ARTHRITIS & RHEUMATISM
Vol. 64, No. 8, August 2012, pp 2773–2780
DOI 10.1002/art.34458

Rates of Hospitalized Bacterial Infection Associated With Juvenile Idiopathic Arthritis and Its Treatment

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Objective. **To compare the incidence of hospitalized bacterial infections among children with and children without juvenile idiopathic arthritis (JIA) and to examine the effects of selected medications.**

Methods. **Using national Medicaid data from 2000 through 2005, we identified a cohort of children with JIA and a comparator cohort of children with attention deficit hyperactivity disorder (ADHD). Exposures to methotrexate (MTX), TNF inhibitors, and oral glucocorticoids (GCs) were determined using pharmacy claims. Patients hospitalized with bacterial infections were identified using coded discharge diagnoses. We calculated adjusted hazard ratios (HR_{adj}) to compare infection incidence rates while adjusting for relevant covariates.**

Results. **We identified 8,479 JIA patients with 13,003 person-years of followup; 36% took MTX and 16% took TNF inhibitors. Compared with ADHD patients, JIA patients who were not currently taking MTX or TNF inhibitors had an increased rate of infection (HR_{adj} 2.0 [95% confidence interval (95% CI) 1.5, 2.5]). Among JIA patients not receiving TNF inhibitor therapy, MTX users had a similar rate of infection as those not currently taking MTX (HR_{adj} 1.2 [95% CI 0.9, 1.7]). TNF inhibitor use (irrespective of MTX) resulted in a similar rate of infection as use of MTX without a TNF inhibitor (HR_{adj} 1.2 [95% CI 0.8, 1.8]). Use of high-dose GCs (≥10 mg/day of prednisone or equivalent) increased the rate of infection as compared with no GC use, after adjustment for MTX and TNF inhibitor use (HR_{adj} 3.1 [95% CI 2.0, 4.7]).**

Conclusion. **Children with JIA had an increased rate of infection compared to children with ADHD. Among children with JIA, the rate of infection was not**

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Supported by the Agency for Healthcare Research and Quality (AHRQ) and the FDA, US Department of Health and Human Services (as part of grant 1U18-HS-017919-0, administered through the AHRQ CERTs Program). Dr. Beukelman's work was supported by the NIH (grant 5KL2-RR-025776 through the University of Alabama at Birmingham Center for Clinical and Translational Science). Dr. Grijalva's work was supported by the NIH (grant 5P60-AR-56116). Dr. Curtis' work was supported by the NIH (grant AR-053351) and the AHRQ (grant R01-HS-018517).

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Dr. Beukelman has received consulting fees, speaking fees, and/or honoraria from Novartis (less than $10,000) and a research grant from Pfizer. Dr. Baddley has received consulting fees, speaking fees, and/or honoraria from Abbott and Merck (less than $10,000 each). A portion of Dr. Delzell's salary was funded by a contract from Amgen. Dr. Lewis has received consulting fees, speaking fees, and/or honoraria from Pfizer, Abbott, and Millennium (less than $10,000 each) and a research grant from Centocor. Dr. Saag has received consulting fees, speaking fees, and/or honoraria from Eli Lilly, Merck, Novartis, Savient, Ardea, Regeneron, URL, and Abbott (less than $10,000 each) and from Amgen (more than $10,000). Dr. Winthrop has received consulting fees, speaking fees, and/or honoraria from Amgen, Genentech, Abbott, and Wyeth (less than $10,000 each). Dr. Curtis has received consulting fees, speaking fees, and/or honoraria from Abbott, Bristol-Myers Squibb, Crescendo, and Pfizer (less than $10,000 each) and from Roche/Genentech, UCB, Centocor, the Consortium of Rheumatology Researchers of North America, and Amgen (more than $10,000 each).

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Submitted for publication November 15, 2011; accepted in revised form February 23, 2012.

increased with MTX or TNF inhibitor use, but was significantly increased with high-dose GC use.

The relationship between juvenile idiopathic arthritis (JIA) and serious bacterial infections has not been extensively studied. The relatively recent introduction of biologic agents, including tumor necrosis factor α (TNF) inhibitors, for the treatment of JIA (1,2) has focused attention on the risks of infection. In adults with rheumatoid arthritis (RA), the most commonly reported serious adverse effect associated with TNF inhibitor therapy has been an increased rate of bacterial infections (3,4). However, numerous studies of the association between TNF inhibitors and infection in adults with RA have reported seemingly conflicting results, most likely owing to fundamental differences in study populations and study designs (5). Among children with JIA, questions persist about a possible increased risk of serious infections associated with the use of TNF inhibitors (6–8).

