

# Trends in Medication Usage in Juvenile Idiopathic Arthritis: Prescribing Trends or Trends in Prescribers?



The International League of Associations for Rheumatology classification of juvenile idiopathic arthritis (JIA) defines 7 categories<sup>1</sup> that represent diverse phenotypes, differing biology, and widely divergent disease courses. Treatment strategies differ between JIA categories; however, little is known about how recent treatment guidelines are interpreted and used by clinicians in routine patient care.

In this issue of *The Journal*, Mannion, *et al* address an important gap in knowledge. These researchers obtained administrative data from a national US commercial insurer, representing about 8 million individuals across all 50 US states<sup>2</sup>. They examined diagnoses and prescriptions written over an 8-year period between 2005 and 2012, determining trends in medication usage for JIA. In particular, they focused on treatments prescribed following the introduction and increased uptake of the anti-tumor necrosis factor- $\alpha$  (anti-TNF- $\alpha$ ) biologics.

Healthcare researchers using administrative databases are able to examine large volumes of anonymized data, with the possibility of population-based research without individual recruitment and consent. In the current study, insurance diagnosis and prescription claims were used to identify patients with JIA. Their lenient diagnosis for JIA required only 1 JIA diagnostic code within 1 calendar year, with patients requalifying in the prevalence estimate each year. Although multiple validation studies of rheumatoid arthritis (RA) have demonstrated greater specificity when a greater number of encounters were required<sup>3,4</sup>, in this case the researchers increased the specificity of the claims diagnosis by studying patients who received prescriptions for disease-modifying antirheumatic drugs (DMARD) and biologics. In fact, the prevalence of JIA in the studied population was likely not greatly overestimated. If the covered individuals reflected the US population, then 24% (1.92 million) were < 18 years old, and the 500 to 1000 patients with JIA identified within each calendar year represent a yearly prevalence of less than 1/2000 children.

Several findings in the current study are worth highlighting. The researchers identified over 4000 unique patients with JIA; however, only 34% were represented in more than 1 calendar year, perhaps reflecting the instability of US insured individuals. The proportion of patients receiving methotrexate (MTX) and anti-TNF- $\alpha$  medications increased over the time period studied. In 2005, 18.4% received MTX compared to 23.2% in 2012. For anti-TNF- $\alpha$ , prescriptions increased from 8.7% of patients to 22.3% over the 8-year period. More striking than the actual percentages are the comparisons of how anti-TNF- $\alpha$  usage increased compared to MTX. In 2005, for each individual taking MTX without anti-TNF- $\alpha$ , there were 0.6 individuals taking an anti-TNF- $\alpha$ . In 2012 this ratio was radically different — for every individual taking MTX without TNF there were then 1.4 individuals taking anti-TNF- $\alpha$  (with or without concurrent MTX).

While one might not be surprised by the rapid increase in the proportion of patients receiving anti-TNF- $\alpha$ , what is most striking is that medication prescriptions were written by 1497 unique providers. At the end of 2005, there were only 215 American Board of Pediatrics (ABP) certified pediatric rheumatologists, with 312 certified by the end of 2012. Even counting an average of 60 fellows-in-training across the United States each year, but not accounting for the retired, lapsed, and non-US certified physicians, the current study suggests that more than 80% of all prescriptions were not written by a pediatric rheumatologist. Unfortunately, it was not possible to ascertain who the prescribing physicians were, but these results further underscore the shortage of pediatric rheumatologists. Workforce data from the ABP demonstrates that, at the end of 2013, there were, on average, 241,729 children for each pediatric rheumatologist. Of course this ratio does not hold true nationwide, and (for those states with at least 1 pediatric rheumatologist) ranges from 36,500 children (Washington, DC) to over 1 million children (in Kentucky) for every

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rheumatologist. At least 10 states continue to be without a single certified pediatric rheumatologist<sup>5</sup>.

So, if a pediatric rheumatologist is not available to care for a child with JIA, one assumes that an adult rheumatologist or a pediatrician provides care (and prescriptions). At least 2 large Canadian population-based studies of patients with RA have shown that being cared for by a rheumatologist (rather than a primary care provider) is the strongest predictor of DMARD initiation<sup>6,7</sup>. No similar study in JIA exists, although the increasing rates of DMARD and biologic use in the current study suggest that adult rheumatologists, rather than pediatricians, are treating JIA.

