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Biologic Switching Among Nonsystemic Juvenile Idiopathic Arthritis Patients: A Cohort Study in the Childhood Arthritis and Rheumatology Research Alliance Registry

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ABSTRACT. ***Objective.*** Biologic medications have significantly improved disease control and outcomes of patients with juvenile idiopathic arthritis (JIA). Current treatment recommendations suggest escalating therapy, including changing biologics if needed, when inactive or low disease activity is not attained. The patterns and reasons for switching biologics in clinical practice in North America are not well described.

Methods. We used the Childhood Arthritis and Rheumatology Research Alliance Registry and included individuals with JIA if they newly started a biologic after January 1, 2008, and had at least 12 months of subsequent observable time. Subjects with systemic JIA were excluded. We compared characteristics of switchers and nonswitchers using chi-square for categorical variables and Wilcoxon rank-sum test for continuous variables, and used linear regression for time analysis.

Results. Of the eligible children, 1361 with JIA in the registry started a biologic (94% tumor necrosis factor inhibitors [TNFi]). Median followup time was 30 months and 349 (26%) switched biologics. Among biologic switchers, ineffectiveness/disease flare was the most common reason for switch (202, 58%). The most common documented switch was from etanercept to another TNFi (221, 63%). The median time to switch to a second biologic decreased substantially from 55.2 months in 2008 to 7.2 months in 2016.

Conclusion. In a multicenter cohort of patients with JIA starting a biologic, one-quarter switched to a second biologic, and the time to switching decreased in recent years. Additional studies should evaluate the outcomes and optimal timing of switching and preferred sequence of biologic use.

Key Indexing Terms: biologic therapy, DMARDS (biologic), juvenile idiopathic arthritis, rheumatology

Juvenile idiopathic arthritis (JIA) represents heterogeneous inflammatory arthritides that present in childhood and are associated with joint pain, joint damage, uveitis, functional impairment, and decreased health-related quality of life.[1] Treatment advances and the availability of newer medications, such as biologics, have allowed a significant proportion of patients to achieve disease remission.[2]

The initial tumor necrosis factor inhibitor (TNFi) biologic agents for rheumatoid arthritis (RA) were followed by a proliferation of multiple classes of biologics approved for various forms of inflammatory arthritis. There has been US Food and Drug Administration (FDA) approval for over 11 biologic and new small molecule agents with at least 7 different mechanisms of action for adults with inflammatory arthritis in the last 20 years.[3,4] Current guidelines for the treatment of adults with RA recommend a treat-to-target approach, including switching of biologics for ongoing moderate or high disease activity[5] to achieve the goal of remission, or at least low disease activity. Current JIA treatment recommendations similarly suggest switching biologic agents in cases of continued moderate to high disease activity, but there are no formal recommendations for

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sequence of biologic use or pattern of switching.[6,7,8] It is unclear if patients who do not sufficiently respond to the first biologic should be switched to a biologic with a different mechanism of action and this may depend on whether the nonresponse was primary failure (inefficacy) or secondary (loss of efficacy).[9,10]

Approximately 25% of patients with RA discontinue their first biologic agent within 1 year for ineffectiveness or adverse events (AEs).[11] In JIA cohorts from the Netherlands and Finland, 83–84% of patients used the first biologic (etanercept [ETN] or infliximab [IFX]) for ≥ 12 months; most patients switched therapy for ineffectiveness or toxicity.[12,13] In the Dutch cohort, only 17% of patients achieved inactive disease within 15 months after switching biologics.[13] A study utilizing US administrative claims from young adults (< 24 yrs old) with JIA or RA reported switching from an initial TNFi to a second TNFi in 6.9–28.6%.[14] However, studies using administrative claims data are unable to elicit reasons for biologic switching. Lack or loss of efficacy may lead to immediate switching in order to control disease activity more quickly. Patients may also have a long delay from the discontinuation of a biologic to the start of a new biologic, a remote switch that could be related to nonmedical reasons or flare of disease after discontinuation for inactive disease.[15]

Since 2015, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry has prospectively enrolled over 10,000 children with rheumatic disease in the United States and Canada, over 85% of whom have JIA.[16] The registry captures detailed medication use and clinical status data to provide a unique and well-suited resource to answer questions about medication usage and switching patterns.

The current data on prescribing patterns in North America related to switching biologics and the reasons for switching in JIA are unknown. The objective of this study was to describe the timing, frequency, and reasons for biologic switching among patients with nonsystemic JIA in a large North American registry.

METHODS

We used CARRA Registry data from > 65 pediatric rheumatology clinics in the US and Canada.[16] Participants are enrolled at active CARRA Registry sites if they meet enrollment criteria, and participation is voluntary for patients and clinicians. Registry sites are compensated after completion of data entry to minimize the frequency of missing data, although "unknown" and "not done" are allowable entries. The data coordinating center manages the data for completeness and accuracy. Data about medication use are collected retrospectively at registry enrollment and prospectively thereafter. After enrollment, data regarding medication use, disease activity, and AEs are collected approximately every 6 months in conjunction with routine clinic visits.