The study of serious infections among children with JIA is complicated by the unclear role of the underlying disease processes. Studies in adult patients have shown an increased risk of infection associated with RA as compared to the general population (9,10) and a positive association between infection risk and RA disease activity and severity (11,12). However, it is not known if there is a similar increase in infection risk among children with JIA.

Reports from studies of cohorts of children with JIA treated with the TNF inhibitor etanercept have revealed a crude rate of serious infection (defined as an infection requiring hospitalization or intravenous antibiotics) of ~2–3 per 100 person-years of TNF inhibitor use (6–8). Although methotrexate (MTX) has been used for decades in the treatment of JIA, there are few estimates of the associated incidence of infection in clinical practice. One cohort of patients treated with MTX had a serious infection rate of 1.3 per 100 person-years, which the authors found to be similar to the infection rate observed with TNF inhibitors (8). Systemic glucocorticoids (GCs) have been shown to significantly increase the risk of infection among adults with RA (9,11,13), but similar studies among children with JIA have not been published. There are no published reports of the overall infection rate in children with JIA in general or in children with JIA not receiving systemic immunosuppressant therapy.

Therefore, it is difficult to interpret the rate of infection associated with TNF inhibitors in children with JIA, since there are few data on background rates of infection among these children, many of whom are also exposed to MTX or systemic GCs. We used national Medicaid data to determine incidence rates of hospitalized bacterial infection among children with JIA in clinical practice and among children without JIA. We sought to answer several questions: What is the rate of infection among children with JIA who are not treated with MTX or TNF inhibitors? How does this rate compare to that in children without JIA? What are the rates of infection among children treated with MTX or TNF inhibitors? How do these rates compare? What role do oral GCs play in the risk of infection?

PATIENTS AND METHODS

Study populations. After obtaining Institutional Review Board approval, we performed this study using the US Medicaid Analytic eXtract (MAX) files from all 50 US states and the District of Columbia. MAX 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 and a comparator cohort of children without JIA who were diagnosed as having attention deficit hyperactivity disorder (ADHD). We chose a comparator cohort of children diagnosed as having a chronic noninflammatory disease in order to increase the proportion of children who had sustained interactions with the health care system and thus remained observable in the claims data during followup (see below). Children diagnosed with ADHD are not known to have a different rate of hospitalized bacterial infection 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 ADHD comparator cohort. These were the most recent data available to us at the time of the study.

We used International Classification of Disease, Ninth Revision (ICD-9) codes and pharmacy claims to identify children with JIA. In order to include all categories of JIA (14), the following ICD-9 diagnoses and codes 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 physician claims with the ICD-9 code for JIA that were at least 7 days, but not more than 183 days, apart were included. Additionally, children who had a single ICD-9–coded physician claim for JIA followed by an outpatient pharmacy claim for a TNF inhibitor or for MTX or leflunomide within 183 days were included.

All children who were <19 years old and who had ≥ 2 physician claims with the ICD-9 code for ADHD (code 314.0) that were at least 7 days, but not more than 183 days, apart were included in the comparator cohort. Children were excluded from the ADHD comparator cohort if they had any physician ICD-9 codes for JIA at any time.

For all children, the start of followup (index date) was the first date when both of the following criteria were met: 183 consecutive days of observable time within the MAX data had

accumulated, and the respective disease cohort definition was satisfied. The 183-day baseline period immediately prior to index dates was used to apply cohort exclusion criteria and assess baseline covariates.

All children with any ICD-9 code on a physician claim or a hospital discharge diagnosis for malignancy, organ transplantation, or human immunodeficiency virus infection were excluded or censored, respectively, if the code occurred during the baseline period or during the followup period. All children with 2 or more ICD-9 codes for other rheumatic diseases (systemic lupus erythematosus and other diffuse connective tissue diseases, vasculitis, or sarcoidosis) that were at least 7 days, but not more than 183 days, apart were excluded. 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 (15). All children who were exposed to other immunomodulatory agents (abatacept, alefacept, anakinra, azathioprine, cyclophosphamide, cyclosporine, efalizumab, 6-mercaptopurine, mycophenolate mofetil, rituximab, and tacrolimus) were excluded or censored, respectively, if the exposure occurred during the baseline period or during the followup period. Additionally, children in the ADHD comparator cohort who were exposed to MTX, leflunomide, or TNF inhibitors were excluded or censored, respectively, if the exposure occurred during the baseline period or during the followup period. In order to ensure that children remained fully observable with respect to medication exposures and hospitalized infection outcomes in the MAX claims database, all children without at least 1 outpatient pharmacy claim every 6 months and full medical benefits every month were censored. Followup was also censored when a hospitalized infection outcome occurred or the study period ended.

