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Incidence of Selected Opportunistic Infections Among Children with Juvenile Idiopathic Arthritis

Timothy Beukelman, MD, MSCE,
The University of Alabama at Birmingham

Fenglong Xie, MS,
The University of Alabama at Birmingham

John W Baddley, MD, MSPH,
The University of Alabama at Birmingham

Lang Chen, PhD,
The University of Alabama at Birmingham

Elizabeth Delzell, ScD,
The University of Alabama at Birmingham

Carlos G Grijalva, MD, MPH,
Vanderbilt University

Melissa L Mannion, MD,
The University of Alabama at Birmingham

Nivedita M Patkar, MD, MSPH,
The University of Alabama at Birmingham

Kenneth G Saag, MD, MSc,
The University of Alabama at Birmingham

Kevin L Winthrop, MD, and
Oregon Health and Science University

Jeffrey R Curtis, MD, MS, MPH
The University of Alabama at Birmingham

On behalf of the Safety Assessment of Biological ThERapeutics (SABER) Collaboration

Abstract

Objective—To compare incidence rates of selected opportunistic infections (OI) among children with and without juvenile idiopathic arthritis (JIA).

Methods—Using United States national Medicaid administrative claims data from 2000 through 2005, we identified a cohort of children with JIA based on physician diagnosis codes and dispensed medications. We defined a non-JIA comparator cohort of children diagnosed with attention deficit hyperactivity disorder (ADHD). We defined 15 types of OI using physician diagnosis or hospital discharge codes, and 7 of these types also required evidence of treatment

Corresponding author: Timothy Beukelman, MD, MSCE. The University of Alabama at Birmingham, Division of Pediatric Rheumatology, 1600 7th Avenue South, CPP 210, Birmingham, AL, 35233-1711. Phone: 205-939-9438. FAX: 205-939-9439. tbeukelman@peds.uab.edu.
Address reprint requests to: Timothy Beukelman, MD, MSCE. The University of Alabama at Birmingham, Division of Pediatric Rheumatology, 1600 7th Avenue South, CPP 210, Birmingham, AL, 35233-1711.

with specific antimicrobials. We calculated infection incidence rates (IR). The rates in the ADHD comparator cohort were standardized to the age, sex, and race distribution of the JIA cohort. We calculated incidence rate ratios (IRR) to compare infection rates.

Results—The JIA cohort included 8,503 children with 13,990 person-years (p-y) of follow-up. The ADHD comparator cohort included 360,362 children with 477,050 p-y of follow-up. When all OI were considered together as a single outcome, there were 42 infections in the JIA cohort (IR 300 per 100,000 p-y; IRR 2.4 [1.7–3.3] versus ADHD). The most common OI among children with JIA were 3 *Coccidioides* (IR 21 per 100,000 p-y; IRR 101 [8.1–5319] versus ADHD); 5 *Salmonella* (IR 35 per 100,000 p-y; IRR 3.8 [1.2–9.5]); and 32 herpes zoster (IR 225 per 100,000 p-y; IRR 2.1 [1.4–3.0]).

Conclusions—OI are rare among children with JIA. Nevertheless, children with JIA had a higher rate of OI, including *Coccidioides*, *Salmonella*, and herpes zoster, than children with ADHD.

INTRODUCTION

The relationship between juvenile idiopathic arthritis (JIA) and opportunistic infections (OI) has not been extensively studied. An increased rate of hospitalized bacterial infections among children with JIA compared to children without JIA, even in the absence of immunosuppressant medication use, has been reported (1). Some OI, in particular tuberculosis, endemic mycoses, *Listeria*, and *Legionella*, occur more frequently among adults with rheumatoid arthritis (RA) who are treated with biologic agents compared to those with RA who do not receive biologics (2, 3). The risks of OI among children with JIA, including those treated with biologics, may be similar to those found in adults with RA, but to our knowledge there are no published controlled reports on this topic. Similar to the increased risk of hospitalized bacterial infections, it is possible that JIA itself may increase the risk of OI, presumably as a result of immune dysregulation or chronic inflammation. We compared incidence rates of selected OI among children with and without JIA. Although we anticipated that OI would be infrequent, we also sought to examine the association of immunosuppressant medications with these infections to the extent possible.