For this study, individuals with JIA and no prior biologic use were included if they newly started a first biologic (index date) from January 1, 2008, and June 30, 2017, and had a minimum of 12 months of subsequent observable time in the registry (including the retrospectively collected medication use data). All available medication data were analyzed through the most recent registry visit prior to June 30, 2018. We restricted our analysis to years when > 1 biologic drug was FDA-approved for JIA: ETN was FDA-approved for polyarticular JIA in 1999, adalimumab (ADA) and abatacept (ABA) were approved in 2008, and tocilizumab (TCZ) in 2013.[17] Measures of disease activity were only available with prospective data collected after 2015 so they were not included in this analysis of biologic switching. We excluded individuals who had systemic JIA, a primary non-JIA rheumatic disease diagnosis, concomitant use of ≥ 2 biologics, or unknown month for biologic initiation.

Subjects were considered switchers if they had ≥ 1 different biologic recorded after the index date; nonswitchers had no recorded exposure to a subsequent biologic. Subjects were considered immediate switchers if they started a second biologic within 6 months after stopping the first biologic; remote switchers started a second biologic > 6 months after stopping the first biologic. We chose a 6-month cutoff for immediate switchers because most patients with JIA are evaluated every 3–4 months and we wanted to allow sufficient time to account for clinical visits, treatment discussions between families and providers, and delays related to insurance approvals.

We used descriptive statistics to compare characteristics of groups based on timing, pattern, and reasons for switching. The characteristics reported at the time of the first biologic were age, sex, race, JIA subtype, presence of uveitis, diagnosis of inflammatory bowel disease (IBD), time from diagnosis to the first biologic, use of cDMARD, and the specific first biologic. Any use of methotrexate (MTX) prior to the first biologic was considered an exposure and frequencies of subcutaneous (SC) and oral MTX were not reported. The biologics that were included in analysis were ETN, ADA, IFX, golimumab (GOL), certolizumab pegol (CZP), TCZ, ABA, anakinra, canakinumab, rilonacept, rituximab, belimumab, ustekinumab, and secukinumab. We included all possible biologics in case of JIA classification change during the observable time. Biologics were grouped as ETN, monoclonal antibody TNFi (ADA, IFX, GOL, CZP), and non-TNFi. Subjects were sorted by reason for discontinuation of the first biologic into 6 categories: ineffectiveness/disease flare, AE, infusion/injection reaction, mild AE/intolerance other than infusion/injection reaction, other, or unknown. Reasons for discontinuation were included in the medication log as determined by each site or provider from a prepopulated list of options in addition to a free text option. The characteristics and pattern of switching between those who stopped for ineffectiveness/disease flare and all other reasons were compared by chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables. We assessed the relationship between calendar year of biologic initiation and time to initiation of a second biologic by linear regression. The time to switch was calculated from the start of the first biologic to the start of the second biologic. We used SAS version 9.4 (SAS Institute) for analysis and considered a P value < 0.05 as significant. The University of Alabama at Birmingham Institutional Review Board approved this analysis (protocol IRB-170112004). Subjects provided informed, written consent for participation in research activity including publication upon enrollment into the CARRA Registry.

RESULTS

There were 1361 children with nonsystemic JIA in the CARRA Registry who started a first biologic in the study period. The median observable time for these children was 30.4 months (IQR 20.2–54.3). Overall, the cohort of new biologic initiators were predominantly female (74%), White (82%), and had polyarticular disease (rheumatoid factor [RF]-positive polyarthritis, RF-negative polyarthritis, and extended oligoarthritis, 64%). At the time of biologic start, the median age was 10 years (IQR 6–13), the median calendar year was 2014 (IQR 2013–2016), and the median time from diagnosis to starting a biologic was approximately 7 months (216 days, IQR 2–37 months). On the index date, almost three-quarters of the subjects were receiving or had received MTX (1003, 74%) and almost all patients started a TNFi (1276, 94%) for their first biologic, primarily ETN (871, 64%). Use of leflunomide (27, 2%) or sulfasalazine (66,

5%) prior to first biologic use was uncommon among biologic initiators.

A total of 349 (26%) individuals switched to a second biologic (Table 1), of whom 261 (75%) switched within 6 months of stopping the first biologic (immediate switchers) and 88 (25%) switched after 6 months (remote switchers). Immediate switchers were more likely to have enthesitis-related arthritis (ERA; 18%) or psoriatic arthritis (PsA; 12%) compared to remote switchers (9% and 10%, respectively). The remote switchers were younger (median age 8 yrs compared to 11 yrs, $P = 0.001$), more likely to be female (88% compared to 76%, $P = 0.009$), more likely to have polyarticular disease of any type (RF-positive 15%, RF-negative 49%, and extended oligoarticular 13% compared to 12%, 43%, and 7%, respectively), and more likely to have used MTX prior to the start of their first biologic (88% compared to 76%, $P = 0.004$) compared to immediate switchers. In terms of comorbidities reported at the time of enrollment into the registry, IBD and uveitis were more common in the remote switcher group (6% and 11%, respectively) compared to the immediate switchers (2% and 8%, respectively), although the absolute numbers were small and statistically nonsignificant.

Time to second biologic. The number of biologic starts per calendar year increased over time. In later years, the proportion of switchers, particularly remote switchers, decreased (Figure 1). The proportion of immediate switchers remained largely stable over time, ranging from 14% (in 2013) to 33% (in 2008). Among switchers, the time from first biologic initiation to second biologic initiation decreased by calendar year ($P < 0.001$).

