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Rates of Malignancy Associated with Juvenile Idiopathic Arthritis and Its Treatment

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Abstract

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

Methods—Using national U.S. Medicaid data from 2000 through 2005, we identified cohorts of children with JIA and without JIA using physician diagnosis codes and dispensed medication prescriptions. Study follow-up began after a 6 month lag period to exclude prevalent and misdiagnosed malignancies. Treatment with methotrexate and TNF inhibitors was categorized as ever 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

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incidence ratios (SIR) were calculated using children without JIA (N=321,821) as the referent group.

Results—The JIA cohort included 7,812 children with a total follow-up time of 12,614 person-years, of whom 1,484 children contributed 2,922 person-years of TNF inhibitor exposure. For all children with JIA versus children without JIA, the SIR was 4.4 (1.8–9.0) for probable and highly probable malignancies. For methotrexate users without TNF inhibitor use, the SIR was 3.9 (0.4–14). Following any use of TNF inhibitors, no probable or highly probable malignancies were identified (SIR 0 (0–9.7)).

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

INTRODUCTION

Tumor necrosis factor alpha inhibitors (TNF 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 United States Food and Drug Administration (FDA) placed a “black box” warning on TNF inhibitors warning of 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 AERS, which relies on voluntary reporting of events and has historically resulted in considerable under-ascertainment of the true number of events (14). The amount of exposure to TNF inhibitors (denominator) was determined from 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 specific therapeutic agents. 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 have demonstrated no increased risk of malignancy associated with TNF inhibitor treatment compared to 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, 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 national United States 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 rates of malignancy among children exposed to different therapeutic agents for JIA to rates of malignancy in children without JIA.

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 of the United States. These files contain medical and pharmacy administrative claims records for low income children enrolled in Medicaid (government medical assistance). We identified a cohort of children with JIA and 2 internal comparator cohorts of children without JIA, one diagnosed with asthma and one diagnosed with attention-deficit hyperactivity disorder (ADHD). We chose comparator cohorts of children diagnosed with chronic diseases in order to increase the proportion of children who remained observable in the claims data during follow-up (see below). Neither childhood asthma nor ADHD is known to be associated with a different rate of malignancy 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 using 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 were accepted: rheumatoid arthritis (714); psoriatic arthritis (696.0); ankylosing spondylitis (720); and inflammatory bowel disease-associated arthritis (713.1 with concurrent 555 or 556). Children who were less than 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 TNF inhibitors or methotrexate or leflunomide within 183 days were included.

Children who were less than 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 follow-up data were available for the JIA cohort, slightly older children were included in the non-JIA comparator cohorts to ensure adequate overlap of children's ages with the JIA cohort during follow-up. Children were excluded from the comparator cohorts if they had any physician 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 follow-up.

All children with any physician ICD-9 code for organ transplantation or human immunodeficiency virus infection were excluded or censored, respectively, if the code occurred before or during follow-up. To increase the specificity for JIA, all children with 2 or more physician 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 less than 6 months of age at the time of disease diagnosis were excluded, due to the uncertainty of a diagnosis of JIA at this age (25). Age, sex, and race were recorded for all children.

For all children, the start of follow-up (index date) was 6 months after the date of the first physician 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 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). Follow-up 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 United States from the Surveillance Epidemiology and End Results (SEER) online database (http://seer.cancer.gov/canques/incidence.html).

Medication exposures

Follow-up 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 (methotrexate or leflunomide); TNF inhibitors (etanercept, infliximab, or adalimumab); and other immunomodulatory agents (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 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 follow-up; however, individual children could contribute person-time to multiple medication exposure groups sequentially based on their treatment course (e.g., when MTX is initiated for a child who did not previously receive systemic therapy or when TNF-α inhibitor therapy is initiated for a child currently receiving MTX). The “all children with JIA” group included all person-time for all children that met the cohort inclusion and exclusion criteria irrespective of therapeutic agent exposure. The “unexposed” medication exposure group included only person-time for children 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 exposed to MTX but never to TNF inhibitors (irrespective of other immunomodulatory agents). The “any TNF inhibitor” medication exposure group included all person-time following exposure to TNF inhibitors (irrespective of MTX or other immunomodulatory agents). The cohort size did not permit dividing the any TNF inhibitor group into those with and without MTX exposure or evaluating 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, 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 fashion by a pediatric rheumatologist (TB) and a pediatric hematologist-oncologist (CBS). 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 and 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 and 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) to the age, sex, and race distribution of all children with JIA in the study using 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 and highly probable, 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 (SIR) and 95% confidence intervals 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 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 JIA unexposed 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 to etanercept.

