrey R. Curtis, MD, MS, MPH, Fenglong Xie, MS, Lang Chen, PhD, Christina J. Bemrich-Stolz, MD, Elizabeth Delzell, ScD, Kenneth G. Saag, MD, MSc: University of Alabama at Birmingham; [2]Kevin Haynes, PharmD, MSCE, James D. Lewis, MD, MSCE: University of Pennsylvania, Philadelphia; [3]Daniel H. Solomon, MD, MPH: Harvard University, Boston, Massachusetts. See Appendix A for additional members of the Safety Assessment of Biological Therapeutics (SABER) Collaboration and their locations.

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Address correspondence to Timothy Beukelman, MD, MSCE, University of Alabama at Birmingham, Division of Pediatric Rheumatology, 1600 7th Avenue South, CPP 210, Birmingham, AL 35233-1711. E-mail: tbeukelman@peds.uab.edu.

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Drug Administration (FDA) placed a "black box warning" on TNF inhibitors concerning the risk of malignancy in children, based on an analysis of spontaneous reports to the Adverse Event Reporting System (AERS) (11). The analysis and interpretation of these spontaneous reports sparked considerable interest and debate about the association between malignancy and TNF inhibitors in children with JIA (12,13).

The FDA faced several challenges when interpreting the spontaneous reports that led to the black box warning. The number of malignancies (numerator) was determined from the AERS database, which relies on voluntary reporting of events and has historically resulted in considerable underascertainment of the true number of events (14). The amount of exposure to TNF inhibitors (denominator) was determined from the manufacturers' estimates. The accuracy of these estimates was not addressed in the FDA report and is unclear.

An additional major challenge is the limited data on the "background" rate of malignancy among children with JIA who are not treated with TNF inhibitors. Chronic autoimmune inflammatory conditions, such as JIA, may be associated with an increased risk of malignancy irrespective of the specific therapeutic agents administered. For example, an increased risk of lymphoma has been observed among adults with rheumatoid arthritis (RA) (15), particularly among those with a high burden of inflammatory activity (16). Furthermore, some recent studies of adults with RA demonstrated no increased risk of malignancy in association with TNF inhibitor treatment as compared to the risk in RA patients who did not receive TNF inhibitors (17–19).

Exposure to multiple medications is a challenge too. Most children with JIA who are treated with TNF inhibitors will also receive other therapeutic agents, either previously or concurrently. The most common of these agents is methotrexate (MTX), which may itself be independently associated with an increased rate of malignancy in children with JIA (20).

In summary, the relationship between JIA and malignancy is uncertain. Recent epidemiologic studies of the association between JIA and malignancy have produced conflicting results (21,22) and, owing to their data sources, have been unable to adequately assess the possible effects of medication exposures.

The use of large administrative claims databases, such as the US Medicaid Analytic eXtract (MAX) files, is a potentially informative approach for evaluating uncommon adverse events of medical therapy (23). Using MAX data, we determined the overall rate of incident malignancy among children with JIA. We further compared the rates of malignancy among children exposed to different therapeutic agents for JIA to the rates of malignancy in children without JIA.

PATIENTS AND METHODS

Study populations. After obtaining Institutional Review Board approval, we performed this study using MAX files from all 50 states and the District of Columbia. These files contain medical and pharmacy administrative claims records for low income children enrolled in the Medicaid program (government medical assistance). We identified a cohort of children with JIA as well as 2 internal comparator cohorts of children without JIA, one diagnosed as having asthma and the other diagnosed as having attention deficit hyperactivity disorder (ADHD). We chose comparator cohorts of children with diagnoses of chronic diseases in order to increase the proportion of children who remained observable in the claims database during followup (see below). Neither childhood asthma nor ADHD is known to be associated with a different rate of malignancy as compared to the general population. Data from the years 2000 through 2005 were used for the JIA cohort and from the years 1999 through 2002 for the comparator cohorts. These were the most recent data available to us at the time of the study.