Reason for switch. Among immediate switchers, the most common reason for discontinuation of the first biologic was ineffectiveness/disease flare (67%; Table 2). Remote switchers were more likely to have discontinued the first biologic for other reasons (56%), most commonly well-controlled disease or planned dose change. After stratification of the groups by immediate or remote switching, we observed few significant demographic or clinical differences between those who switched for ineffectiveness/disease flare and those who switched for other reasons (Table 1). MTX use was more frequent among those who switched for ineffectiveness (80%) compared to those that switched for other reasons (77%) or nonswitchers (72%, $P = 0.03$). Immediate switchers who discontinued the first biologic for ineffectiveness/disease flare compared to all other reasons were more likely to be older (11 yrs, IQR 8–14 vs 9 yrs, IQR 6–13), less likely to have uveitis at the start of the first biologic (5% and 15%, respectively), and more likely to use SC MTX prior to the first biologic (54% and 41%, respectively). Among immediate switchers, the proportions of individuals switching for ineffectiveness/disease flare and all other reasons was similar between those initially started on ETN or ADA ($P = 0.6$). Among the remote switchers, we observed no demographic differences between those who switched for ineffectiveness/disease flare and all other reasons. However, among these remote switchers, the proportion of individuals discontinuing the first biologic for ineffectiveness/disease flare and all other reasons was different between those initially started on ETN (29% and 71%, respectively) or ADA (58% and 42%, respectively, chi-square $P = 0.045$).

Type of biologic switch. While all groups were most likely to start a TNFi as the first biologic, subjects who started ETN were more likely to be immediate switchers (22%) or remote switchers (7%) than nonswitchers (71%) compared to those that started ADA (immediate switchers 15%, remote switchers 4%, nonswitchers 82%, $P = 0.0005$). When analyzed by former (2008–2012; ETN: immediate switchers 26%, remote switchers 18%, nonswitchers 56% and ADA: immediate switchers 27%, remote switchers 7%, nonswitchers 66%, $P = 0.2$) or latter (2013–2018; ETN: immediate switchers 21%, remote switchers 4%, nonswitchers 75% and ADA: immediate switchers 13%, remote switchers 3%, nonswitchers 84%, $P = 0.009$) study periods, these patterns remained, although the differences were only statistically significant in the latter half of the study period. The initial use of all other biologics was not significantly different between groups and was overall infrequent.

The most common type of switch, regardless of the reason, was ETN to a monoclonal TNFi (63%; Figure 2). Among those who started biologics besides ETN, those who switched for ineffectiveness/flare were more likely to switch to other non-ETN biologics (81%); those who switched for other reasons were more likely to switch to ETN (57%).

Second switch. There were 105 individuals who switched from a second to a third biologic. The most common reason for a second switch remained ineffectiveness/disease flare (75%), followed by unknown reason (11%), and mild AE or intolerance of delivery (8%). Among these patients, the most common type of switch was from a monoclonal TNFi to a non-TNFi (51%). There were no differences in patient characteristics between those who switched for ineffectiveness/disease flare compared to all other reasons between the second switchers (data not shown).

DISCUSSION

In a multicenter cohort of JIA patients in North America, 26% of new biologic initiators switched to a different biologic over a median 30.4 months of follow-up. This proportion is similar to previously reported data from JIA patients in the US and Europe, and is lower than reported rates of switching in patients with RA.[11,12,13,14,18] The time to switch significantly decreased by calendar year in this cohort, with a median of 55.2 months if the biologic was started in 2008 compared to 7.2 months in 2016, the last full year of data. TNFi were the most common initial biologic, but the subjects who started ETN were more likely to be switchers compared to those who started ADA (29% and 18%, respectively).

The characteristics of immediate switchers were different from remote switchers. Remote switchers were less likely to switch for ineffectiveness or disease flare and more likely to discontinue the first biologic for other reasons such as well-controlled disease, intolerance of administration, injection/infusion reactions, or less commonly, AEs. The remote switchers were younger, were more likely to have polyarticular disease, and had more MTX use at biologic initiation, suggesting the possibility of a more severe disease course, although that was not analyzed in this study. Alternatively, these individuals also started a biologic earlier by calendar year, providing more observational

Table 1. Comparison of characteristics at the time of first biologic initiation within either immediate or remote switching group by reason for discontinuation.

