

Recent Trends in Medication Usage for the Treatment of Juvenile Idiopathic Arthritis and the Influence of Tumor Necrosis Factor Inhibitors

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ABSTRACT. Objective. Using administrative data from a large commercial US health insurer, we investigated temporal trends in medication use among children diagnosed with juvenile idiopathic arthritis (JIA). **Methods.** Children with ≥ 1 physician diagnosis code for JIA in the calendar years 2005 through 2012 were included. Use of tumor necrosis factor inhibitors (TNFi), methotrexate (MTX), nonsteroidal antiinflammatory drugs (NSAID), and oral glucocorticoids (GC) was determined. Temporal changes in medication usage were evaluated with the Cochran-Armitage test for trend. We used paired t-tests to evaluate the use of NSAID and GC in the 6 months before and after new TNFi use.

Results. We identified 4261 unique individuals with JIA. The proportion of patients receiving TNFi increased from 8.7% in 2005 to 22.4% in 2012 ($p < 0.0001$). MTX use increased from 18.4% to 23.2% ($p = 0.02$). NSAID use decreased from 49% to 40% ($p = 0.02$). GC use was relatively unchanged. Following new TNFi use, the mean number of NSAID prescriptions (among prevalent users) decreased from 2.8 to 2.0 ($p < 0.0001$), and the mean daily GC dose (among prevalent users) decreased from 7.3 mg/day to 3.9 mg/day ($p < 0.0001$). Many new TNFi users (57%) had not used MTX in the previous 6 months, and only 37% had any concurrent MTX use in the 6 months following new TNFi use.

Conclusion. TNFi use in the treatment of JIA increased 2- to 3-fold over the last 8 years. New TNFi use was associated with decreased NSAID and GC use. TNFi may be replacing, rather than complementing, MTX in the treatment of many patients. (J Rheumatol First Release Aug 1 2014; doi:10.3899/jrheum.140012)

Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS

METHOTREXATE

TUMOR NECROSIS FACTOR INHIBITORS

The treatment of juvenile idiopathic arthritis (JIA) has changed dramatically over the last few decades, owing to the introduction of effective therapeutic agents and with the increasing recognition that JIA is usually not a self-limited condition¹. The historical foundation of treatment of JIA had consisted of nonsteroidal antiinflammatory drugs (NSAID) and oral glucocorticoids (GC) in conjunction with targeted intraarticular GC injections of selected joints. In 1992,

methotrexate (MTX) was shown to be effective in the treatment of juvenile arthritis in a randomized placebo-controlled clinical trial² and its use in routine clinical practice steadily increased. Similarly, in 2000, the first biologic agent, the tumor necrosis factor- α inhibitor (TNFi) etanercept (ETN), was shown to be effective in the treatment of JIA³. Additional TNFi have been shown to be effective in the treatment of JIA^{4,5}, as have biologic agents with different mechanisms of action^{6,7,8,9}. Also introduced into the market at about the same time as the first TNFi were the selective cyclooxygenase 2 (COX-2) inhibitors, 1 of which, celecoxib, was specifically studied in JIA and found to be at least as effective as naproxen¹⁰. The relative frequency with which celecoxib is used in clinical practice for the treatment of JIA is unclear. The addition of traditional disease-modifying antirheumatic drugs (DMARD) such as MTX and biologic DMARD has enabled many patients with JIA to achieve disease remission, which was previously infrequently attained¹.

TNFi have continued to demonstrate effectiveness and safety in followup studies of randomized trials^{11,12} and have become fundamental to the treatment of JIA¹³, but little is known about the actual use of these medications in clinical

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practice. Specifically, it is unclear the extent to which TNFi use has increased relative to MTX, NSAID, and GC use. Also unclear is the effect that initiating TNFi use has on the use of other medications at the individual patient level. One may suspect that the increased use of TNFi would be associated with decreased use of NSAID and GC owing to improved control of the signs and symptoms of disease, but this has not been well-studied. Systemic GC use has remained prevalent; a study of patients enrolled in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry reported that 42% of all children with a history of arthritis involving 5 or more joints had received GC during their disease courses¹⁴. Several randomized studies of adults with rheumatoid arthritis¹⁵ and at least 2 studies of children with JIA^{4,16} have demonstrated the superior effectiveness of combination therapy of TNFi plus MTX compared to TNFi alone, but it is unclear how often children receive this combination therapy. The American College of Rheumatology (ACR) Recommendations for the Treatment of JIA call for a trial of MTX prior to initiation of TNFi¹³, but whether this recommendation is followed in clinical practice is unclear.