JIA was defined according to the International Classification of Disease, Ninth Revision (ICD-9) codes and pharmacy claims. In order to include all categories of JIA (24), the following ICD-9 codes and diagnoses were accepted: rheumatoid arthritis, code 714; psoriatic arthritis, code 696.0; ankylosing spondylitis, code 720; and inflammatory bowel disease–associated arthritis, code 713.1, with concurrent code 555 or 556. Children who were <16 years old and who had 2 or more JIA ICD-9 codes from physician evaluation and management claims that were at least 7 days, but not more than 183 days, apart were included. Additionally, children who had a single JIA ICD-9 code followed by an outpatient pharmacy claim for a TNF inhibitor, MTX, or leflunomide within 183 days were included.

Children who were <19 years old and who had 2 or more physician evaluation and management claim ICD-9 codes for asthma (493) or ADHD (314.0) that were at least 7 days, but not more than 183 days, apart were included in the respective comparator cohorts. Because more years of followup data were available for the JIA cohort, slightly older children were included in the non-JIA comparator cohorts to ensure adequate overlap of the children's ages with the JIA cohort during followup. Children were excluded from the comparator cohorts if they had any physician evaluation ICD-9 codes for JIA at any time. Children in the comparator cohorts who were exposed to methotrexate, leflunomide, TNF inhibitors, or other immunomodulatory agents (defined below) were excluded or censored, respectively, if the exposure occurred before or during followup.

All children with any physician evaluation ICD-9 code for organ transplantation or human immunodeficiency virus infection were excluded or censored, respectively, if the code occurred before or during followup. To increase the specificity for JIA, all children with 2 or more physician evaluation ICD-9 codes for other rheumatic diseases that were at least 7 days,

but not more than 183 days, apart were excluded. These other rheumatic diseases included systemic lupus erythematosus and other diffuse connective tissue diseases, vasculitis, and sarcoidosis. All children <6 months of age at the time of diagnosis were excluded because of the uncertainty of a diagnosis of JIA at this age (25). The age, sex, and race of each child were recorded.

For all children, the start of followup (index date) was 6 months after the date of the first physician evaluation ICD-9 code of the pair of codes that satisfied the respective disease cohort definition. This provided a 6-month lag period for assessment of prevalent malignancies or initial misdiagnoses of malignancy (17). Children with any physician evaluation ICD-9 code for malignancy at any time prior to the index date were excluded. In order to ensure that children remained fully observable within the MAX database, children without at least 1 outpatient pharmacy claim every 6 months and full medical benefits every month were censored (17). Followup was also censored when the malignancy outcome occurred or the study period ended.

As an additional, external comparator, we obtained population-based estimates of malignancy incidence rates in the US from the Surveillance, Epidemiology, and End Results (SEER) online database (http://seer.cancer.gov/canques/incidence.html).

Medication exposures. Followup observation time among children in the JIA cohort was further categorized into medication exposure groups based on outpatient pharmacy claims for classes of therapeutic agents. We first defined 3 classes of therapeutic agents: MTX (consisting of either MTX or leflunomide); TNF inhibitors (consisting of etanercept, infliximab, or adalimumab); and other immunomodulatory agents (consisting of abatacept, alefacept, anakinra, azathioprine, cyclophosphamide, cyclosporine, efalizumab, 6-mercaptopurine, mycophenolate mofetil, rituximab, or tacrolimus).

Exposure status for each therapeutic agent class was categorized as ever exposed versus never exposed. Once exposure to a therapeutic agent class occurred, the "ever exposed" status for that particular class was maintained for the duration of the study followup; however, individual children could contribute person-time to multiple medication exposure groups sequentially based on their treatment course (e.g., when MTX was initiated for a child who did not previously receive systemic therapy or when TNFα inhibitor therapy was initiated for a child currently receiving MTX).