	All Biologic Initiators, N = 1361	All Switchers, n = 349	Immediate Switchers				Remote Switchers			
			All, n = 261	Ineffective/ Disease Flare, n = 175 (67%)	Other, n = 86 (33%)	*P**	All, n = 88	Ineffective/ Disease Flare, n = 27 (31%)	Other, n = 61 (69%)	*P**
Age, yrs, median (IQR)	10 (6–13)	10 (7–13)	11 (8–14)	11 (8–14)	9 (6–13)	0.009	8 (4–12)	7 (4–10)	9 (4–12)	0.22
Female	1012 (74)	274 (79)	197 (76)	133 (76)	64 (74)	0.73	77 (88)	24 (89)	53 (87)	0.79
White	1121 (82)	290 (83)	214 (82)	146 (83)	68 (79)	0.39	76 (86)	24 (89)	52 (85)	0.65
JIA subtype						0.53				0.03
RF+ poly	158 (12)	45 (13)	32 (12)	23 (13)	9 (11)		13 (15)	2 (7)	11 (18)	
RF– poly	594 (44)	156 (45)	113 (43)	74 (42)	39 (45)		43 (49)	10 (37)	33 (54)	
Persistent oligo	159 (12)	18 (5)	17 (7)	14 (8)	3 (4)		1 (1)	1 (4)	0	
Extended oligo	13 (8)	29 (8)	18 (7)	9 (5)	9 (11)		11 (13)	2 (7)	9 (15)	
ERA	180 (13)	56 (16)	48 (18)	34 (19)	14 (16)		8 (9)	5 (19)	3 (5)	
PsA	124 (9)	39 (11)	30 (12)	19 (11)	11 (13)		9 (10)	5 (19)	4 (7)	
Undifferentiated	24 (2)	6 (2)	3 (1)	2 (1)	1 (1)		3 (3)	2 (7)	1 (2)	
Uveitis	97 (7)	32 (9)	22 (8)	9 (5)	13 (15)	0.02	10 (11)	2 (7)	8 (13)	0.44
IBD	33 (2)	10 (3)	5 (2)	3 (2)	2 (2)	0.7	5 (6)	2 (7)	3 (5)	0.64
MTX use (all)	1003 (74)	275 (79)	198 (76)	138 (79)	60 (70)	0.11	77 (88)	24 (89)	53 (87)	0.79
Medication starting						0.77**				0.24**
TNFi (all)	1276 (94)	333 (95)	250 (96)	168 (96)	82 (95)	0.81	83 (94)	27 (100)	56 (92)	0.13
Etanercept	871 (64)	254 (73)	191 (73)	131 (75)	60 (70)		63 (72)	18 (67)	45 (74)	
Adalimumab	332 (24)	61 (18)	49 (19)	32 (18)	17 (20)		12 (14)	7 (26)	5 (8)	
Infliximab	62 (5)	15 (4)	7 (3)	3 (2)	4 (5)		8 (9)	2 (7)	6 (10)	
Golimumab	6 (0.4)	3 (1)	3 (1)	2 (1)	1 (1)		5 (6)	0	5 (8)	
Non-TNFi (all)	85 (6)	16 (5)	11 (4)	7 (4)	4 (5)	0.81	3 (3)	0	3 (5)	0.13
Time from diagnosis to biologic start, months, median (IQR)	7.2 (2.0–37.1)	5.1 (1.4–23.8)	5.0 (1.3–23.8)	4.9 (1.2–19.0)	5.9 (1.6–40.4)	0.33	5.5 (1.8–22.0)	3.5 (0.0–8.7)	6.1 (1.8–25.8)	0.11
Time from start of 1st biologic to start of 2nd biologic, months, median (IQR)	N/A	13.1 (6.4–29.7)	9.6 (5.2–19.8)	8.9 (5.3–17.5)	11.6 (4.9–24.7)	0.38	34.1 (21.1–52.3)	23.8 (15.8–41.5)	40.2 (22.6–54.1)	0.04
Time from discontinuation of 1st biologic to start of 2nd biologic, days, median (IQR)	N/A	8 (0–189)	0 (0–23)	0 (0–14)	7 (0–78)	< 0.001	577 (323–945)	356 (245–717)	678 (394–1037)	0.007

Values are n (%) unless otherwise indicated. * Comparison between ineffectiveness/disease flare and other reasons for discontinuation. ** Comparison between ineffectiveness/disease flare and other reasons for discontinuation for all individual medications. ERA: enthesitis-related arthritis; IBD: inflammatory bowel disease; JIA: juvenile idiopathic arthritis; MTX: methotrexate; oligo: oligoarthritis; PO: oral administration; poly: polyarthritis; PsA: psoriatic arthritis; RF: rheumatoid factor; SC: subcutaneous administration; TNF: tumor necrosis factor inhibitor.