A total of 265 malignancies were identified by our outcome algorithm: 10 in JIA, 68 in ADHD, and 193 in asthma (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 tissue) were identified in the MTX without TNF inhibitor group, and 1 malignancy (uterus) was identified in the any TNF inhibitor group.

There were no malignancies 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 approximately 1.4 to 4.5 times higher for the various JIA medication exposure groups compared to the 2 internal comparator cohorts of children without JIA, and similar relative rates were seen for hematologic malignancy. The SEER external comparator standardized malignancy rates were significantly lower than the ADHD and asthma internal comparator rates. Comparing the standardized malignancy rates for the entire JIA cohort and the ADHD cohort versus SEER estimates resulted in SIR of 5.3 (95% CI 2.5–9.7) and 1.6 (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 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; 3 (30%) possible). The crude and standardized rates of probable and highly probable incident malignancies are shown in Table 3. The standardized rates of the combination of probable and highly probable incident malignancies for the ADHD and asthma comparator cohorts most closely approximated the standardized rate of 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 SIR of 3.7 (1.5–7.6) and 0.9 (0.7–1.1), respectively.

The SIR estimates of the JIA medication exposure groups compared to ADHD are shown in Table 4 for overall malignancy and Table 5 for hematologic malignancy. 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 for all children with JIA was significantly elevated at 4.4 (1.8–9.0), and the SIR for the JIA unexposed group was similarly elevated at 6.9 (2.3–16). The SIR for the any TNF inhibitor group was not significantly elevated (SIR 1.6 (0.03–8.3)), and there were no probable or highly probable malignancies among children exposed to any TNF inhibitor (SIR 0 (0–9.7)). SIR estimates for the hematologic malignancies were similar to the overall malignancy results, but with much larger confidence intervals due to 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% confidence intervals (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 without TNF inhibitor compared to the unexposed group was 0.6 (0.1–3.6). There were no probable or highly probable malignancies identified among children exposed to TNF inhibitors.

DISCUSSION

We found an increased incidence of malignancy among children with JIA when compared to children without JIA. Our results are comparable to those of some, but not all, prior studies. A recently published study by Simard, *et al* 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 (22). The authors reported that among all 5,296 children diagnosed with JIA since 1987, there was an adjusted relative risk of overall

malignancy of 2.3 (1.2–4.4). The authors of this study could not examine medication exposures in a detailed fashion. However, when follow-up 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 cannot be solely attributed to TNF inhibitor therapy. Using a database of commercial insurance claims from the United States, Harrison, *et al* preliminarily reported a hazard ratio of 2.8 (0.9–8.3) for overall malignancy among 3,605 children diagnosed with JIA who had not been exposed to TNF inhibitors or other biologics compared to matched children without JIA (28). Hence, both of these studies using different data sources reported results similar to those of our study. In contrast, Bernatsky, *et al* estimated a SIR of 0.12 (0.0–0.70) for overall malignancy among 1,834 children diagnosed with JIA at 3 major Canadian pediatric rheumatology centers versus expected rates generated from tumor registries (21). The explanation for this different result is unclear. Prior to these recent studies, Thomas, *et al* reported no increased rate of overall malignancy among children in Scotland diagnosed with juvenile chronic arthritis, though this study was limited to 896 children with resultant wide confidence intervals surrounding the estimates (29).

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, though we also found an increased rate of malignancies among children not treated with systemic immunosuppression. 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 for misclassification bias exists. 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 follow-up 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 with JIA. Among all children exposed to etanercept in the United States, 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* combined preliminary data from 3 prospective JIA biologics registries and estimated a SIR for overall malignancy of 3.7 (0.5–13.4) for children with JIA exposed to etanercept compared to the general population of children without JIA (32). This SIR is similar to the estimate that we and others have found among all JIA patients irrespective of treatment compared to children without JIA and 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 methodology that has been commonly used in studies of adult RA (33). Furthermore, concurrent treatment with MTX or TNF inhibitors in the setting of physician 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 MAX data may have been misclassified as not being 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 two 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 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 follow-up (58% for MTX and 50% for TNF inhibitors). The mean duration of study follow-up following known exposure to TNF inhibitors was 24 months. This duration of follow-up may be insufficient to capture the long-term or cumulative effects of TNF inhibitors. Finally, despite using the largest available claims database in the United States, our sample size still resulted in relatively wide confidence intervals, indicative of the rarity of incident malignancy in childhood.