The "all children with JIA" group included all person-time data for all of the children who met the cohort inclusion and exclusion criteria irrespective of therapeutic agent exposure. The "unexposed" medication exposure group included only person-time data for children who were not exposed to any of the therapeutic agent classes (MTX, TNF inhibitors, or other immunomodulatory agents). The "MTX without TNF inhibitor" medication exposure group included person-time data for exposure to MTX but never to TNF inhibitors (irrespective of other immunomodulatory agents). The "any TNF inhibitor" medication exposure group included all person-time data following exposure to TNF inhibitors (irrespective of MTX or other immunomodulatory agents). The cohort size did not permit us to divide the "any TNF inhibitor" group into those with and without MTX exposure or to evaluate malignancy rates associated with specific TNF inhibitors. We also evaluated malignancy outcomes for children following exposure to other immunomodulatory agents irrespective of exposure to MTX or TNF inhibitors.

Outcome identification. We used an adapted version of a previously validated malignancy-finding algorithm (17) using ICD-9 codes, procedure codes, and pharmacy claims to identify incident malignancy outcomes. The algorithm was initially developed to identify lymphoma, leukemia, and breast, colorectal, gastric, and lung cancer in Medicare claims data. For the current study, the diagnostic, procedure, and pharmacy codes were expanded to capture the full range of solid malignancies.

The accuracy of our outcome identification algorithm has not been validated against a gold standard, such as biopsy pathology reports, in the pediatric population. Therefore, we performed a sensitivity analysis of the outcome by evaluating the certainty of incident malignancy based on available claims data. The entire claims history for all identified outcomes was comprehensively reviewed in a blinded manner by a pediatric rheumatologist (TB) and a pediatric hematologist-oncologist (CJB-S). Claims related to arthritis, asthma, or ADHD were redacted from the histories to maintain blinding of the disease cohorts and medication exposures.

Incident malignancies were categorized as highly probable (>2 ICD-9 codes for the same form of malignancy plus evidence of cancer treatment), probable (>2 ICD-9 codes for the same malignancy over a period of more than 1 month or ≤2 ICD-9 codes for the same malignancy plus evidence of cancer treatment); or possible (all other identified malignancies). There was no unresolved discordance between the two reviewers.

Statistical analysis. We evaluated overall malignancy rates and hematologic malignancy rates (leukemia and lymphoma). It was anticipated that the limited number of malignancy outcomes would not allow for multivariable regression modeling. Therefore, we standardized the malignancy rates for each cohort and medication exposure group (including the SEER external comparator group) to the age, sex, and race distribution of all children with JIA in the study by use of weighted averages. We calculated the age, sex, and race standardized rates of malignancy corresponding to the different levels of certainty of the incident malignancy outcome (all identified outcomes, probable plus highly probable, and highly probable only) in the cohorts of children with JIA and without JIA. For the cohorts of children without JIA, we observed which level of certainty of the outcome produced an estimate of the standardized rate of incident malignancy that most closely approximated the expected rates based on external SEER data. We generated standardized incidence ratios (SIRs) and 95% confidence intervals (95% CIs) using the malignancy rates from the internal comparator cohorts of children without JIA to calculate the expected number of malignancies (26). We did not calculate the cumulative duration of disease or the cumulative duration of exposure to medications because we were unable to use an incident JIA cohort or an incident exposure (new-user analysis) design (27). These approaches would have excluded a substantial proportion of the children in our analysis.

Centers for Medicare and Medicaid Services (CMS) regulations prohibit reporting tabular cell counts less than 11

Table 1. Characteristics of the study cohorts*

	JIA cohort (n = 7,812)	Asthma cohort (n = 652,234)	ADHD cohort (n = 321,821)
Age, median (IQR) years	10.5 (6.3–13.7)	6.1 (2.8–11.0)	9.7 (7.7–12.0)
% female	64	41	24
Race/ethnicity, %			
White	52	38	64
African American	17	31	20
Latino	20	20	6
Other/unknown	11	11	10
Followup, median (IQR) years	1.1 (0.4–2.4)	0.7 (0.3–1.6)	0.9 (0.4–1.9)
Medication exposures, no. (%)†			
MTX	3,423 (44)	–	–
TNF inhibitors	1,484 (19)	–	–
Other immunomodulatory agents	398 (5)	–	–

* JIA = juvenile idiopathic arthritis; ADHD = attention deficit hyperactivity disorder; IQR = interquartile range.
† Three classes of therapeutic agents were defined: methotrexate (MTX; consisting of either MTX or leflunomide); tumor necrosis factor (TNF) inhibitors (etanercept, infliximab, or adalimumab); and other immunomodulatory agents (abatacept, alefacept, anakinra, azathioprine, cyclophosphamide, cyclosporine, efalizumab, 6-mercaptopurine, mycophenolate mofetil, rituximab, or tacrolimus).

for research using MAX files. CMS permission was obtained for the presentation of results.