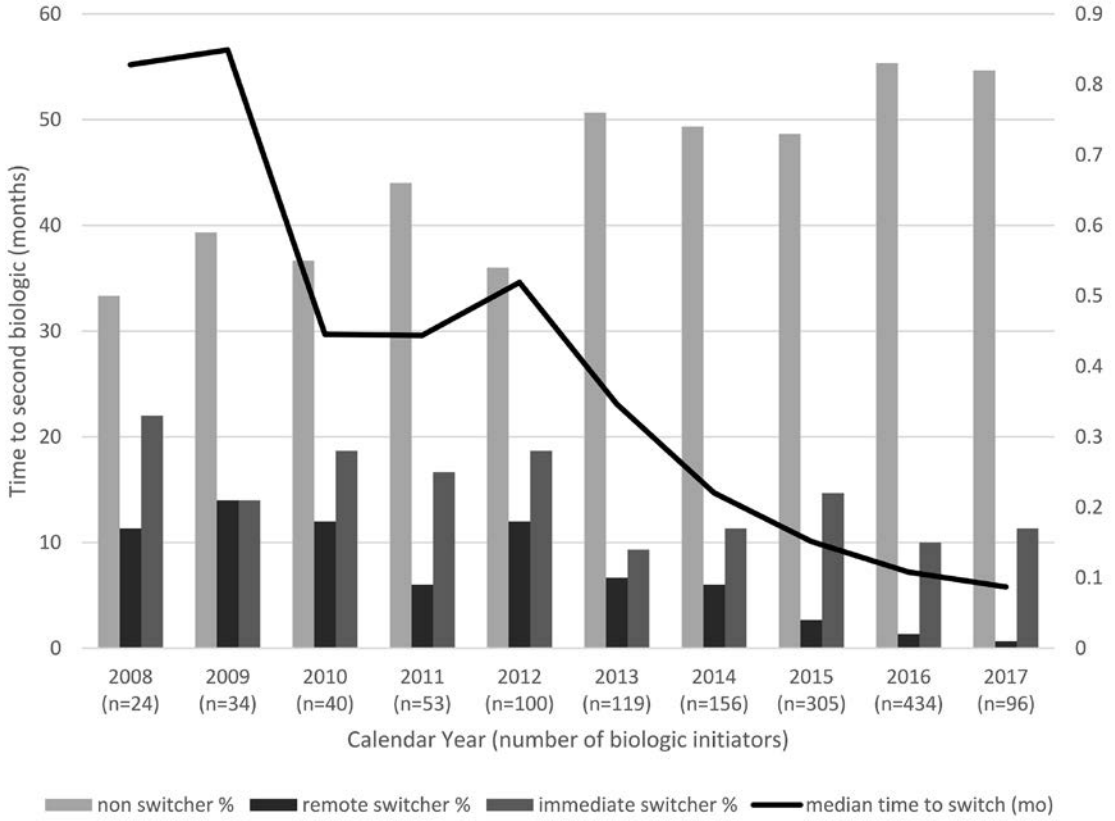

Figure 1. Time to switch (months) and switch category by calendar year of first biologic start. Test for trend of time to switch by index year for all switchers $p < 0.0001$ (F 222.24, index year $\beta = -166.4$, SE 11.2). SE: standard error.

Table 2. Reason for discontinuation of first biologic.

	Immediate Switchers, n = 261	Remote Switchers, n = 88
AE	13 (5)	1 (1)
Ineffective/disease flare	175 (67)	27 (31)
Infusion/injection reaction	6 (2)	1 (1)
Mild AE/intolerance of delivery mode	30 (11)	4 (5)
Other[a]	19 (7)	50 (57)
Unknown	18 (7)	5 (6)

Values are n (%). [a] Other reasons included disease well-controlled, interval patient growth, planned dose change, chronic nonadherence, financial cost, insurance requirement, change in juvenile idiopathic arthritis category. AE: adverse event.

time to observe a remote switch. These patients may have had to switch medications for nonmedical reasons upon restarting biologics for return of disease or following a drug holiday for an AE (e.g., severe infection).

In general, the proportion of immediate switchers by calendar year ranged from 14% to 33%, indicating that the first biologic is effective and tolerated 70–80% of the time. We observed an increase in biologic initiators over time and decreased time to a second biologic that may indicate that patients and providers are less willing to tolerate disease activity or side effects with more experience using biologics and with the availability of medications with different mechanisms of action. This is consistent with the observation that TNFi are prescribed more frequently in more recent years.[14,19] However, we also observed less remote switching over time, which may in part reflect shorter durations of follow-up among more recently enrolled subjects, resulting in an artifact of the time-limited opportunity to become switchers.

Individuals with persistent oligoarticular JIA were less likely to switch biologics during follow up compared to individuals with ERA or PsA. The decreased switching frequency in oligoarticular patients might be expected, given that oligoarticular JIA usually has a milder disease course and good response to medications.[20,21] This increased switching among patients with ERA and PsA may imply that certain biologics are preferred or more effective as first-line treatment compared to others.[22,23]

We restricted inclusion to those individuals who newly started a biologic after 2008 to reduce the limitation of only 1 FDA-approved biologic for JIA prior to that time. While switching medications was possible prior to this time, the FDA approval of ADA and ABA allowed other biologics to be a standard option. However, the use of ABA as a first or second biologic remained much lower than ETN or the monoclonal TNFi in this study; this could be related to ABA's intravenous route of administration (SC administration was only approved in 2017).[24] Individuals who started ETN were more likely to switch compared to those who started ADA in this cohort, similar to a