It is not known how enrollment in Medicaid 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 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 of the ADHD cohort to determine the SIR results presented in the manuscript, 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 follow-up. None of the cohorts were intended to be incident diagnosis cohorts, and all follow-up 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 pre-dated the methotrexate era of treatment (29). Concern of a possible increased risk of lymphoma associated with methotrexate 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 with JIA 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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References

1. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000; 342(11):763–9. [PubMed: 10717011]
2. Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis. 2004; 63(12): 1638–44. [PubMed: 15115709]
3. Henrickson M, Reiff A. Prolonged efficacy of etanercept in refractory enthesitis-related arthritis. J Rheumatol. 2004; 31(10):2055–61. [PubMed: 15468375]
4. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008; 359(8):810–20. [PubMed: 18716298]
5. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum. 2008; 58(5):1496–504. [PubMed: 18438876]
6. Ruperto N, Lovell DJ, Cuttica R, Woo P, Meiorin S, Wouters C, et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension. Ann Rheum Dis. 2010; 69(4):718–22. [PubMed: 20237125]
7. Prince FH, Twilt M, ten Cate R, van Rossum MA, Armbrust W, Hoppenreijs EP, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. Ann Rheum Dis. 2009; 68(5):635–41. [PubMed: 18413443]

8. Onel KB, Onel K. Anti-tumor necrosis factor therapy and cancer risk in patients with autoimmune disorders. Arthritis Care Res (Hoboken). 2010; 62(7):1024–8. [PubMed: 20506257]
9. Yildirim-Toruner C, Kimura Y, Rabinovich E. Hodgkin's lymphoma and tumor necrosis factor inhibitors in juvenile idiopathic arthritis. J Rheumatol. 2008; 35(8):1680–1. [PubMed: 18671328]
10. Imundo L. Hodgkin's lymphoma associated with anti-TNF use in juvenile idiopathic arthritis: supplemental case report. J Rheumatol. 2008; 35(8):1681. [PubMed: 18671329]
11. Diak P, Siegel J, La Grenade L, Choi L, Lemery S, McMahon A. Tumor necrosis factor alpha blockers and malignancy in children: Forty-eight cases reported to the food and drug administration. Arthritis Rheum. 2010; 62(8):2517–24. [PubMed: 20506368]
12. Cron RQ, Beukelman T. Guilt by association - what is the true risk of malignancy in children treated with etanercept for JIA? Pediatr Rheumatol Online J. 2010; 8(1):23. [PubMed: 20712883]
13. Lehman TJ. Should the food and drug administration warning of malignancy in children receiving tumor necrosis factor alpha blockers change the way we treat children with juvenile idiopathic arthritis? Arthritis Rheum. 2010; 62(8):2183–4. [PubMed: 20506203]
14. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006; 29(5):385–96. [PubMed: 16689555]
15. Smitten AL, Simon TA, Hochberg MC, Suissa S. A meta-analysis of the incidence of malignancy in adult patients with rheumatoid arthritis. Arthritis Res Ther. 2008; 10(2):R45. [PubMed: 18433475]
16. Baecklund E, Iliadou A, Askling J, Ekbom A, Backlin C, Granath F, et al. Association of chronic inflammation, not its treatment, with increased lymphoma risk in rheumatoid arthritis. Arthritis Rheum. 2006; 54(3):692–701. [PubMed: 16508929]
17. Setoguchi S, Solomon DH, Weinblatt ME, Katz JN, Avorn J, Glynn RJ, et al. Tumor necrosis factor alpha antagonist use and cancer in patients with rheumatoid arthritis. Arthritis Rheum. 2006; 54(9):2757–64. [PubMed: 16947774]
18. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum. 2007; 56(9):2886–95. [PubMed: 17729297]
19. Askling J, van Vollenhoven RF, Granath F, Raaschou P, Fored CM, Baecklund E, et al. Cancer risk in patients with rheumatoid arthritis treated with anti-tumor necrosis factor alpha therapies: does the risk change with the time since start of treatment? Arthritis Rheum. 2009; 60(11):3180–9. [PubMed: 19877027]
20. Cleary AG, McDowell H, Sills JA. Polyarticular juvenile idiopathic arthritis treated with methotrexate complicated by the development of non-Hodgkin's lymphoma. Arch Dis Child. 2002; 86(1):47–9. [PubMed: 11806884]
21. Bernatsky S, Rosenberg AM, Oen KG, Duffy CM, Ramsey-Goldman R, Labrecque J, et al. Malignancies in Juvenile Idiopathic Arthritis: A Preliminary Report. J Rheumatol. 2011; 38(4): 760–3. [PubMed: 21239753]
22. Simard JF, Neovius M, Hagelberg S, Askling J. Juvenile idiopathic arthritis and risk of cancer: a nationwide cohort study. Arthritis Rheum. 2010; 62(12):3776–82. [PubMed: 20827782]
23. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol. 2005; 58(4):323–37. [PubMed: 15862718]
24. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004; 31(2):390–2. [PubMed: 14760812]
25. Petty, RE.; Cassidy, JT. Chronic arthritis in childhood. In: Cassidy, JT.; Petty, RE.; Laxer, RM.; Lindsley, CB., editors. Textbook of Pediatric Rheumatology: Sixth Edition. Philadelphia: Saunders Elsevier; 2011. p. 211-35.
26. Breslow, NE.; Day, NE. Statistical Methods in Cancer Research. Vol. II, The Design and Analysis of Cohort Studies. Lyon, France: International Agency for Research on Cancer; 1987. Rates and rate standardization; p. 48-79.
27. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol. 2003; 158(9):915–20. [PubMed: 14585769]