METHODS

Study populations

After obtaining Institutional Review Board approval, we performed this study using United States Medicaid Analytic eXtract (MAX) files from all 50 U.S. states and the District of Columbia from the years 2000 through 2005. MAX 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 a comparator cohort of children without JIA who were diagnosed with attention-deficit hyperactivity disorder (ADHD), as previously described (1). In brief, we identified children with 2 or more JIA or ADHD physician diagnosis codes that were at least 7 days but not more than 183 days apart. Children who had a single JIA physician diagnosis code followed by an outpatient pharmacy claim for tumor necrosis factor (TNF) inhibitor, methotrexate, or leflunomide within 183 days were also included. Because JIA may be associated with immunodeficiencies (4), we also separately examined OI among children diagnosed with JIA and immunodeficiency.

For all children, the start of follow-up (index date) was the first date when both of the following criteria were met: (1) accumulated 90 consecutive days of observable time within the MAX data and (2) satisfied the respective disease cohort definition. The 90 day baseline period immediately prior to index dates was used to assess for prevalent or initially misdiagnosed OI (which excluded patients from analysis) and to assess current medication

exposures. Follow-up was censored when an OI outcome occurred, exclusion criteria were met (as previously described), subjects became no longer observable in the data, or the study period ended, whichever occurred first (1).

Medication exposures

Exposure status was determined using pharmacy and procedure claims for MTX (methotrexate or leflunomide), TNFi (etanercept, infliximab, or adalimumab), and oral systemic glucocorticoids (GC). "Current medication use" ended 30 days after the days supplied by each filled prescription. We analyzed 4 medication exposure groups of primary interest: (1) no current MTX or TNFi use, (2) current MTX use without current TNFi use, (3) current TNFi use irrespective of MTX use; (4) current GC use irrespective of MTX or TNFi.

Outcome identification

We identified infections with *Aspergillus*, *Blastomyces*, *Histoplasma*, *Coccidioides*, *Cryptococcus*, *Legionella*, *Listeria, Salmonella*, *Nocardia*, *Toxoplasma*, Pneumocystis, JC virus (progressive multifocal leukoencephalopathy), tuberculosis, non-tuberculuous *Mycobacterium*, and herpes zoster using all available inpatient and outpatient physician diagnosis and hospital discharge codes. Owing to concern about diagnosis codes possibly being associated with resolved or indolent infections, infections with mycoses and tuberculosis also required evidence of treatment with specific systemic anti-fungal and anti-mycobacterial medications, respectively, within 90 days of the diagnosis code. In the primary analysis, we required herpes zoster infection diagnoses to include evidence of specific anti-viral medication treatment within 90 days of the diagnosis to increase specificity for the outcome. We also identified herpes zoster diagnoses irrespective of concurrent anti-viral therapy as part of a sensitivity analysis. We performed an analysis of all OI combined together as a single outcome and also evaluated each OI individually.

Primary varicella infection (chicken pox) is not an OI. Nevertheless, children without fully competent immune function, owing either to immunosuppressant medications or autoimmunity, may be prone to more severe primary varicella infections. To evaluate this among children with JIA, we identified children with a hospital discharge diagnosis of primary varicella infection (without a concurrent diagnosis of herpes zoster) who also received critical care services during the hospitalization. Hospitalization without critical care services may not necessarily reflect a severe primary varicella infection, owing to hospitalization to facilitate administration of intravenous immunoglobulin therapy, intravenous antiviral therapy, and/or careful observation.