RESULTS

Characteristics of the study cohorts are shown in Table 1. There were differences in the age, sex, and race distributions of the cohorts, and this was accounted for in the standardization procedure. Nearly one-half of the JIA cohort was exposed to MTX and nearly one-fifth was exposed to TNF inhibitors during the study period. The unexposed JIA group comprised 4,617 individuals who contributed a median of 0.8 person-years of observation. The MTX without TNF inhibitor group comprised 2,750 individuals who contributed a median of 1.0 person-years, and the any TNF inhibitor group comprised 1,484 individuals who contributed a median of 1.5 person-years. Approximately 90% of the TNF inhibitor exposure was etanercept treatment.

A total of 265 malignancies were identified by our outcome algorithm: 10 in the JIA cohort, 68 in the ADHD cohort, and 193 in the asthma cohort (6 malignancies occurred among children included in both the ADHD and asthma cohorts). Among the children with JIA, 6 malignancies (3 brain, 1 leukemia, 1 soft tissue, and 1 gastrointestinal tract) were identified in the unexposed group, 3 malignancies (2 leukemia and 1 soft

Table 2. Crude and standardized rates of all malignancies and of hematologic malignancies in the study cohorts*

		All malignancies		Hematologic malignancies	
Cohort	Person-years of followup	Crude rate per 100,000 person-years (95% CI)	Standardized rate	Crude rate per 100,000 person-years (95% CI)	Standardized rate
JIA cohort					
All JIA patients	12,614	79.3 (42.7–147.3)	79.3	23.8 (7.7–73.7)	23.8
Medication exposure					
Unexposed	5,671	105.8 (47.5–235.5)	106.5	17.6 (2.5–125.1)	21.1
MTX without TNF inhibitor	3,894	77.0 (24.8–238.8)	75.9	51.3 (12.8–205.2)	46.2
Any TNF inhibitor	2,922	34.2 (4.8–242.9)	37.0	0 (0–126.3)	0
Asthma cohort	675,794	28.6 (24.8–32.9)	27.1	10.5 (8.3–13.3)	10.4
ADHD cohort	391,984	17.4 (13.4–22.0)	23.7	7.4 (5.1–10.6)	9.3
SEER external controls	–	–	15.0	–	6.1

* All rates were standardized to the age, sex, and race distribution of the entire cohort of patients with JIA. The group designated as "unexposed" included only person-years data for children who had not been exposed to any of the 3 classes of therapeutic agents: MTX, TNF inhibitors, or other immunomodulatory agents (see Patients and Methods for details). 95% CI = 95% confidence interval; SEER = Surveillance, Epidemiology, and End Results (see Table 1 for other definitions).

Table 3. Crude and standardized rates of probable and highly probable incident malignancies for the study cohorts*

Cohort	Incident malignancies			
	Probable and highly probable		Highly probable only	
	Crude rate per 100,000 person-years (95% CI)	Standardized rate	Crude rate per 100,000 person-years (95% CI)	Standardized rate
JIA cohort				
All JIA patients	55.4 (26.4–116.3)	55.4	31.7 (11.9–84.4)	31.7
Medication exposure				
Unexposed	88.2 (36.7–211.8)	89.6	52.9 (17.1–163.9)	59.3
MTX without TNF inhibitor	51.3 (12.8–205.0)	52.1	25.6 (3.6–181.9)	22.5
Any TNF inhibitor	0 (0–126.0)	0	0 (0–126.0)	0
Asthma cohort	17.9 (15.0–21.4)	16.5	13.5 (11.0–16.5)	12.3
ADHD cohort	11.2 (8.4–15.1)	13.0	8.9 (6.4–12.4)	9.7
SEER external controls	–	15.0	–	15.0