28. Harrison M, Nordstron B, Gu Y, Mercaldi C, Aquino P, Mines D. Risk of malignancy in biologics-naive juvenile arthritis patients. Ann Rheum Dis. 2010; 69(Suppl 3):631. [PubMed: 20215140]
29. Thomas E, Brewster DH, Black RJ, Macfarlane GJ. Risk of malignancy among patients with rheumatic conditions. Int J Cancer. 2000; 88(3):497–502. [PubMed: 11054684]
30. Jones OY, Spencer CH, Bowyer SL, Dent PB, Gottlieb BS, Rabinovich CE. A multicenter case-control study on predictive factors distinguishing childhood leukemia from juvenile rheumatoid arthritis. Pediatrics. 2006; 117(5):e840–4. [PubMed: 16651289]
31. Marwaha RK, Kulkarni KP, Bansal D, Trehan A. Acute lymphoblastic leukemia masquerading as juvenile rheumatoid arthritis: diagnostic pitfall and association with survival. Ann Hematol. 2010; 89(3):249–54. [PubMed: 19727722]
32. Harrison M, Cummins C, Horneff G, Southwood TR, Mines D. Cancer risk in juvenile arthritis patients exposed to etanercept: results from three observational cohorts. Ann Rheum Dis. 2010; 69(Suppl3):147.
33. MacLean CH, Louie R, Leake B, McCaffrey DF, Paulus HE, Brook RH, et al. Quality of care for patients with rheumatoid arthritis. JAMA. 2000; 284(8):984–92. [PubMed: 10944644]
34. Gonzalez-Perez A, Fernandez-Vidaurre C, Rueda A, Rivero E, Garcia Rodriguez LA. Cancer incidence in a general population of asthma patients. Pharmacoepidemiol Drug Saf. 2006; 15(2): 131–8. [PubMed: 16287212]
35. Smith MY, Sobel RE, Wallace CA. Monitoring the long-term safety of therapies for children with juvenile idiopathic arthritis: time for a consolidated patient registry. Arthritis Care Res (Hoboken). 2010; 62(6):800–4. [PubMed: 20535790]

Table 1

Characteristics of study cohorts

	All JIA	Asthma	ADHD
Number of children	7,812	652,234	321,821
Median age in years (IQR)	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
Median follow-up in years (IQR)	1.1 (0.4–2.4)	0.7 (0.3–1.6)	0.9 (0.4–1.9)
Medication exposures			
MTX	3423 (44%)		
TNF inhibitors	1484 (19%)		
Other immunomodulatory agents	398 (5%)		

JIA = juvenile idiopathic arthritis; ADHD = attention-deficit hyperactivity disorder; IQR = inter-quartile range; MTX = methotrexate or leflunomide; TNF inhibitors = etanercept, infliximab, or adalimumab

Table 2

Crude and standardized rates of all malignancy and hematologic malignancy for the study cohorts. All rates are standardized to the age, sex, and race distribution of the "all children with JIA" cohort.