Health insurer administrative claims data contain a reliable source of outpatient pharmacy fills and physician encounter diagnosis codes for each beneficiary that provide an accurate account of real-world medication use¹⁷. Using national claims data from a large commercial insurer, we sought to characterize the use of medications in the treatment of JIA over time and determine changes in therapy associated with the initiation of TNFi. We sought to determine the use of MTX prior to or concurrent with TNFi, and whether the initiation of a TNFi reduced the use of GC and prescription NSAID in patients with JIA.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, we performed our study using national commercial insurance administrative claims data from January 2005 through September 2012 with claims from all 50 US states and the District of Columbia. The commercial insurer provides medical coverage to more than 18 million individuals through numerous employer-sponsored and individual plans. For each calendar year, we included all patients who were age ≤ 16 years at the start of the calendar year (to increase the sensitivity for newly diagnosed cases of JIA) and received at least 1 International Classification of Disease, 9th ed (ICD-9) code associated with a physician encounter that was consistent with JIA: 714 [juvenile rheumatoid arthritis (JRA)], 720 [spondyloarthropathy (SpA)], and 696.0 [psoriatic arthritis (PsA)]. Patients were included in the analysis for each year that they met the inclusion criteria.

In the analyses of yearly temporal trends in medication use, subjects were only included if they had full medical and pharmacy benefits for all 12 months of the respective calendar year (for the first 9 months in 2012). Medication use was defined by at least 1 pharmacy or infusion claim during the respective calendar year. Treatment with TNFi [adalimumab, ETN, infliximab (IFX), golimumab, or certolizumab], MTX, NSAID (including celecoxib, the only COX-2 inhibitor available during the study period), and oral GC, was determined. We performed a sensitivity analysis by requiring patients to receive at least 2 JIA diagnosis codes (> 7 days apart) in the same calendar year. We also evaluated medication use among children with

at least 1 diagnosis code consistent with JIA and at least 1 ICD-9 diagnosis code for uveitis (364.0, 364.1, 364.3) in the same calendar year.

New TNFi users were defined by having at least 6 months of preceding eligibility without evidence of any TNFi use and at least 6 months of followup data available following new TNFi initiation. Only the first instance of any new TNFi use was included for each individual patient. We assigned each new TNFi user to an arthritis diagnosis according to the most frequent ICD-9 code received during the 12-month new-user observation period: 714 (JRA), 720 (SpA), and 696.0 (PsA).

Patient characteristics were collected for all children with at least 1 JIA diagnosis code and the subset of new TNFi users. Significant changes in medication use over time were evaluated with the Cochran-Armitage test for trend. We compared the number of filled prescriptions for NSAID and the cumulative mean daily GC dose (in prednisone equivalents) before and after the initiation of TNFi using paired t-tests. These analyses were performed among 2 groups of patients: users of NSAID and GC during the 6-month period prior to new TNFi use (prevalent users), and all new TNFi users. The use of MTX before and after new TNFi use was evaluated. Patient characteristics associated with different patterns of MTX use were compared using chi-square and ANOVA. All p values were 2-sided and considered significant at values ≤ 0.05 . Data analyses were performed using JMP Version 10.0 and SAS software, Version 9.3 (SAS institute Inc.).

RESULTS

There were a total of 4261 unique patients with 1 JIA code (Table 1; with a range of 818 to 1004 patients per calendar yr) and 2532 with 2 JIA codes within the same calendar year (with a range of 550 to 617 patients per calendar yr) during the study period. Most of the patients had a diagnosis code for juvenile rheumatoid arthritis (714). The median age was 11 years old [interquartile range (IQR) 7–14], and most of the patients (64.4%) were female. Only 34% of patients were included in more than 1 calendar year of the study results. There were 1497 unique prescriber identification numbers associated with filled MTX, TNFi, NSAID, and GC prescriptions for the 4261 unique patients during the study period.

Table 1. Patient characteristics for all children with ≥ 1 JIA code and for new TNFi users. Data presented are n (%) unless noted.