* All rates were standardized to the age, sex, and race distribution of the entire cohort of patients with JIA. The group designated as "unexposed" included only person-years data for children who had not been exposed to any of the 3 classes of therapeutic agents: MTX, TNF inhibitors, or other immunomodulatory agents (see Patients and Methods for details). 95% CI = 95% confidence interval; SEER = Surveillance, Epidemiology, and End Results (see Table 1 for other definitions).

tissue) were identified in the MTX without TNF inhibitor group, and 1 malignancy (uterus) was identified in the any TNF inhibitor group. No malignancies were identified among children with JIA following exposure to other immunomodulatory agents.

The crude and standardized malignancy rates are shown in Table 2. The standardized rates of overall malignancy ranged from ~1.4 to 4.5 times higher in the various JIA medication exposure groups as compared to the 2 internal comparator cohorts of children without JIA, and similar relative rates were seen for hematologic malignancy. The standardized malignancy rates in the SEER external comparator cohort were significantly lower than the ADHD and asthma internal comparator rates. Comparing the standardized malignancy rates in the entire JIA cohort and in the ADHD cohort versus the SEER estimates resulted in SIRs of 5.3 (95% CI 2.5–9.7) and 1.6 (95% CI 1.3–1.9), respectively.

Comprehensive review of the entire claims histories of identified outcomes confirmed a variable degree of certainty for true incident malignancy. Of the total of 265 identified outcomes using our claims algorithm, 127 (48%) were highly probable, 41 (15%) were probable, and 97 (37%) were possible according to our definitions. The distribution of certainty of incident malignancy was similar in the JIA cohort compared to all children in the study (4 [40%] highly probable, 3 [30%] probable, and 3 [30%] possible). The crude and standardized rates of probable and highly probable incident malignancies are shown in Table 3. The standardized rates in the combination of probable and highly probable incident malignancies for the ADHD and asthma comparator cohorts most closely approximated the standardized rate in the SEER external comparator. Comparing the standardized rates of probable and highly probable malignancy in the entire JIA cohort and the ADHD cohort versus SEER estimates resulted in SIRs of 3.7 (95% CI 1.5–7.6) and 0.9 (95% CI 0.7–1.1), respectively.

The SIR estimates of overall malignancies and of hematologic malignancies in the JIA medication exposure groups compared to the ADHD group are shown in Table 4 and Table 5, respectively. Within each JIA medication exposure group, the SIR estimates were fairly stable irrespective of the certainty of the malignancy outcome. The SIR for probable and highly probable incident malignancy in all children with JIA was significantly elevated at 4.4 (95% CI 1.8–9.0), and the SIR for the JIA unexposed group was similarly elevated at 6.9 (95% CI 2.3–16). The SIR for the any TNF inhibitor group was not significantly elevated at 1.6 (95% CI 0.03–8.3), and there were no probable or highly probable malignancies among children exposed to any TNF inhibitor (SIR 0 [95% CI 0–9.7]). SIR estimates for the hematologic malignancies were similar to the overall malignancy results, but with much larger confidence intervals because of fewer outcome events. Compared to the SIR estimates generated from the ADHD comparator cohort, SIR estimates generated from the asthma comparator cohort were similar, with nearly complete overlap of the respective 95% CIs (data not shown).