Medication exposures. Exposure status was determined using pharmacy and procedure claims for MTX (consisting of either MTX or leflunomide), TNF inhibitor (consisting of etanercept, infliximab, or adalimumab), and oral GCs. "Current medication use" ended 30 days after the total number of days of medication supplied by the last medication claim. We analyzed 3 medication exposure groups of primary interest: 1) no current MTX or TNF inhibitor use, 2) current MTX use without current TNF inhibitor use, and 3) current TNF inhibitor use irrespective of MTX use. The daily dose of oral GCs was determined by summing the total dosage of dispensed oral GCs in prednisone equivalents during the 60 days prior to the date of interest (e.g., the index date) and dividing by 60. The daily dose of oral GCs was categorized as none, low (>0 but <10 mg of prednisone equivalents per day), or high (≥10 mg of prednisone equivalents per day). All medication exposure episodes were included in the main analysis (prevalent-user design), and children could contribute followup time to >1 medication exposure group sequentially based on their clinical treatment course.

Outcome identification. Hospitalized bacterial infections were identified by examining all ICD-9 codes in any position from inpatient hospital discharge diagnoses. We used an adapted list of ICD-9 codes that had previously been validated in adult RA patients against medical records review to identify bacterial infections (16). It was not possible to determine whether the bacterial infection was the primary reason for the hospital admission or whether the infection developed during the hospitalization.

Statistical analysis. We determined crude infection rates for children with ADHD and for children with JIA with the 3 medication exposure groups of primary interest, with and without current oral GC use. We calculated absolute differences in the crude infection rates associated with TNF inhibitor use and MTX use.

We used Cox proportional hazard regression models to compare the incidence of infections among the exposure groups in the study. We calculated adjusted hazard ratios (HR_{adj}) by adjusting for patient characteristics, including age, sex, race, and the presence of ICD-9 codes indicating hospitalized bacterial infections, outpatient bacterial infections, asthma, and diabetes mellitus during the baseline period. Because patients could contribute person-time to >1 episode of medication exposure, a sandwich variance estimator was applied to account for additional correlations in the data (17). To evaluate the possibility of statistical interactions between oral GC use and TNF inhibitor use and hospitalized infection among children with JIA, we evaluated separate hazard models for children with and without current oral GC use on the index date. We also evaluated hazard models that included the daily dose of GCs after the index date as a time-varying covariate by updating the daily dose of oral GCs for all study subjects each time an infection outcome occurred.

We performed a secondary analysis of JIA patients that was restricted to new users of TNF inhibitors compared to new users of MTX without current or prior TNF inhibitor (new user design) (18); new use was defined as no prior pharmacy claims for the medication during the previous 6 months. In addition, we conducted sensitivity analyses to evaluate the robustness of our findings. First, the infection outcome identification was restricted to the primary hospital discharge diagnosis. Second, we repeated all analyses with current medication use extended to include 90 days after the total number of days of medication supplied by the last pharmacy claim. We also compared the duration of hospitalizations among the study exposure groups using the Wilcoxon rank sum test. Owing to the known association between JIA and specific immunodeficiencies (19,20), we excluded children with any diagnosis code for immunodeficiency at any time and repeated the analyses.