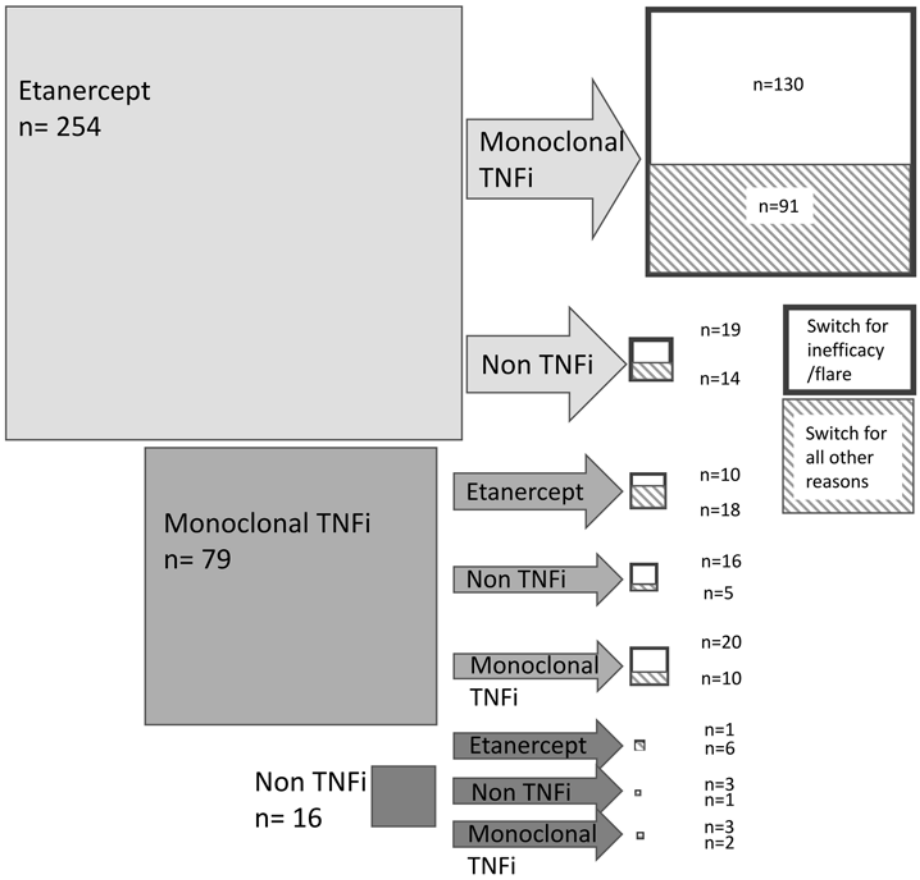

Figure 2. Type of first biologic switch by medication and reason for discontinuation of first biologic. Frequency of medication use for all biologic initiators: etanercept, n = 871 (64%); monoclonal TNFi, n = 405 (30%); non-TNFi, n = 85 (6%). TNFi: tumor necrosis factor inhibitor.

US administrative claims–based analysis from the same period.[14] In the German Biologics in Pediatric Rheumatology (BIKER) Registry, ETN was the most common first biologic (79.9%), but it was an uncommon second biologic (4.1%).[18] Patients in the BIKER Registry discontinued ADA more frequently than ETN or TCZ, and the overall switch rate (51%) was higher than in our cohort (26%).[18] The most common reason for switching among all biologics was inefficacy and while uncommon overall, switching for intolerance was more common for ADA compared to ETN.[18] This could be related to the pain associated with injection of the formulation of ADA prior to the availability of the low-volume/citrate-free formulation.[25]

The CARRA Registry provides a robust data source to evaluate medication use patterns among patients with JIA in North America. The characteristics of all biologic initiators in this cohort is consistent with previously reported epidemiology of JIA, including race, sex, age, and subtype distribution,[1] and the early recruitment of patients with polyarticular disease to the CARRA Registry.[16] The early enrichment of patients with polyarticular disease may have contributed to enrollment bias for more severely affected patients. ETN was the most commonly prescribed biologic in this cohort of patients, limiting our ability to provide a more detailed analysis of any other biologic medication. Future studies will include stratification for disease activity and allow for analytic adjustment of differences in patient characteristics. For this analysis, we included data about medication use prior to enrollment in the registry using the retrospective medication logs. This allowed for more data to evaluate switching patterns among a current cohort of JIA patients, but did restrict our ability to analyze clinical reasons or disease activity responses to switching. We were limited by the lack of clinical data in the retrospective medication logs to better characterize disease activity before and after biologic initiation or switching. Analysis of prospective data with clinical assessments will be included as the registry continues to grow in number of subjects and observable prospective data.

In summary, we have presented an overview of patterns and trends of biologic switching within the CARRA Registry. Within the registry, there was more rapid but less frequent switching in recent years. Understanding these prescribing patterns and reasons for switch can help to inform future studies on the optimal timing and sequence for biologic switching and subsequent clinical outcomes.