There were numerically fewer malignancies in the MTX and TNF inhibitor exposure groups compared to the unexposed children with JIA. The rate ratio for probable or highly probable malignancy for MTX with-

Table 4. SIRs for all malignancies in the JIA medication exposure groups versus the ADHD cohort, by certainty of malignancy outcome based on comprehensive review of entire claims histories*

Cohort	SIR (95% CI) for all malignancies		
	All incident malignancies identified	Probable and highly probable incident malignancies	Highly probable incident malignancies only
JIA cohort			
All JIA patients	3.3 (1.6–6.1)	4.4 (1.8–9.0)	3.3 (0.9–8.5)
Medication exposure			
Unexposed	4.6 (1.7–10)	6.9 (2.3–16)	6.2 (1.4–17)
MTX without TNF inhibitor	3.3 (0.7–9.5)	3.9 (0.4–14)	2.3 (0.01–14)
Any TNF inhibitor	1.6 (0.03–8.3)	0 (0–9.7)	0 (0–13)

* Highly probable was defined as >2 International Classification of Diseases, Ninth Revision (ICD-9) codes for the same form of malignancy and evidence of cancer treatment. Probable was defined as either >2 ICD-9 codes for the same malignancy over a period of >1 month or ≤2 ICD-9 codes for the same malignancy plus evidence of cancer treatment. The group designated as "unexposed" included only data for children who had not been exposed to any of the 3 classes of therapeutic agents: MTX, TNF inhibitors, or other immunomodulatory agents (see Patients and Methods for details). SIRs = standardized incidence ratios; 95% CI = 95% confidence interval (see Table 1 for other definitions).

out TNF inhibitor compared to the unexposed group was 0.6 (95% CI 0.1–3.6). No probable or highly probable malignancies were identified among children exposed to TNF inhibitors.

DISCUSSION

We found an increased incidence of malignancy among children with JIA as compared to children without JIA. Our results are comparable to those of some, but not all, previous studies. A recently published study by Simard et al (22) used extensive linkage of Swedish national registers to estimate the relative risk of incident malignancy associated with JIA versus a matched general population comparator cohort. The authors reported that among all 5,296 children diagnosed as having JIA since 1987, there was an adjusted relative risk of overall malignancy of 2.3 (95% CI 1.2–4.4). The investigators of that study could not examine medication exposures in a detailed manner. However, when followup was censored in 1999 (to coincide with the introduction of TNF inhibitor therapy) the results were similar, which implies that the observed increased malignancy rate could not be solely attributed to TNF inhibitor therapy. Using a database of commercial insurance claims from the US, Harrison et al (28) preliminarily reported a hazard ratio of 2.8 (95% CI 0.9–8.3) for overall malignancy among 3,605 children diagnosed as having JIA who had not been exposed to TNF inhibitors or other biologic agents as compared to matched children without JIA. Hence, both of these studies using different data sources reported results similar to those of our study.

In contrast, Bernatsky et al (21) estimated a SIR of 0.12 (95% CI 0.0–0.70) for overall malignancy among

Table 5. SIRs for hematologic malignancies in the JIA medication exposure groups versus the ADHD cohort, by certainty of malignancy outcome based on comprehensive review of entire claims histories*

Cohort	SIR (95% CI) for hematologic malignancies		
	All incident malignancies identified	Probable and highly probable incident malignancies	Highly probable incident malignancies only
JIA cohort			
All JIA patients	2.5 (0.5–7.3)	2.9 (0.3–10)	3.5 (0.4–13)
Medication exposure			
Unexposed	2.3 (0.07–11)	3.9 (0.1–19)	4.6 (0.1–23)
MTX without TNF inhibitor	5.0 (0.5–19)	4.2 (0.02–25)	4.9 (0.03–30)
Any TNF inhibitor	0 (0–14)	0 (0–23)	0 (0–28)

* Highly probable was defined as >2 International Classification of Diseases, Ninth Revision (ICD-9) codes for the same form of malignancy and evidence of cancer treatment. Probable was defined as either >2 ICD-9 codes for the same malignancy over a period of >1 month or ≤2 ICD-9 codes for the same malignancy plus evidence of cancer treatment. The group designated as "unexposed" included only data for children who had not been exposed to any of the 3 classes of therapeutic agents: MTX, TNF inhibitors, or other immunomodulatory agents (see Patients and Methods for details). SIRs = standardized incidence ratios; 95% CI = 95% confidence interval (see Table 1 for other definitions).