RESULTS

We identified 8,479 children with JIA with a total of 13,003 person-years of followup as well as 360,489 children with ADHD with a total of 454,698 person-years of followup (Table 1). There were significant differences in the sex and race distributions between the JIA and ADHD cohorts. The median followup time was comparable between the two cohorts. Greater proportions of children with JIA were receiving oral GCs on their index dates and had hospitalized infections during the baseline period as compared to children with ADHD. The proportion of children with asthma was similar in the two cohorts. During the followup period, treatment with MTX represented 96% of the MTX use

Table 1. Characteristics of the study patients*

	JIA cohort (n = 8,479)	ADHD cohort (n = 360,489)
Age, mean ± SD years	9.7 ± 4.4	9.8 ± 3.2
% female	64	24
Race/ethnicity, %		
White	52	64
African American	17	20
Latino	20	6
Other/unknown	11	10
Followup, median (IQR) years	1.1 (0.5–2.2)	0.9 (0.4–1.9)
Bacterial infection at baseline, no. (%)		
Hospitalized	402 (4.7)	2,941 (0.8)
Outpatient	4,004 (47)	133,760 (37)
Asthma, no. (%)	669 (7.9)	23,045 (6.4)
Diabetes mellitus, no. (%)	56 (0.7)	842 (0.2)
Current oral GC use		
Current use on index date, no. (%)	1,326 (16)	6,973 (1.9)
Daily dose on index date, median (IQR) mg	10 (4–23)	6 (3–13)
Medication use during followup, no. (%)		
Oral GCs	2,532 (30)	33,388 (9.3)
MTX	3,090 (36)	–
TNF inhibitor	1,315 (16)	–

* JIA = juvenile idiopathic arthritis; ADHD = attention deficit hyperactivity disorder; IQR = interquartile range; GC = glucocorticoid (prednisone equivalents); MTX = methotrexate (consisting of either MTX or leflunomide); TNF = tumor necrosis factor (TNF inhibitors consisting of etanercept, infliximab, or adalimumab).

and etanercept represented 90% of the TNF inhibitor use.

We identified 365 and 4,398 hospitalized infection outcomes in the JIA and ADHD cohorts, respectively. Table 2 shows the types of bacterial infections by disease cohort. Urinary tract infections were relatively more frequent in JIA patients (0.5 per 100 person-years versus 0.1 per 100 person-years; $P < 0.0001$), and this may be attributed to the much higher proportion of females in this cohort (64%) as compared to the ADHD cohort (24%).

Table 2. Hospitalized bacterial infection types by cohort*

Infection type	No. (%) in JIA cohort	No. (%) in ADHD cohort
Upper respiratory tract	110 (30)	1,544 (35)
Pneumonia	87 (24)	891 (20)
Bacteremia/septicemia	67 (18)	523 (12)
Urinary tract/pyelonephritis	65 (18)	402 (9)
Skin and soft tissue	44 (12)	616 (14)
Abdominal abscess	20 (6)	629 (14)
Gastroenteritis	30 (8)	331 (8)
Total hospitalized bacterial infections	365	4,398

* Only infection outcome types representing ≥5% of infections are shown. Some hospitalized infections were associated with >1 discharge diagnosis (e.g., pneumonia and bacteremia). The total number of hospitalized bacterial infections was used as the denominator for calculating the percentages. JIA = juvenile idiopathic arthritis; ADHD = attention deficit hyperactivity disorder.

Overall, the crude infection rate was nearly 3-fold higher among children diagnosed as having JIA (2.8 per 100 person-years) than among children diagnosed as having ADHD (1.0 per 100 person-years) (Table 3). Among children with JIA, the crude infection rates were ~2–3 per 100 person-years for all medication exposure groups. Compared with no current use of oral GCs, current use of oral GCs was associated with an increased crude rate of infection among children in all groups.

The absolute increase in the crude infection rate between children currently taking TNF inhibitors irrespective of MTX use as compared to MTX use without current TNF inhibitor use was not significant (rate difference 0.2 per 100 person-years [95% confidence interval (95% CI) –0.1, 1.3]). The rate difference between TNF inhibitor use and MTX use was also not significant if the comparison was restricted to either children not currently taking oral GCs (rate difference 0.5 per 100 person-years [95% CI –0.7, 1.6]) or children currently taking oral GCs (rate difference –1.4 per 100 person-years [95% CI –4.9, 2.2]).