What experience and comfort level do these prescribers have, and what guidelines do they have to follow? In 2011, the first recommendations for the treatment of JIA were published by the American College of Rheumatology (ACR). They were designed to provide guidance for patterns of practice and not to dictate the care of a particular patient<sup>8</sup>. The guidelines were developed using the Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method<sup>9</sup> to derive recommendations that were as evidence-based as possible. Experienced pediatric rheumatologists from the United States, Canada, and Europe (world leaders) participated in the core expert panel and the task force panel, and the rigorous guidelines methodology included evaluation of over 1500 clinical scenarios by each task force member. To paraphrase the guidelines, initiation of an anti-TNF- $\alpha$  is recommended in a patient with moderate to high disease activity and active arthritis despite intraarticular steroid injections and  $\geq 3$  months of MTX. Patients with enthesitis-related arthritis (ERA) may not require MTX trial prior to anti-TNF- $\alpha$ . Notably, these guidelines were published in 2011 and revised in 2013, following most of the time period covered in the current study<sup>8,10</sup>.

If we believe that adult rheumatologists are caring for many patients with JIA, we might expect that patients with JIA would be treated similarly to patients with RA. Like JIA, there are ACR RA guidelines, and these too are fairly cumbersome. To recommend treatment, a practitioner must first determine disease duration [early (< 6 months), 6–24 months, or > 24 months] and then assess features of poor prognosis and determine whether low, moderate, or high disease activity is present. Similarly to JIA guidelines, in adults MTX is the initial DMARD of choice in most cases. Anti-TNF- $\alpha$  in combination with MTX is recommended in early RA in the presence of poor prognostic features and high disease activity. Anti-TNF- $\alpha$  is also recommended for patients who fail MTX and have moderate or high disease activity<sup>11,12</sup>. So, if a physician follows published guidelines, only rarely does a patient receive anti-TNF- $\alpha$  without concomitant DMARD. On the presumption that the current study reflects “real-world practice,” we may (or may not) be surprised that results differ from the guidelines. Ignoring

patients with ERA and psoriatic arthritis (because treatment guidelines may differ for when to use an anti-TNF- $\alpha$ ), 52% (150 of 290 individuals) with JIA received new anti-TNF- $\alpha$  therapy without MTX either concurrently or within the prior 6 months. Although it is possible that MTX was given and stopped more than 6 months before anti-TNF- $\alpha$  initiation, it is more likely that anti-TNF- $\alpha$  therapy is being prescribed frequently as first-line therapy without concurrent DMARD or DMARD failure.

Is this similar to the “real-world practice” of RA? In fact, a recent study of over 1500 patients from 57 rheumatology practices in northern California showed similar but less dramatic trends. Half of all patients receiving DMARD were prescribed biologics in recent years although only 9.5% of patients seen in 2009 received a biologic without concomitant DMARD therapy<sup>13</sup>.

As a pediatric rheumatologist, I believe that a patient with JIA requires early and aggressive treatment to attain and sustain remission, but it is not yet clear what this remission-inducing regimen should be, and how it should differ by JIA phenotype and course. The only clinical trial to date that has examined this question is the Trial of Early Aggressive Therapy in Polyarticular JIA (TREAT), which compared anti-TNF- $\alpha$  plus MTX plus prednisone to MTX alone in early disease. TREAT failed to demonstrate a difference in its primary outcome of clinical inactive disease at 6 months, but did confirm that MTX alone was efficacious. Perhaps more important was that, for all patients, the earlier in the disease course that treatment was started, the better the chance of disease control<sup>14</sup>.

Mannion’s study confirms that US prescribing trends have changed over the last decade for the treatment of JIA. Although we do not know what proportion of children are being cared for by pediatric rheumatologists, physicians who are seeing patients with JIA are prescribing more anti-TNF- $\alpha$  agents, and earlier, and perhaps without concomitant DMARD. We need a cost-benefit analysis of this early and increased anti-TNF- $\alpha$  use, comparing short and longterm disease outcomes between patients who receive very early anti-TNF- $\alpha$  to those who were deferred an extra 3 to 6 months in consideration of the consensus treatment guidelines. Perhaps a comparison between patients in Canada and the United States would provide the data for this analysis, because Canadian payors almost universally require DMARD failure prior to biologic coverage. Food for thought.

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