1,834 children diagnosed as having JIA at 3 major Canadian pediatric rheumatology centers versus expected rates generated from tumor registries. The explanation for this different result is unclear. Prior to these recent studies, Thomas et al (29) had reported no increased rate of overall malignancy among children in Scotland diagnosed as having juvenile chronic arthritis, although that study was limited to 896 children, with resultant wide confidence intervals surrounding the estimates.

Thus, most, but not all, studies addressing this question have identified an increased risk of malignancy in children with JIA. There are several plausible reasons to believe that JIA may be associated with an increased risk of malignancy. First, there is precedence in that RA is associated with an increased risk of malignancy, particularly lymphoma (15,16). Medications that are used to treat JIA suppress the immune system, which would be expected to potentially increase the risk of selected malignancies, although we also found an increased rate of malignancies among children not treated with systemic immunosuppressive agents. On the other hand, it is possible that children with JIA undergo more careful screening for cancer and that the observed association is due to a detection bias. However, given that few childhood cancers remain undiagnosed for extended periods of time, this seems a less plausible explanation. Finally, because malignancy, in particular acute leukemia, may initially be mistakenly clinically diagnosed as JIA (30,31), the potential exists for misclassification bias. We attempted to decrease the possibility of misclassification by requiring a 6-month lag period between the first disease ICD-9 code and the start of followup observation. Nevertheless, some misdiagnoses may have occurred.

Among 1,484 children with JIA with 2,922 person-years of observation following exposure to TNF inhibitors, we did not find a strong association between TNF inhibitors and malignancy and we did not identify any cases of lymphoma. When we restricted our outcome definition to probable and highly probable incident malignancies, there were no malignancies identified following exposure to TNF inhibitors. The FDA's study of TNF inhibitors did not report disease-specific malignancy rates based on the indication for TNF inhibitor therapy (11). However, the authors did report drug-specific malignancy rates, and treatment with etanercept in clinical practice can be assumed to have been largely for children diagnosed as having JIA. Among all children exposed to etanercept in the US, the authors reported no increased rate of overall malignancy (6 malignancies identified) but an approximate 5-fold increase in the rate of lymphoma (3 lymphomas identified). Harrison et al (32) combined preliminary data from 3 prospective JIA biologic agents registries and estimated a SIR for overall malignancy of 3.7 (95% CI 0.5–13.4) for children with JIA exposed to etanercept as compared to the general population of children without JIA (32). This SIR is similar to the estimate that we and other investigators have found among all JIA patients irrespective of treatment as compared to children without JIA, and it does not suggest a strong association between TNF inhibitor therapy and malignancy.

Our study had limitations common to observational studies of administrative claims data. We did not have access to medical records. Accordingly, we could not directly verify the diagnoses of JIA or malignancy. However, we required 2 or more JIA ICD-9 codes separated in time, a method that has been commonly used in studies of adult RA (33). Furthermore, concurrent treatment with MTX or TNF inhibitors in the setting of physician evaluation ICD-9 codes for JIA can be expected to be reasonably specific for this diagnosis. Some individuals with remote past exposures to MTX or TNF inhibitors prior to their appearance in the MAX database may have been misclassified as not having been exposed. To ascertain the certainty of incident malignancy and perform sensitivity analyses of the outcome, comprehensive review of the entire claims history was performed by 2 expert clinicians. Our estimates of probable and highly probable incident malignancy rates for the comparator cohorts of children without JIA approximated those reported in the SEER data, suggesting reasonable accuracy for true incident malignancy. We could not directly estimate or adjust for JIA disease activity or severity. Therefore, medication channeling by prescribers with resultant confounding between TNF inhibitor use and malignancy is possible (i.e., "sicker" patients received TNF inhibitors and were also more likely to develop malignancy). This confounding, if present, would have strengthened the association between TNF inhibitors and malignancy, and we did not observe a strong association in our study.