Statistical analysis

We calculated crude infection incidence rates (IR) for children with JIA. We calculated IR for children with ADHD that were standardized to the age, sex, and race distribution of the JIA cohort. We calculated incidence rate ratios (IRR) to compare infection rates between the JIA and ADHD cohorts. Owing to concerns about the precision of our estimates, we did not determine IRR if only a single infection outcome occurred among children with JIA. If there was more than 1 infection outcome in each of the medication groups, then we determined IRR for 3 medication comparisons of interest (1): current GC versus no current GC; current MTX versus no current MTX or TNFi; current TNFi with or without MTX versus current MTX without TNFi. Centers for Medicare and Medicaid Services regulations prohibit reporting tabular cell counts less than 11 for research using MAX files.

To provide an additional reference point for our OI incidence estimates, we identified incidence rates from the United States Centers for Disease Control and Prevention (CDC)

for the OI that are nationally notifiable diseases. For OI that are not notifiable to the CDC, we performed a targeted literature search to identify published population incidence rate estimates.

RESULTS

Table 1 lists the characteristics of the study patients. We identified 8,503 children with JIA with a total of 13,990 person-years of follow-up, and 360,362 children with ADHD with a total of 477,050 person-years of follow-up. There were significant differences in the sex and race distributions between the JIA and ADHD cohorts, and these were accounted for in the standardization procedure. The median duration of follow-up in the 2 cohorts was similar and was approximately one year.

Table 2 lists the incidence rates for OI. When all OI were considered as a single outcome, there were 42 infections among all children with JIA. The resultant IRR was 2.4 [95% confidence interval (CI) 1.7 – 3.3] for children with JIA compared to children with ADHD. When OI were identified individually, among all children with JIA, there were no identified infections with *Aspergillus*, *Blastomyces*, *Histoplasma*, *Cryptococcus*, *Legionella*, *Listeria*, JC virus, or tuberculosis. There was 1 infection each with *Nocardia*, non-tuberculous *Mycobacterium*, *Toxoplasma*, and *Pneumocystis*. There were 3 *Coccidioides* infections, 5 *Salmonella* infections, and 32 herpes zoster cases. (In 2 patients with JIA, diagnosis codes for different OI appeared in the baseline and follow-up periods.) When herpes zoster cases were excluded from the combined OI analysis, there was an increased rate of infection among children with JIA compared to children with ADHD (IRR 4.2 [95% CI 2.1 – 7.6]).

Table 2 also shows published population incidence rates for OI. In general, the incidence rates in the comparator ADHD group were similar to these estimates.

Most of the identified OI were due to herpes zoster, and these infections were more common among all children with JIA compared to children with ADHD (IRR 2.1 [95% CI 1.4 – 3.0]). The 32 children with JIA and herpes zoster had the following current medication exposures: 16 without MTX or TNFi; 7 with MTX but without TNFi; 9 with TNFi irrespective of MTX; and 6 with GC. Table 3 demonstrates that there was not a marked association of current medication use with the relative rates of herpes zoster. If the definition of herpes zoster was a single physician diagnosis code without the requirement for concurrent anti-viral therapy, the incidence remained elevated among children with JIA compared to ADHD (IRR 1.6 [95% CI 1.1 – 2.1]). Among children with JIA, there were 12 children with hospital discharge diagnoses for primary varicella, but no hospitalizations were associated with critical care services.

When compared to children with ADHD, the infection rate for all children with JIA was increased for *Salmonella* (IRR 3.8 [95% CI 1.2 – 9.5]) and markedly increased for *Coccidioides* (IRR 102 [95% CI 8.1 – 5319]). Of the 3 children with JIA and *Coccidioides* infections, 2 had no current exposure to MTX, TNF, or GC; 1 had current exposure to MTX, but not to TNF or GC; and none had a history of exposure to TNF since the start of the study baseline period.

Among 128 children with JIA and a concurrent diagnosis of primary immunodeficiency, there were 3 OI (IR 1,102 per 100,000 person-years). All 3 OI were herpes zoster. Diagnosis codes for immunodeficiency appeared prior to the herpes zoster diagnosis in 2 of the 3 children.