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Gotte, B. Gottlieb, C. Gracia, T. Graham, S. Grevich, T. Griffin, J. Griswold, A. Grom, M. Guevara, P. Guittar, M. Guzman, M. Hager, T. Hahn, O. Halyabar, E. Hammelev, M. Hance, A. Hanson, L. Harel, S. Haro, J. Harris, O. Harry, E. Hartigan, J. Hausmann, A. Hay, K. Hayward, J. Heiart, K. Hekl, L. Henderson, M. Henrickson, A. Hersh, K. Hickey, P. Hill, S. Hillyer, L. Hiraki, M. Hiskey, P. Hobday, C. Hoffart, M. Holland, M. Hollander, S. Hong, M. Horwitz, J. Hsu, A. Huber, J. Huggins, J. Hui-Yuen, C. Hung, J. Huntington, A. Huttenlocher, M. Ibarra, L. Imundo, C. Inman, A. Insalaco, A. Jackson, S. Jackson, K. James, G. Janow, J. Jaquith, S. Jared, N. Johnson, J. Jones, J. Jones, J. Jones, K. Jones, S. Jones, S. Joshi, L. Jung, C. Justice, A. Justiniano, N. Karan, K. Kaufman, A. Kemp, E. Kessler, U. Khalsa, B. Kienzle, S. Kim, Y. Kimura, D. Kingsbury, M. Kitcharoensakkul, T. Klausmeier, K. Klein, M. Klein-Gitelman, B. Kompelien, A. Kosikowski, L. Kovalick, J. Kracker, S. Kramer, C. Kremer, J. Lai, J. Lam, B. Lang, S. Lapidus, B. Lapin, A. Lasky, D. Latham, E. Lawson, R. Laxer, P. Lee, P. Lee, T. Lee, L. Lentini, M. Lerman, D. Levy, S. Li, S. Lieberman, L. Lim, C. Lin, N. Ling, M. Lingis, M. Lo, D. Lovell, D. Lowman, N. Luca, S. Lvovich, C. Madison, J. Madison, S. Magni Manzoni, B. Malla, J. Maller, M. Malloy, M. Mannion, C. Manos, L.. Marques, A. Martyniuk, T. Mason, S. Mathus, L. McAllister, K. McCarthy, K. McConnell, E. McCormick, D. McCurdy, P. McCurdy Stokes, S. McGuire, I. McHale, A. McMonagle, C. McMullen-Jackson, E. Meidan, E. Mellins, E. Mendoza, R. Mercado, A. Merritt, L. Michalowski, P. Miettunen, M. Miller, D. Milojevic, E. Mirizio, E. Misajon, M. Mitchell, R. Modica, S. Mohan, K. Moore, L. Moorthy, S. Morgan, E. Morgan Dewitt, C. Moss, T. Moussa, V. Mruk, A. Murphy, E. Muscal, R. Nadler, B. Nahal, K. Nanda, N. Nasah, L. Nassi, S. Nativ, M. Natter, J. Neely, B. Nelson, L. Newhall, L. Ng, J. Nicholas, R. Nicolai, P. Nigrovic, J. Nocton, B. Nolan, E. Oberle, B. Obispo, B. O'Brien, T. O'Brien, O. Okeke, M. Oliver, J. Olson, K. O'Neil, K. Onel, A. Orandi, M. Orlando, S. Osei-Onomah, R. Oz, E. Pagano, A. Paller, N. Pan, S. Panupattanapong, M. Pardeo, J. Paredes, A. Parsons, J. Patel, K. Pentakota, P. Pepmueller, T. Pfeiffer, K. Phillippi, D. Pires Marafon, K. Phillippi, L. Ponder, R. Pooni, S. Prahalad, S. Pratt, S. Protopapas, B. Puplava, J. Quach, M. Quinlan-Waters, C. Rabinovich, S. Radhakrishna, J. Rafko, J. Raisian, A. Rakestraw, C. Ramirez, E. Ramsay, S. Ramsey, R. Randell, A. Reed, A. Reed, A. Reed, H. Reid, K. Remmel, A. Repp, A. Reyes, A. Richmond, M. Riebschleger, S. Ringold, M. Riordan, M. Riskalla, M. Ritter, R. Rivas-Chacon, A. Robinson, E. Rodela, M. Rodriquez, K. Rojas, T. Ronis, M. Rosenkranz, B. Rosolowski, H. Rothermel, D. Rothman, E. Roth-Wojcicki, K. Rouster – Stevens, T. Rubinstein, N. Ruth, N. Saad, S. Sabbagh, E. Sacco, R. Sadun, C. Sandborg, A. Sanni, L. Santiago, A. Sarkissian, S. Savani, L. Scalzi, L. Schanberg, S. Scharnhorst, K. Schikler, A. Schlefman, H. Schmeling, K. Schmidt, E. Schmitt, R. Schneider, K. Schollaert-Fitch, G. Schulert, T. Seay, C. Seper, J. Shalen, R. Sheets, A. Shelly, S. Shenoi, K. Shergill, J. Shirley, M. Shishov, C. Shivers, E. Silverman, N. Singer, V. Sivaraman, J. Sletten, A. Smith, C. Smith, J. Smith, J. Smith, E. Smitherman, J. Soep, M. Son, S. Spence, L. Spiegel, J. Spitznagle, R. Sran, H. Srinivasalu, H. Stapp, K. Steigerwald, Y. Sterba Rakovchik, S. Stern, A. Stevens, B. Stevens, R. Stevenson, K. Stewart, C. Stingl, J. Stokes, M. Stoll, E. Stringer, S. Sule, J. Sumner, R. Sundel, M. Sutter, R. Syed, G. Syverson, A. Szymanski, S. Taber, R. Tal, A. Tambralli, A. Taneja, T. Tanner, S. Tapani, G. Tarshish, S. Tarvin, L. Tate, A. Taxter, J. Taylor, M. Terry, M. Tesher, A. Thatayatikom, B. Thomas, K. Tiffany, T. Ting, A. Tipp, D. Toib, K. Torok, C. Toruner, H. Tory, M. Toth, S. Tse, V. Tubwell, M. Twilt, S. Uriguen, T. Valcarcel, H. Van Mater, L. Vannoy, C. Varghese, N. Vasquez, K. Vazzana, R. Vehe, K. Veiga, J. Velez, J. Verbsky, G. Vilar, N. Volpe, E. von Scheven, S. Vora, J. Wagner, L. Wagner-Weiner, D. Wahezi, H. Waite, J. Walker, H. Walters, T. Wampler Muskardin, L. Waqar, M. Waterfield, M. Watson, A. Watts, P. Weiser, J. Weiss, P. Weiss, E. Wershba, A. White, C. Williams, A. Wise, J. Woo, L. Woolnough, T. Wright, E. Wu, A. Yalcindag, M. Yee, E. Yen, R. Yeung, K. Yomogida, Q. Yu, R. Zapata, A. Zartoshti, A. Zeft, R. Zeft, Y. Zhang, Y. Zhao, A. Zhu, C. Zic.