The time window of potential increased risk of malignancy following initiation or cessation of MTX or TNF inhibitors is not known. Accordingly, we simply classified children as "ever exposed" to these medications. Though a conservative approach, this assumption may potentially result in an underestimate of the malignancy rate if the true risk of malignancy returns to baseline quickly after cessation of treatment. However, the majority of children in the MTX without TNF

inhibitor and the any TNF inhibitor medication exposure groups continued their therapies and had a corresponding outpatient pharmacy claim within 60 days of the end of their study followup (58% for MTX and 50% for TNF inhibitors). The mean duration of study followup following known exposure to TNF inhibitors was 24 months. This duration of followup may be insufficient to capture the long-term or cumulative effects of TNF inhibitors. Finally, despite using the largest available claims database in the US, our sample size still resulted in relatively wide confidence intervals, indicating the rarity of incident malignancy in childhood.

It is not known how enrollment in the Medicaid program may affect the incidence of malignancy or the treatment of JIA. Nevertheless, all children in this study were enrolled in Medicaid, and therefore, low socioeconomic status cannot be a potential confounder in the determination of relative rates of malignancy. We used an internal comparator of children with ADHD to attenuate concerns about the method of identification of malignancy outcomes in the MAX data.

We assumed that ADHD and childhood asthma were not associated with a different incidence of malignancy as compared to the general population, though there is evidence to suggest that this assumption may not be true among adults with asthma (34). Nevertheless, we used the malignancy rates in the ADHD cohort to determine the SIR results presented herein, and the results generated using the asthma cohort were similar.

More recent data were not available to us at the time of this study, owing to the lag time and financial cost inherent in the creation and release of national MAX files by CMS. Compared to the JIA cohort, we had access to fewer calendar years of data for the comparator cohorts but many more person-years of followup. None of the cohorts were intended to be incident diagnosis cohorts, and all followup time after the index date was considered equal for all subjects. There was no anticipated calendar effect on malignancy rates, and all rates of malignancy were standardized to the age distribution of the entire JIA cohort. We hope to conduct future analyses of more recent MAX data to provide more definitive estimates of the incidence of malignancy in children with JIA.

Prior to the FDA's new warning of an increased rate of malignancy among children receiving TNF inhibitors compared to children in the general population, there was relatively little scientific study of a possible increased risk of malignancy attributable to JIA. To our knowledge, the only published formal analysis was the previously mentioned small study of children with juvenile arthritis that largely predated the era of MTX treatment (29). Concern about a possible increased risk of lymphoma associated with MTX therapy was later raised (20), but was never systematically studied. The results of our current study highlight the critical importance of appropriate comparator groups when evaluating the safety of new therapeutic agents and strengthen the case for the proposed inception of a disease-based (rather than medication-based) consolidated safety registry for children with JIA (35).

In summary, we found a significantly increased rate of incident malignancy among children diagnosed as having JIA as compared to children without JIA. JIA treatment, including TNF inhibitors, did not appear to be significantly associated with the development of malignancy. Larger and longer-term studies of the association between malignancy and JIA and its treatment are needed to confirm our findings.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Beukelman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Beukelman, Haynes, Curtis, Xie, Chen, Delzell, Saag, Lewis.

Acquisition of data. Beukelman, Haynes, Xie, Saag.

Analysis and interpretation of data. Beukelman, Curtis, Xie, Chen, Bemrich-Stolz, Delzell, Saag, Solomon, Lewis.

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APPENDIX A: MEMBERS OF THE SAFETY ASSESSMENT OF BIOLOGICAL THERAPEUTICS (SABER) COLLABORATION

Members of the SABER Collaboration, in addition to the authors of this article, are as follows: Parivash Nourjah (AHRQ); Robert Glynn, Mary Kowal, Joyce Lii, Jeremy Rassen, and Sebastian Schneeweiss (Brigham and Women's Hospital); Leslie Harrold (Fallon Medical Center and University of Massachusetts); David Graham, Carolyn McCloskey, Rita Ouellet-Hellstrom, and Kristin Phucas (FDA); Lisa Herrinton and Liyan Liu (Kaiser Permanente Northern California); Marcia Raebel (Kaiser Permanente Colorado); Nivedita Patkar (University of Alabama at Birmingham); and Marie Griffin, Carlos Grijalva, and Ed Mitchel (Vanderbilt University).