DISCUSSION

Using Medicaid administrative claims data, we observed a 2-fold higher incidence rate of OI among children with JIA compared to children without JIA. In particular, we observed higher rates of infection with herpes zoster, *Salmonella*, and *Coccidioides*. There was not a marked association between specific immunosuppressant medication use and herpes zoster, although the precision of our estimates was limited by the relatively small number of observed infections. In addition, none of the 3 children with JIA and incident *Coccidioides* infections were exposed to TNFi during the study period. In a similar previous study, we demonstrated that JIA was associated with a 2-fold increased risk of hospitalized bacterial infection compared to children without JIA, in the absence of current immunosuppressant medication use (1). Our current study revealed that there may be a similar increased risk of OI associated with JIA as well, and no other comparable studies of OI have been published to date, to our knowledge.

Most of the cases of OI in both JIA and ADHD were due to herpes zoster, which may be more likely to be treated with antiviral medications in children with JIA. Nevertheless, when the herpes zoster definition was limited to physician diagnosis without the requirement for concurrent antiviral medication, the infection rate among children with JIA remained elevated compared to children with ADHD. Similarly, when herpes zoster infections were excluded from the combined OI outcome, the overall infection rate among children with JIA remained elevated compared to children with ADHD. The increased rate of OI among all children with JIA compared to children without JIA highlights the critical importance of appropriate comparator groups when evaluating the safety of new therapeutic agents (11). Children diagnosed with JIA and immunodeficiency had a higher rate of OI, but all observed infections were herpes zoster.

Our study had limitations common to observational studies that use administrative claims data. The median follow-up time of 1.2 years in the JIA cohort was relatively short, but this was a prevalent diagnosis cohort that included patients with long-standing disease. We did not have access to medical records and could not directly verify the diagnoses of JIA or ADHD or of OI. For infections such as tuberculosis or mycoses, a physician diagnoses code may represent chronic, asymptomatic, or indolent infections. Accordingly, we required evidence of specific antimicrobial treatment in the definition of these infections. However, this may have biased the results toward the identification of more infections among the children with JIA owing to a lower threshold for systemic treatment. The sensitivity to identify cases of tuberculosis infection was very likely compromised by the fact that most individuals in the United States receive anti-tuberculosis medications directly from their local health department; consequently, these medications frequently do not appear in claims data. However, this misclassification was assumed to be non-differential (i.e., children with JIA and ADHD were equally likely to receive their anti-tuberculosis medications from their local health department). Our incidence rates for OI in the ADHD comparator cohort were similar to estimates from the CDC and other published sources. Some of the OI may cause arthritis and in our study may instead represent initial misdiagnoses of JIA. We attempted to identify and exclude misdiagnoses during the 90 day baseline period. Nevertheless, one case of *Salmonella* in the JIA cohort was diagnosed 2 days after the index date and was not followed by any subsequent diagnosis codes for JIA. The other identified OI outcomes appeared unlikely to represent potential misdiagnoses of JIA.

In summary, children with JIA were diagnosed with incident OI more frequently than children with ADHD, although infections were very uncommon in both groups. Immunosuppressant medication use was not associated with a marked increased risk of infection among children with JIA. The study of OI is limited by their rarity; nevertheless,

the potential risk attributable to the underlying JIA disease process must be taken into account when evaluating the safety of new medications.

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Table 1

Characteristics of study patients.

	JIA	ADHD
Number of patients	8,503	360,362
Median Age in years (IQR)	10.1 (5.9 – 13.3)	9.4 (7.3 – 11.8)
Female	5,421 (64%)	85,814 (24%)
Race		
White	4,402 (52%)	230,608 (64%)
Black	1,448 (17%)	72,471 (20%)
Latino	1,721 (20%)	21,076 (6%)
Other/Unknown	932 (11%)	36,207 (10%)
Median Years of Follow-up (IQR)	1.2 (0.6 – 2.4)	1.0 (0.5 – 2.0)
Total Follow-up (person-years) *	13,990	477,050
Current GC use on index date	1,471 (17%)	7,109 (2%)
Median daily GC dose among users (IQR)	10 mg (4.2 – 22.5)	6.3 mg (2.7 – 12.5)
Any GC use during follow-up	3,098 (36%)	37,615 (10%)
Any MTX use during follow-up	3,491 (41%)	n/a
Any TNFi use during follow-up	1,392 (16%)	n/a

* follow-up for analysis of all opportunistic infections considered as single outcome

JIA = juvenile idiopathic arthritis; ADHD = attention deficit hyperactivity disorder; IQR = interquartile range; GC = glucocorticoid; MTX = methotrexate or leflunomide; TNFi = tumor necrosis factor alpha inhibitor (etanercept, infliximab, or adalimumab); n/a = not applicable

Table 2

Infection incidence rates in children with and children without JIA.