REFERENCES

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369:767-78.
2. Shoop-Worrall SJW, Kearsley-Fleet L, Thomson W, Verstappen SMM, Hyrich KL. How common is remission in juvenile idiopathic arthritis: a systematic review. Semin Arthritis Rheum 2017; 47:331-7.
3. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. JAMA 2018;320:1360-72.
4. U.S. Food & Drug Administration. FDA drug safety communication: update on tumor necrosis (TNF) blockers and risk for pediatric malignancy. [Internet. Accessed March 22, 2021.] Available from: www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-update-tumor-necrosis-factor-tnf-blockers-and-risk-pediatric
5. Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2016;68:1-26.
6. 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 2011;63:465-82.
7. Ravelli A, Consolaro A, Horneff G, Laxer RM, Lovell DJ, Wulffraat NM, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis 2018;77:819-28.
8. Ringold S, Angeles-Han ST, Beukelman T, Lovell D, Cuello CA, Becker ML, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for non-systemic polyarthritis, sacroiliitis, and enthesitis. Arthritis Rheumatol 2019;71:717-34.
9. Brown S, Everett CC, Naraghi K, Davies C, Dawkins B, Hulme C, et al. Alternative tumour necrosis factor inhibitors (TNFi) or abatacept or rituximab following failure of initial TNFi in

rheumatoid arthritis: the switch RCT. Health Technol Assess 2018;22:1-280.
10. Rubbert-Roth A, Szabó MZ, Kedves M, Nagy G, Atzeni F, Sarzi-Puttini P. Failure of anti-TNF treatment in patients with rheumatoid arthritis: the pros and cons of the early use of alternative biological agents. Autoimmun Rev 2019;18:102398.
11. Souto A, Maneiro JR, Gómez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology 2016;55:523-34.
12. Tynjälä P, Vähäsalo P, Honkanen V, Lahdenne P. Drug survival of the first and second course of anti-tumour necrosis factor agents in juvenile idiopathic arthritis. Ann Rheum Dis 2009;68:552-7.
13. Otten MH, Prince FH, Anink J, Ten Cate R, Hoppenreijs EP, Armbrust W, et al. Effectiveness and safety of a second and third biological agent after failing etanercept in juvenile idiopathic arthritis: results from the Dutch National ABC Register. Ann Rheum Dis 2013;72:721-7.
14. Lee WJ, Briars L, Lee TA, Calip GS, Suda KJ, Schumock GT. Use of tumor necrosis factor-alpha inhibitors in children and young adults with juvenile idiopathic arthritis or rheumatoid arthritis. Pharmacotherapy 2016;36:1201-9.
15. Teeple A, Ginsburg S, Howard L, Huff L, Reynolds C, Walls D, et al. Patient attitudes about non-medical switching to biosimilars: results from an online patient survey in the United States. Curr Med Res Opin 2019;35:603-9.
16. Beukelman T, Kimura Y, Ilowite NT, Mieszkalski K, Natter MD, Burrell G, et al. The new Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry: design, rationale, and characteristics of patients enrolled in the first 12 months. Pediatr Rheumatol Online J 2017;15:30.
17. U.S. Food & Drug Administration. Juvenile arthritis: discoveries lead to newer treatments. 2016. [Internet. Accessed March 22, 2021.] Available from: www.fda.gov/consumers/consumer-updates/juvenile-arthritis-discoveries-lead-newer-treatments
18. Horneff G, Klein A, Klotsche J, Minden K, Huppertz HI, Weller-Heinemann F, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther 2016;18:272.
19. Mannion ML, Xie F, Curtis JR, Beukelman T. Recent trends in medication usage for the treatment of juvenile idiopathic arthritis and the influence of tumor necrosis factor inhibitors. J Rheumatol 2014;41:2078-84.
20. Selvaag AM, Aulie HA, Lilleby V, Flatø B. Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis. Ann Rheum Dis 2016;75:190-5.
21. Minden K, Niewerth M, Listing J, Biedermann T, Bollow M, Schöntube M, et al. Long-term outcome in patients with juvenile idiopathic arthritis. Arthritis Rheum 2002;46:2392-401.
22. Donnithorne KJ, Cron RQ, Beukelman T. Attainment of inactive disease status following initiation of TNF-α inhibitor therapy for juvenile idiopathic arthritis: enthesitis-related arthritis predicts persistent active disease. J Rheumatol 2011;38:2675-81.
23. Otten MH, Prince FH, Ten Cate R, van Rossum MA, Twilt M, Hoppenreijs EP, et al. Tumour necrosis factor (TNF)-blocking agents in juvenile psoriatic arthritis: are they effective? Ann Rheum Dis 2011;70:337-40.
24. U.S. Food & Drug Administration. New pediatric labeling information database - detail. Abatacept. 2017. [Internet. Accessed March 22, 2021.] Available from: www.accessdata.fda.gov/scripts/sda/sdDetailNavigation.cfm?sd=labelingdatabase&id=4E2CE16326746993E-053564DA8C0FC5A&rownum=4
25. Gely C, Marin L, Gordillo J, Mañosa M, Bertoletti F, Cañete F, et al. Impact of pain associated with the subcutaneous administration of adalimumab. Gastroenterol Hepatol 2020;43:9-13.