Characteristics	≥ 1 JIA code, n = 4261	New TNFi User, n = 344
Median age, yrs	11 (IQR 7–14)	13 (IQR 9–15)
Female	2742 (64.4)	230 (66.9)
US census region		
Midwest	609 (14.3)	51 (14.8)
Northeast	1367 (32.1)	93 (27.0)
South	1395 (32.7)	124 (36.1)
West	890 (20.9)	76 (22.1)
JIA diagnosis codes		
714	3898 (91.5)	313 (91.0)
720	334 (7.8)	40 (11.6)
696.0	310 (7.3)	44 (12.8)
No. calendar years observed		
1 yr	2793 (66)	76 (22.1)
≥ 2 yrs	1468 (34)	268 (77.9)

JIA: juvenile idiopathic arthritis; TNFi: tumor necrosis factor inhibitors; IQR: interquartile range.

The proportion of patients with JIA using MTX and TNFi significantly increased over time (Figure 1). In 2005, 8.7% of patients with 1 JIA code received TNFi compared to 22.4% in 2012 ($p \geq 0.0001$). Over the same time period, the proportion of MTX users increased from 18.4% to 23.2% ($p = 0.02$). Conversely, the proportion of NSAID users decreased from 49.2% in 2005 to 40.4% in 2012 ($p = 0.02$). GC use did not exhibit a significant trend over time ($p = 0.4$); the proportions ranged from 19.8% in 2005 to 16.1% in 2012 with small increases and decreases from year to year.

When restricted to patients with 2 or more JIA diagnosis codes within the same calendar year, similar increases in MTX and TNFi use were observed. The increase in TNFi use was significant ($p < 0.0001$), increasing from 13.6% in 2005 to 30.3% in 2012. The trend for MTX use was significant ($p = 0.05$), with proportions increasing from 25.9% in 2005 to 32.4% in 2012. Use of NSAID decreased significantly over time, from 60.8% in 2005 to 44.2% in 2012 ($p < 0.0001$). Again, the use of GC did not demonstrate a trend ($p = 0.2$), with the proportion of users being 22.8% in 2005 and 19.3% in 2012.

Among children with at least 1 diagnosis code for JIA and at least 1 diagnosis code for uveitis in each calendar year (total of 387 unique patients for all yrs), the proportion of TNFi use increased significantly from 11.0% in 2005 to 29.1% in 2012 ($p < 0.0001$), similar to the trend seen among children with 2 or more diagnosis codes for JIA.

Over the study period, TNFi use increased dramatically compared to MTX use. In 2005, there were 0.6 users of any

TNFi for each individual user of MTX without use of TNFi. This ratio increased to 1.4 in 2012; that is, in 2012, there were 40% more children receiving TNFi (with or without concurrent MTX) than there were children receiving MTX without TNFi.

The use of celecoxib was uncommon throughout the study period. The prevalence of celecoxib use over the entire study period for children with ≥ 1 JIA code was 4% without any evidence of trend over time ($p = 0.2$). Likewise, the proportion of prescription NSAID users that used selective COX-2 inhibitors remained relatively unchanged at about 7% over the study period.

Over the entire study period, ETN was used most frequently (71.5% of all TNFi use), followed by adalimumab (28.6%), and IFX (14.9%). The proportion of ETN use reached its peak of 82.6% in 2007 and then decreased to 61.8% in 2011 (trend $p < 0.0001$). The proportion of IFX use was highest in 2005 (17.7%) and then decreased to 12.4% in 2012 (trend $p = 0.1$). The proportion of adalimumab use steadily increased from 8.9% in 2005 to 33.1% in 2011 (trend $p < 0.0001$).

Other medications used for the treatment of inflammatory arthritis were infrequently used in this JIA population. Hydroxychloroquine and sulfasalazine were used in about 5% and 3% of the patients, respectively, over the entire study period. Abatacept, anakinra, leflunomide, rituximab, and tocilizumab were each used by fewer than 2% of patients in any calendar year.

We identified 344 new TNFi users. Some of their characteristics were different from all patients with JIA (Table 1),