Children with JIA who were not currently taking MTX or TNF inhibitors had an ~2-fold increase in the rate of infection as compared to children with ADHD after adjustment for patient characteristics, including the daily dose of oral GCs on the index date (Table 4). Patients currently taking MTX without TNF inhibitors

Table 3. Crude rates of hospitalized bacterial infection, by disease cohort and medication exposures*

	Person-years of observation	No. of hospitalized bacterial infections	Infection rate per 100 person-years (95% CI)		
			Overall rate	By oral GC use	
				No current use	Current use†
JIA cohort					
Entire cohort	13,003	365	2.8 (2.5, 3.1)	2.3 (2.1, 2.6)	6.9 (5.6, 8.5)
No current MTX, no current TNF inhibitor	8,777	222	2.5 (2.2, 2.9)	2.2 (1.9, 2.6)	7.3 (5.2, 10.1)
Current MTX, no current TNF inhibitor	2,646	88	3.3 (2.7, 4.0)	2.4 (1.8, 3.2)	7.1 (5.0, 9.9)
Current TNF inhibitor, irrespective of MTX	1,580	55	3.5 (2.6, 4.5)	2.9 (2.1, 4.0)	5.8 (3.4, 9.1)
ADHD cohort	454,698	4,398	1.0 (0.9, 1.0)	0.9 (0.9, 1.0)	5.0 (4.4, 5.7)

* 95% CI = 95% confidence interval; JIA = juvenile idiopathic arthritis; MTX = methotrexate (consisting of either MTX or leflunomide); TNF = tumor necrosis factor (TNF inhibitors consisting of etanercept, infliximab, or adalimumab); ADHD = attention deficit hyperactivity disorder.
† Current oral glucocorticoid (GC) use represents use during study followup.

did not have a significantly increased rate of infections (HR_{adj} 1.2 [95% CI 0.9, 1.7]) as compared to those not currently taking MTX or TNF inhibitors. Similarly, those currently taking TNF inhibitors irrespective of MTX use did not have an increased rate of infections (HR_{adj} 1.2 [95% CI 0.8, 1.8]) as compared to those currently taking MTX without current TNF inhibitors. The comparison of concurrent TNF inhibitor and MTX use versus MTX use without TNF inhibitor produced similar results (HR_{adj} 1.2 [95% CI 0.7, 1.8]).

In contrast, GC use was significantly associated with an increased rate of infections. In the comparison of current TNF inhibitor use irrespective of MTX versus current MTX use without TNF inhibitor use, the HR_{adj} for the use of high-dose oral GCs on the index date (≥10 mg/day of prednisone equivalents) was 3.1 (95% CI 2.0, 4.7) and the HR_{adj} for the use of low-dose oral GCs was 1.3 (95% CI 0.9, 2.1) as compared to those who were not currently taking oral GCs on the index date. Similar HR_{adj} estimates were obtained for current oral GC use in the other medication exposure group comparisons (data not shown).

Because of the possible statistical interaction between the use of oral GCs and the use of TNF inhibitors with regard to the risk of infection, separate hazard models were analyzed for children who were and those who were not taking oral GCs on their index dates. We did not find evidence of interaction when comparing TNF inhibitor use irrespective of MTX use versus MTX use without TNF inhibitor use. Among patients who were not currently taking oral GCs on their index date, the HR_{adj} associated with TNF inhibitor use was 1.3 (95% CI 0.7, 2.3), and the HR_{adj} associated with TNF inhibitor use among patients who were currently taking oral GCs on their index date was 1.1 (95% CI 0.7, 1.8).

To further explore the relationship between oral GC use and infection, we adjusted for current use of oral GCs after the index date as a time-varying covariate. The HR_{adj} for the use of GCs and the use of TNF inhibitors were similar to those that only adjusted for the daily dose of current oral GCs at baseline (data not shown). An interaction term between the GC dose and TNF inhibitor use was not statistically significant in this time-varying GC dose model.

Results of the new user design analyses were similar to the results of the primary analyses. New users of TNF inhibitor had an HR_{adj} of 1.2 (95% CI 0.5, 2.9) for infection as compared to new users of MTX without

Table 4. Relative hazard of hospitalized bacterial infections*

JIA cohort medication exposure group	Referent group	Relative hazard (95% CI)	
		Unadjusted	Adjusted†
No current MTX, no current TNF inhibitor	ADHD cohort	3.3 (2.6, 4.1)	2.0 (1.5, 2.5)
Current MTX, no current TNF inhibitor	JIA cohort: no current MTX, no current TNF inhibitor	1.3 (1.0, 1.7)	1.2 (0.9, 1.7)
Current TNF inhibitor, irrespective of MTX	JIA cohort: current MTX, no current TNF inhibitor	1.3 (0.9, 1.9)	1.2 (0.8, 1.8)

* JIA = juvenile idiopathic arthritis; 95% CI = 95% confidence interval; MTX = methotrexate (consisting of either MTX or leflunomide); TNF = tumor necrosis factor (TNF inhibitors consisting of etanercept, infliximab, or adalimumab); ADHD = attention deficit hyperactivity disorder.
† Adjusted for patient age, sex, race, hospitalized bacterial infection during baseline, outpatient bacterial infection during baseline, asthma, diabetes mellitus, and glucocorticoid (GC) dose on the index date (defined as none, low [<10 mg of prednisone equivalents per day], or high [≥10 mg of prednisone equivalents per day]).

current or prior TNF inhibitor use. The HR_{adj} for those who took high-dose GCs as compared to those who did not take GCs on the index date was 3.2 (95% CI 1.1, 8.8).