Infection	IR per 100,000 person-years (95% CI)			IRR (95% CI) (JIA vs ADHD)
	JIA (~13,990 person-yrs)	ADHD (Standardized) (~477,050 person-yrs)	Published Rate (Reference)	
All Infections	300 (216 – 406)	125 (115 – 135)		2.4 (1.7 – 3.3)
Herpes zoster	225 (154 – 318)	106 (97 – 116)	88–171 (5, 6)	2.1 (1.4 – 3.0)
All infections *except* herpes zoster	86 (44 – 150)	21 (17 – 25)		4.2 (2.1 – 7.6)
Salmonella	35 (11 – 81)	9 (7 – 12)	26 (7)	3.8 (1.2 – 9.5)
Coccidioides	21 (4 – 61)	0.2 (0.005 – 1)	0.7 (7)	101 (8.1 – 5319)
non-TB *Mycobacteria*	7 (0.2 – 39)	2 (0.7 – 3)	> 4 (8)	
Nocardia	7 (0.2 – 39)	4 (2 – 6)	*(9)	
Pneumocystis	7 (0.2 – 39)	0 (0 – 0.8)	†(9)	
Toxoplasma	7 (0.2 – 39)	5 (3 – 7)	*(9)	
Blastomyces	0 (0 – 26)	0.2 (0.005 – 1)	0.1 (10)	
Histoplasma	0 (0 – 26)	0.2 (0.005 – 1)	0.2 (10)	
JC virus	0 (0 – 26)	0.2 (0.005 – 1)	†(9)	
Cryptococcus	0 (0 – 26)	0 (0 – 0.8)	*(9)	
Tuberculosis	0 (0 – 26)	0 (0 – 0.8)	1.4 (7)	
Legionella	0 (0 – 26)	0 (0 – 0.8)	0.03 (7)	
Listeria	0 (0 – 26)	0 (0 – 0.8)	0.03 (7)	
Aspergillus	0 (0 – 26)	0 (0 – 0.8)	*(9)	

Person-years of follow-up listed is for analysis of all opportunistic infections considered as single outcome. Person-years of follow-up for individual infection outcomes is slightly greater.

*has been reported in immunocompetent children;

†has not been reported in immunocompetent children; JIA = juvenile idiopathic arthritis; ADHD = attention deficit hyperactivity disorder; IR = incidence rate; IRR = incidence rate ratio; CI = confidence interval; TB = tuberculous

Table 3

Associations between current medications and herpes zoster infections among children with JIA.

Current Medication Exposure	Person-years of Follow-up	Herpes zoster IR per 100,000 person-years (95% CI)	IRR (95% CI)
No MTX, No TNFi	9,465	169 (97 – 275)	
Current MTX, No TNFi	2,995	234 (94 – 482)	1.4 (0.5 – 3.6) compared to No MTX, No TNFi
Current TNFi, Irrespective of MTX	1,765	510 (233 – 968)	2.2 (0.7 – 6.9) compared to Current MTX, No TNFi
No Current GC	12,614	206 (135 – 302)	
Current GC	1,612	372 (137 – 810)	1.8 (0.6 – 4.5) compared to No Current GC

JIA = juvenile idiopathic arthritis; IR = incidence rate; IRR = incidence rate ratio; CI = confidence interval; MTX = methotrexate or leflunomide; TNFi = tumor necrosis factor alpha inhibitor (etanercept, infliximab, or adalimumab); GC = glucocorticoid