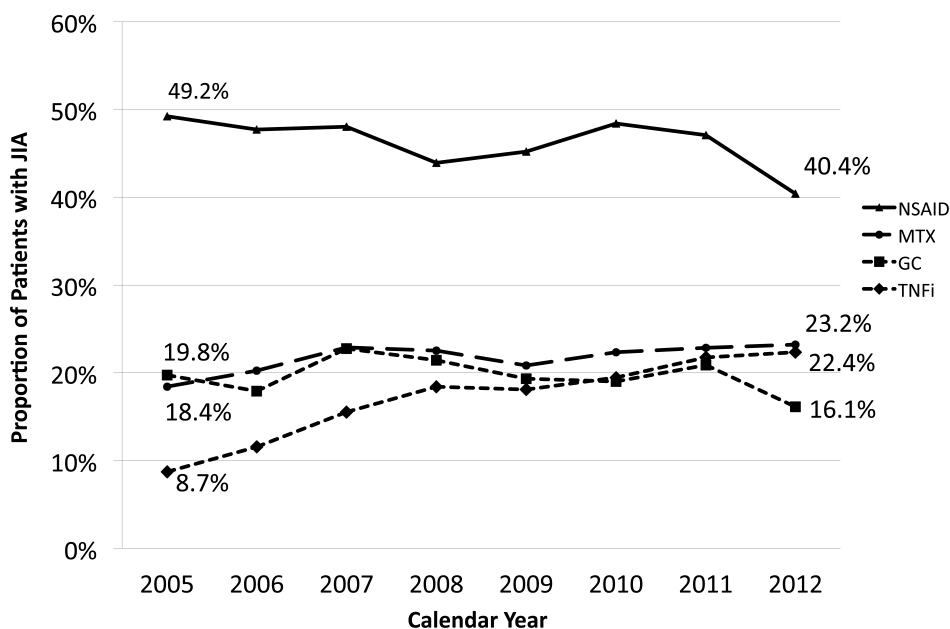


Figure 1. Proportion of patients with JIA receiving TNFi, MTX, NSAID, and GC by calendar year. JIA: juvenile idiopathic arthritis; TNFi: tumor necrosis factor inhibitors; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drugs; GC: glucocorticoids.

such as the duration of observation (78% of new TNFi users with ≥ 2 yrs of followup compared to 34% of all patients) and the frequency of diagnosis codes for PsA and SpA. (The duration of observation is longer in this subset of patients owing to the requirement for 6 months of baseline data and 6 months of followup data.) The most commonly initiated TNFi were ETN (70%), adalimumab (19%), and IFX (10%).

One possible contributing factor to the increasing proportion of children with JIA receiving TNFi over time could be the initiation of TNFi therapy in progressively younger patients as physicians gained comfort with this new class of medications; however, this was not observed in our data. The median age of new TNFi users did not decrease over time and ranged from 11.5 years (IQR 9–13) in 2005 to 13 years (IQR 8–16) in 2012.

New TNFi use was associated with a reduction in the number of filled NSAID prescriptions (Table 2). This reduction was significant among prevalent NSAID users ($n = 194$), with a mean decrease of 0.85 prescriptions over the 6-month period following new TNFi use ($p < 0.0001$).

New TNFi use was associated with a reduction in GC use (Table 3). In the 6 months following new TNFi use, there was a reduction in the mean daily dose of GC of 1.1 mg per day among all new TNFi users ($p = 0.0002$) and 3.4 mg per day among prevalent users of GC ($p < 0.0001$). Among the prevalent users of GC, 60% (75/126) did not have GC use in the 6 months following initiation of TNFi. Conversely, 17 patients (5% of all new TNFi users) who did not have GC use in the 6 months prior to new TNFi use received GC in the 6 months after new TNFi use at a mean dose of 3.5 mg/day.

The use of MTX before and after new TNFi use did not necessarily follow the expected patterns (Table 4). Many patients (57%) received new TNFi without having received MTX in the prior 6 months. Most patients with new TNFi use did not receive concurrent therapy with MTX; only 37% of patients received any MTX in the 6 months following new TNFi use. The initiation of both new MTX and new TNFi concurrently was infrequent too; only 11% of children without MTX use in the 6 months prior to new TNFi use started using MTX in the following 6 month period. Of all new TNFi users, 51% did not receive MTX in the combined 12-month period.

The use of MTX before new TNFi varied based on the arthritis diagnosis. Patients with SpA ($n = 30$) or PsA ($n = 24$) diagnoses had higher frequencies of TNFi use without prior MTX use (90% and 75%, respectively) compared to patients diagnosed with JRA (150/290, 51.7%), and these differences were statistically significant ($p < 0.0001$ for both comparisons). There were no significant differences in the patterns of MTX use before or after TNFi use with respect to census region of residence ($p = 0.7$), age ($p = 0.2$), or presence of uveitis diagnosis codes ($p = 0.8$).

The proportions of new TNFi users with MTX use before or after starting TNFi did not change significantly by year during the study period. When evaluating the use of MTX in the 12 months before and after new TNFi use, the results were similar. Specifically, 47% of new TNFi users did not receive MTX in the 12 months prior to new TNFi use and only 48% received any MTX in the 12 months following new TNFi use.