Restricting hospitalized infection outcomes to the primary discharge diagnosis produced similar results. In the comparison of JIA patients who were not currently taking MTX or TNF inhibitors versus ADHD patients, the HR_{adj} was 2.2 (95% CI 1.7, 3.0). The HR_{adj} for TNF inhibitor use irrespective of MTX use versus MTX use without TNF inhibitor use was 1.0 (95% CI 0.6, 1.6). The median duration of hospitalization with infection was 4 days for children with ADHD, children with JIA not currently taking MTX or TNF inhibitors, children with JIA currently taking MTX but not TNF inhibitors, and children with JIA currently taking TNF inhibitors ($P > 0.3$ for each comparison). Restricting the study period to the years of overlapping data for the JIA and ADHD cohorts (i.e., 2000–2002) yielded similar results, albeit with wider confidence intervals (data not shown). We repeated all analyses after increasing the exposure risk window for current medication use from 30 days to 90 days after the last pharmacy claim and the results were similar (data not shown). There were 89 children with JIA (1.0%) and 372 children with ADHD (0.1%) who were diagnosed as having immunodeficiencies. Exclusion of these children from the analyses also yielded similar results (data not shown).

DISCUSSION

We observed a 2-fold increase in the rates of hospitalized bacterial infections in children with JIA who were not currently being treated with MTX or TNF inhibitors as compared to children without JIA, controlling for oral GC dose, sex, and other factors at the start of followup. This finding suggests that the inflammatory or autoimmune process of JIA may predispose children to infection irrespective of therapy. Similar findings have been observed in adults with RA as compared to the general population (9,10). Among adults with RA, the risk of infection has been shown to increase with increasing disease severity (11,12), which further supports the theory that inflammation may predispose to infection. Although immunodeficiency diagnoses were 10-fold more common among children with JIA than among children without JIA, this difference did not explain the increased rate of infection that was observed.

The adjusted risk of infection associated with MTX use was similar to that in children who were not receiving MTX or TNF inhibitors. Although MTX has been used in the treatment of JIA for decades, there are few estimates of the associated relative risk of infection in children. Our results are consistent with the general impression of practicing pediatric rheumatologists that MTX therapy does not significantly increase the risk of serious bacterial infections (21).

The adjusted risk of infection associated with TNF inhibitor use was similar to the adjusted risk associated with MTX use without TNF inhibitor use. There were few hospitalized infections, and this resulted in relatively wide 95% CIs for the infection risk; nevertheless, based upon the upper bound of the 95% CIs, the possibility of a doubling of the risk of infection with TNF inhibitor use as compared to MTX use was excluded statistically.

Even after adjustment for TNF inhibitor and MTX use as well as other relevant covariates, the risk of infection increased 3-fold with the use of high-dose GCs as compared to no use of GCs. Similarly increased risks of infection with GCs have been observed in studies of adults with RA (11,13), including a dose-dependent increased risk (9). However, interpretation of these findings is complicated because oral GC use is likely to be associated with disease activity and severity. Assessing the GC dose in a time-varying manner did not influence our findings.

We restricted comparisons of infection rates for children receiving TNF inhibitors to only children who were receiving MTX because the accepted current clinical practice is to initiate TNF inhibitors in children whose JIA has failed to respond to MTX therapy (22). Accordingly, most children not currently receiving MTX are likely to have JIA that is less active and less severe as compared to children receiving TNF inhibitors, and this may influence the risk of infection (5).