Cohort	Person-Years of Follow-Up	All Malignancy		Hematologic Malignancy	
		Crude Rate per 100K person-years (95% CI)	Standardized Rate	Crude Rate per 100K person-years (95% CI)	Standardized Rate
All children with JIA	12,614	79.3 (42.7–147.3)	79.3	23.8 (7.7–73.7)	23.8
JIA unexposed	5,671	105.8 (47.5–235.5)	106.5	17.6 (2.5–125.1)	21.1
JIA MTX without TNF inhibitor	3,894	77.0 (24.8–238.8)	75.9	51.3 (12.8–205.2)	46.2
JIA any TNF inhibitor	2,922	34.2 (4.8–242.9)	37.0	0 (0–126.3)	(zero)
Asthma	675,794	28.6 (24.8–32.9)	27.1	10.5 (8.3–13.3)	10.4
ADHD	391,984	17.4 (13.4–22.0)	23.7	7.4 (5.1–10.6)	9.3
SEER external control	---	---	15.0	---	6.1

JIA = juvenile idiopathic arthritis; ADHD = attention-deficit hyperactivity disorder; MTX = methotrexate or leflunomide; TNF inhibitor = etanercept, infliximab, or adalimumab; SEER = Surveillance Epidemiology and End Results

Table 3

Crude and standardized rates of probable and highly probable incident malignancies for the study cohorts. All rates are standardized to the age, sex, and race distribution of the “all children with JIA” cohort.

Cohort	Probable and Highly Probable Incident Malignancies		Highly Probable Incident Malignancies Only	
	Crude Rate per 100K person-years (95% CI)	Standardized Rate	Crude Rate per 100K person-years (95% CI)	Standardized Rate
All children with JIA	55.4 (26.4–116.3)	55.4	31.7 (11.9–84.4)	31.7
JIA unexposed	88.2 (36.7–211.8)	89.6	52.9 (17.1–163.9)	59.3
JIA MTX without TNF inhibitor	51.3 (12.8–205.0)	52.1	25.6 (3.6–181.9)	22.5
JIA any TNF inhibitor	0 (0–126.0)	(zero)	0 (0–126.0)	(zero)
Asthma	17.9 (15.0–21.4)	16.5	13.5 (11.0–16.5)	12.3
ADHD	11.2 (8.4–15.1)	13.0	8.9 (6.4–12.4)	9.7
SEER external control		15.0		15.0

JIA = juvenile idiopathic arthritis; ADHD = attention-deficit hyperactivity disorder; MTX = methotrexate or leflunomide; TNF inhibitor = etanercept, infliximab, or adalimumab; SEER = Surveillance Epidemiology and End Results

Table 4

Standardized incidence ratios compared to ADHD cohort for all malignancy for the JIA medication exposure groups by certainty of malignancy outcome based on comprehensive review of entire claims histories.

Cohort	Standardized Incidence Ratios for All Malignancy (95% CI)		
	All Identified Incident Malignancies	Probable and Highly Probable Incident Malignancies	Highly Probable Cases Incident Malignancies
All children with JIA	3.3 (1.6–6.1)	4.4 (1.8–9.0)	3.3 (0.9–8.5)
JIA unexposed	4.6 (1.7–10)	6.9 (2.3–16)	6.2 (1.4–17)
JIA MTX without TNF inhibitor	3.3 (0.7–9.5)	3.9 (0.4–14)	2.3 (0.01–14)
JIA any TNF inhibitor	1.6 (0.03–8.3)	0 (0–9.7)	0 (0–13)

Highly probable was defined as >2 ICD-9 codes for the same form of malignancy and evidence of cancer treatment. Probable was defined as >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 and evidence of cancer treatment.

JIA = juvenile idiopathic arthritis; ADHD = attention-deficit hyperactivity disorder; MTX = methotrexate or leflunomide; TNF inhibitor = etanercept, infliximab, or adalimumab; ICD-9 = International Classification of Disease, Ninth Revision

Table 5

Standardized incidence ratios compared to ADHD cohort for hematologic malignancy for the JIA medication exposure groups by certainty of malignancy outcome based on comprehensive review of entire claims histories.

Cohort	Standardized Incidence Ratios for Hematologic Malignancy (95% CI)		
	All Identified Incident Malignancies	Probable and Highly Probable Incident Malignancies	Highly Probable Cases Incident Malignancies
All children with JIA	2.5 (0.5–7.3)	2.9 (0.3–10)	3.5 (0.4–13)
JIA unexposed	2.3 (0.07–11)	3.9 (0.1–19)	4.6 (0.1–23)
JIA MTX without TNF inhibitor	5.0 (0.5–19)	4.2 (0.02–25)	4.9 (0.03–30)
JIA any TNF inhibitor	0 (0–14)	0 (0–23)	0 (0–28)

Highly probable was defined as >2 ICD-9 codes for the same form of malignancy and evidence of cancer treatment. Probable was defined as >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 and evidence of cancer treatment.

JIA = juvenile idiopathic arthritis; ADHD = attention-deficit hyperactivity disorder; MTX = methotrexate or leflunomide; TNF inhibitor = etanercept, infliximab, or adalimumab; ICD-9 = International Classification of Disease, Ninth Revision