Table 2. The use of NSAID in the 6 months prior to and the 6 months following new initiation of TNFi use.

	No. NSAID Users Prior to New TNFi Use	No. NSAID Users Following New TNFi Use	p	Mean No. NSAID Prescriptions Prior to New TNFi Use (SD)	Mean No. NSAID Prescriptions Following New TNFi Use (SD)	Mean Change in No. NSAID Prescriptions (95% CI)	p
All new TNFi users, n = 344	194 (56%)	149 (43%)	0.0006	1.6 (1.9)	1.2 (1.8)	-0.4 (0.2–0.6)	0.0003
Prevalent NSAID users, n = 194	194 (100%)	125 (64%)	< 0.0001	2.8 (1.7)	2.0 (2.0)	-0.9 (0.5–1.2)	< 0.0001

NSAID: nonsteroidal antiinflammatory drugs; TNFi: tumor necrosis factor inhibitors.

Table 3. The use of GC in the 6 months prior to and the 6 months following new initiation of TNFi use.

	No. GC Users Prior to New TNFi Use	No. of GC Users Following New TNFi Use	p	Mean Daily GC Dose Prior to New TNFi Use (SD)	Mean Daily GC Dose Following New TNFi Use (SD)	Mean Change in Daily GC Dose (95% CI)	p
All new TNFi users, n = 344	126 (37%)	68 (20%)	< 0.0001	2.7 mg (5.8)	1.6 mg (4.8)	-1.1 mg (0.5–1.6)	0.0002
Prevalent GC users, n = 126	126 (100%)	51 (40%)	< 0.0001	7.3 mg (7.7)	3.9 mg (7.3)	-3.4 mg (2.0–4.9)	< 0.0001

GC: glucocorticoids (in prednisone equivalents); TNFi: tumor necrosis factor inhibitors.

Table 4. The use of MTX in the 6 months prior to and the 6 months following new initiation of TNFi use.

MTX use prior to new TNFi	MTX Use Following New TNFi Use		Total
	Yes	No	
Yes	108 (31%)	41 (12%)	149 (43%)
No	21 (6%)	174 (51%)	195 (57%)
Total	129 (37%)	215 (63%)	

MTX: methotrexate; TNFi: tumor necrosis factor inhibitors.

DISCUSSION

Using data from a large national commercial health insurer in the United States, we analyzed recent changes in medication use in the treatment of JIA. The use of TNFi in the treatment of JIA increased 2- to 3-fold over the last 8 years, with a less pronounced increase in the use of MTX. Over the same time period, there was decreased use of prescription NSAID. At the individual patient level, new initiation of TNFi was followed by decreased use of NSAID and GC.

An analysis of medication use in the CARRA Registry, a prospective observational cohort of children enrolled by pediatric rheumatologists from more than 50 clinical sites in the United States, also reported about TNFi and MTX use in the treatment of JIA¹⁴. At the time of enrollment, 71% of patients had ever received MTX and 44% had ever received TNFi. By comparison, we observed that among children with ≥ 2 JIA diagnosis codes in 2012, 32% received MTX and 30% received TNFi. The true discrepancy between these results is not easy to determine because the CARRA Registry study reported ever use and our current study reported on use per calendar year for an open cohort of children enrolled in the health insurance plan. We cannot accurately determine “ever use” from these data. Additionally, all children in the CARRA Registry are treated by pediatric rheumatologists, who identify individual patients and consent to their taking part; this likely affects the patients’ characteristics and reflects treatment decisions made by pediatric rheumatologists. In contrast, our current study included unselected children diagnosed with JIA, irrespective of the treating physician or patient characteristics. It is not known how many children with JIA are treated by physicians other than pediatric rheumatologists in the United States, but the proportion is believed to be significant (i.e., greater than 40%)^{18,19}. In our study, children diagnosed with JIA filled prescriptions for MTX, TNFi, NSAID, and GC that were associated with 1497 different unique prescriber identification numbers. Because there are only about 350 board certified pediatric rheumatologists in the United States, many other providers must be writing prescriptions for these medications.

Interestingly, there was a trend of decreasing prescription

NSAID use among patients with JIA. This appeared to coincide with the increased use of MTX and TNFi, and may reflect better overall disease control with fewer residual symptoms including pain. Use of celecoxib, a selective COX-2 inhibitor, remained uncommon in the JIA population without much variation in use over the last 8 years despite being approved by the US Food and Drug Administration for the treatment of JIA during the study period in December 2006. GC use among all patients remained prevalent and relatively stable during the study period, despite the increased use of MTX and TNFi. The reasons for this finding are unclear, but may reflect strong preferences for the use of GC by individual physicians. A related finding was reported in the aforementioned study of the CARRA Registry participants: about 9% of all patients with JIA were currently receiving GC at the time of enrollment despite the frequent use of MTX and TNFi in this cohort of patients¹⁴.