In addition to concerns about a possible overall increased risk of infection, there have been worrisome, albeit uncontrolled, reports of severe soft-tissue infections associated with the use of TNF inhibitors (23–25). In this large cohort, we did not observe enough soft-tissue infections (<11) associated with TNF inhibitor use to perform an adjusted analysis, and the severity of soft-tissue infections cannot be accurately ascertained using the ICD-9 coding system. Nevertheless, the crude rates of hospitalized soft-tissue infections were not different between children treated with TNF inhibitors irrespective of MTX as compared to children treated with MTX without TNF inhibitor (0.4 per 100 person-years versus 0.3 per 100 person-years, respectively; $P > 0.6$).

Our study had limitations common to observa-

tional studies that use administrative claims data. We did not have access to medical records and could not directly verify the diagnoses of JIA, ADHD, or infection. However, we required 2 or more JIA ICD-9 codes separated in time, a method that has commonly been used in studies of adult RA (26). We used diagnosis codes for ADHD to identify a comparator group of children without JIA who were likely to generate subsequent Medicaid claims observable in the MAX data; thus, whether or not the diagnosis of ADHD was accurate is not material to this study. To identify hospitalized bacterial infections, we used an adapted list of ICD-9 codes that was previously validated against medical record review and found to demonstrate >80% sensitivity and specificity (16). We could not directly measure or adjust for JIA disease activity or severity. Therefore, medication channeling by prescribers, with resultant confounding between medication use and infection, is possible (i.e., the "sicker" patients received TNF inhibitors and were also more likely to develop infections). This confounding, if present, would have strengthened the association between medications and infection. Since we did not observe a strong association between TNF inhibitors and infection in our study, this is unlikely to have created appreciable bias in these results. Nevertheless, this confounding may explain a portion of the observed association between oral GC use and infection. Similarly, if the clinical decision to admit a child with an infection to the hospital was influenced by the child's current medication regimen rather than the severity of the infection, then bias could result. If present, this bias would strengthen the association between immunosuppressant medications and hospitalized infection.

In addition to these limitations, we used specific medication exposure definitions that may have influenced the results. The time window of potential increased risk of infection following initiation or cessation of MTX or TNF inhibitors is not precisely known. We considered current medication exposure up to 30 days after a missed prescription refill. We incorporated this refill grace period in order to maintain continuity within medication exposure episodes and to increase our ability to identify hospitalized infections that may have arisen after current medications were temporarily suspended owing to a minor infection that subsequently resulted in hospitalization. Increasing this refill grace period window to 90 days did not significantly affect the results. Sample size constraints limited our ability to perform a study restricted to new users of MTX and TNF inhibitors, which is typically regarded as the preferred study design (5,18). Nevertheless, a secondary analysis restricted to new users of TNF inhibitors versus new users of MTX resulted in an infection risk estimate for TNF inhibitor use that was very similar to our primary analysis of prevalent users, albeit with wider confidence intervals. We were unable to analyze agent-specific infection rates for the TNF inhibitors because etanercept was the only agent labeled for use by the US Food and Drug Administration during the study period and consequently represented 90% of the TNF inhibitor use. We could not determine precise daily doses of GCs from pharmacy claims, owing to several common behaviors, such as physician prescribing on an "as-needed" basis and patient nonadherence to the written prescription or self-administration from a cache of previously prescribed medication.

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 Centers for Medicare and Medicaid Services. Compared to the JIA cohort, we had access to fewer calendar years of data for the ADHD comparator cohort, but many more person-years of followup. We therefore allowed slightly older children to be included in the comparator cohort to ensure adequate overlap of children's ages with the JIA cohort, and we adjusted for age in our regression models. Furthermore, there was no anticipated calendar effect on infection rates. We formally tested this assumption by restricting our analyses to the calendar years common to both cohorts (2000 through 2002), and the results were similar.

In summary, children with JIA have higher rates of serious infection than do children without JIA, and this occurs independently of the effect of treatment with GCs, MTX, or TNF inhibitors. Among children with JIA, the rate of infection associated with MTX or TNF inhibitor use was similar. In contrast, compared with no GC use, the use of high-dose oral GCs (≥10 mg/day of prednisone equivalents) was consistently and independently associated with a more than doubling of the rate of subsequent infection. These data suggest that the use of steroid-sparing treatment strategies may reduce the risk of serious infections in children with JIA.

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, Xie, Chen, Baddley, Delzell, Grijalva, Lewis, Ouellet-Hellstrom, Patkar, Saag, Winthrop, Curtis.
Acquisition of data. Beukelman, Delzell, Ouellet-Hellstrom, Patkar, Saag, Curtis.
Analysis and interpretation of data. Beukelman, Xie, Chen, Baddley, Delzell, Grijalva, Lewis, Ouellet-Hellstrom, Patkar, Saag, Winthrop, Curtis.