For individual patients, the new use of TNFi was followed by decreased use of prescription NSAID and GC. Ostensibly, this is the result of improved disease control with the use of TNFi, consistent with published clinical trials^{3,4}. In addition to improved disease control, this reduction in co-medication use may represent an important benefit of TNFi therapy when considering the potential adverse effects of chronic NSAID²⁰ and especially, GC use²¹. (Of course, TNFi have potential adverse effects as well²².) The observed reduction in GC dose (mean 1.1 mg/day reduction among all new TNFi users and 3.4 mg/day reduction among prevalent GC users) is likely clinically significant. All-cause mortality and cardiovascular-related mortality have been shown to be significantly associated with small differences in daily GC dose (HR 1.07 per mg/day and 1.08 per mg/day, respectively) in adults with RA²³.

The use of MTX and TNFi in our study population did not appear consistent with published recommendations or clinical studies of effectiveness. The ACR Recommendations clearly recommend a trial of MTX prior to the initiation of TNFi¹³. Despite this, only about 50% of new TNFi users had used MTX in the recent past. Of note, most of this study period predates the publication of the ACR Recommendations in April 2011. Numerous studies have demonstrated the superior treatment effect of TNFi used in combination with MTX compared to TNFi used alone^{4,16,24}. Despite this, the majority of new TNFi users did not use concurrent MTX therapy in the year following initiation of TNFi. One possible clinical reason to initiate TNFi without first using MTX might be the concern about disease severity or poor prognosis. It may be believed that sometimes arthritis is too severe to tolerate a trial period of MTX. In this situation, the use of concurrent therapy with TNFi and MTX may be reasonably expected; however, this pattern of use was observed only infrequently. Admittedly, we could not observe events that occurred prior to enrollment in the health insurance plan (“left-censoring”). Thus, some

patients may have had a remote history of prior MTX use when we observed new TNFi use, but this is unlikely to represent the majority of patients. Overall, it appears that TNFi may be replacing MTX rather than complementing MTX among many patients and prescribers.

In general, TNFi are often more effective than MTX and may be better tolerated than MTX with respect to non-serious adverse drug experiences (e.g., nausea). This combination of positive factors may be perceived by prescribers as outweighing the increased direct medication cost of TNFi and the uncertain safety of TNFi use for durations beyond those observed thus far. It is unclear why more children did not receive concurrent therapy with TNFi and MTX, although this may also be related to the sometimes limited tolerability of MTX²⁵.

Our study had important limitations. We used data from a single large private commercial insurer; medication use among patients with different insurance may be different. Nevertheless, the data are from a national population of beneficiaries without specific restriction to particular healthcare providers or geographic regions, and provide a more comprehensive view of prescription medication use in the real-world setting. Prescription patterns are influenced by myriad coverage policies in addition to provider preference, and could explain some of the patterns observed in the data. As over-the-counter medications are generally not covered by commercial insurance, it is not known how many patients received nonprescription NSAID during the study period.

Administrative claims data do not contain any clinical information including patient weight, and the diagnosis of JIA could not be confirmed for any of the patients. Accordingly, the numerical values of the proportions of children with medication use in our study are challenging to interpret because the number of children with true JIA in the denominator is uncertain. Nevertheless, the relative changes in medication use over time are valid reflections of medication use in the treatment of JIA, as one would not anticipate significant changes in the proportion of “false positive” or “rule-out” diagnoses codes for JIA over the time period of our study. We favored a highly sensitive definition of JIA to include all possible patients. An analysis using a more specific definition of JIA (2 diagnosis codes in a calendar year) resulted in increased proportions of medication use as expected, but importantly the overall trends in medication usage remained parallel to those using the more sensitive JIA definition.

We observed that there have been considerable changes in the treatment of JIA over the last 8 years, including the increased use of TNFi and the decreased use of prescription NSAID. The usage patterns of MTX and TNFi were surprising and did not appear consistent with published studies of effectiveness or current treatment recommendations that suggest that TNFi should be used after a trial of

MTX and then concurrently with MTX. Additional studies are warranted to better understand these medication usage trends and the factors that determine them.

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