REFERENCES

1. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al, for the Pediatric Rheumatology Collaborative Study Group. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med 2000;342:763–9.
2. 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;359:810–20.
3. Patkar NM, Teng GG, Curtis JR, Saag KG. Association of infections and tuberculosis with antitumor necrosis factor α therapy. Curr Opin Rheumatol 2008;20:320–6.
4. Askling J, Dixon W. The safety of anti-tumour necrosis factor therapy in rheumatoid arthritis. Curr Opin Rheumatol 2008;20: 138–44.
5. Solomon DH, Lunt M, Schneeweiss S. The risk of infection associated with tumor necrosis factor α antagonists: making sense of epidemiologic evidence [review]. Arthritis Rheum 2008;58: 919–28.
6. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al, for the Pediatric Rheumatology Collaborative Study Group. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 2008;58:1496–504.
7. Horneff G, De Bock F, Foeldvari I, Girschick HJ, Michels H, Moebius D, et al, and the German and Austrian Paediatric Rheumatology Collaborative Study Group. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis 2009;68:519–25.
8. Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum 2009;60:2794–804.
9. Smitten AL, Choi HK, Hochberg MC, Suissa S, Simon TA, Testa MA, et al. The risk of hospitalized infection in patients with rheumatoid arthritis. J Rheumatol 2008;35:387–93.
10. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Frequency of infection in patients with rheumatoid arthritis compared with controls: a population-based study. Arthritis Rheum 2002;46:2287–93.
11. Doran MF, Crowson CS, Pond GR, O'Fallon WM, Gabriel SE. Predictors of infection in rheumatoid arthritis. Arthritis Rheum 2002;46:2294–300.
12. Au K, Reed G, Curtis JR, Kremer JM, Greenberg JD, Strand V, et al, on behalf of the CORRONA Investigators. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis 2011;70:785–91.
13. Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of serious infections in rheumatoid arthritis. Rheumatology (Oxford) 2007;46:1157–60.
14. 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;31:390–2.
15. Petty RE, Cassidy JT. Chronic arthritis in childhood. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors. Textbook of pediatric rheumatology. 6th ed. Philadelphia: Saunders; 2011. p. 211–35.
16. Patkar NM, Curtis JR, Teng GG, Allison JJ, Saag M, Martin C, et al. Administrative codes combined with medical records based criteria accurately identified bacterial infections among rheumatoid arthritis patients. J Clin Epidemiol 2009;62:321–7.
17. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. J Am Stat Assoc 1989;84:1074–8.
18. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 2003;158:915–20.
19. Barkley DO, Hohermuth HJ, Howard A, Webster DB, Ansell BM. IgA deficiency in juvenile chronic polyarthritis. J Rheumatol 1979;6:219–24.
20. Cassidy JT, Petty RE, Sullivan DB. Abnormalities in the distribution of serum immunoglobulin concentrations in juvenile rheumatoid arthritis. J Clin Invest 1973;52:1931–6.
21. Ilowite NT, Laxer RM. Pharmacology and drug therapy. In: Cassidy JT, Petty RE, Laxer RM, Lindsley CB, editors. Textbook of pediatric rheumatology. 6th ed. Philadelphia: Saunders; 2011. p. 71–126.
22. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res (Hoboken) 2011;63:465–82.
23. Kaur PP, Derk CT, Chatterji M, Dehoratius RJ. Septic arthritis caused by Actinobacillus ureae in a patient with rheumatoid arthritis receiving anti-tumor necrosis factor-α therapy. J Rheumatol 2004;31:1663–5.
24. Fitch PG, Cron RQ. Septic abscess in a child with juvenile idiopathic arthritis receiving anti-tumor necrosis factor-α therapy [letter]. J Rheumatol 2006;33:825–6.
25. Morishita K, Petty R, Cairns R, Bolaria R, Cabral D, Turvey S. Serious musculoskeletal infections in children receiving anti-tumor necrosis factor-α therapy: a case series. Clin Rheumatol 2010;29: 677–81.
26. MacLean CH, Louie R, Leake B, McCaffrey DF, Paulus HE, Brook RH, et al. Quality of care for patients with rheumatoid arthritis. JAMA 2000;284:984–92.

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

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