Impact of approval of biologic disease modifying anti-rheumatic drugs on juvenile idiopathic arthritis outcomes

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A thesis

submitted in partial fulfillment of the

requirements for the degree of

Master of Public Health

University of Washington

2021

Committee:

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Program Authorized to Offer Degree:

Epidemiology

University of Washington

Abstract

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Introduction: Juvenile idiopathic arthritis (JIA) affects nearly 300,000 US children, causing pain and physical disability. In clinical trials, biologic disease modifying antirheumatic drugs (bDMARDs) have been shown to decrease disease activity. We examined the effects of increased use of bDMARDs in real-world settings.

Methods: We conducted a retrospective cohort study to assess outcomes in two cohorts of children diagnosed with JIA at Seattle Children's Hospital (SCH). The exposure of interest was time period of JIA diagnosis representing pre- and post-bDMARD availability, with the earlier cohort consisting of all children diagnosed 1998-2000 (N=194) and the later cohort consisting of all children diagnosed 2015-2017 (N=240). Electronic medical records and chart review were used to assess dates of diagnosis and outcomes of achieving inactive disease, disease flare occurrence, and hospitalization for infection. Poisson regression was used to estimate relative risks (RRs) and 95% confidence intervals (CIs) for these outcomes among children in the more recent cohort relative to the early cohort, adjusted for age at diagnosis, JIA category, and receipt of any intraarticular glucocorticoid injection. Children were followed

up for up to three years. The mean days to inactive disease and time in inactive disease were also assessed and compared using t-tests.

Results: Among children with three full years of follow up, the mean numbers of days to inactive disease were 237 days (sd 233) in the later cohort vs. 306 days (sd 239) in early cohort (p=0.02). The mean numbers of days in inactive disease for those in the later and early cohorts were 652 days (sd 306) and 621 days (sd 281, p=0.39), respectively. RR for achievement of inactive disease status in the late vs. early cohort was RR 1.01 (95%CI: 0.94-1.07). Among children who had achieved inactive disease status, the RR for flare occurrence was 1.21 (95% CI: 0.99-1.50). These results did not vary greatly by sex or race/ethnicity, but the risk of flare occurrence was slightly greater among children with oligoarticular-persistent JIA (RR 1.37, 95% CI: 0.86-1.97). Hospitalization for infection was not assessed due to low numbers.

Conclusion: With the exception of fewer days until inactive disease and a suggestion of increased time in inactive disease in the later cohort when bDMARDS were more in use, we did not observe strong evidence of differences in these disease outcomes between the cohorts in which these drugs were more and less available. Further studies to examine time to inactive disease, time to disease flare after inactive disease is achieved, and time in inactive disease is warranted to better understand the impact of the approval of bDMARDs on JIA outcomes outside of clinical trials.

Introduction

Juvenile idiopathic arthritis (JIA) as defined by the International League of Associations for Rheumatology (ILAR) is a heterogeneous group of chronic arthritides diagnosed in children < 16 years of age without known cause.[1] The annual incidence rate for 1996-2009 was ~12/100,000 children in the United States[2] with a current prevalence of ~ 300,000 children. [3] Little is known about etiology, but it is likely multifactorial, involving genetic and environmental factors.

Although JIA is rarely fatal, affected children may experience a wide range of debilities, including joint pain/stiffness resulting in reduced mobility, growth issues, and vision problems.[3,4] Biologic disease modifying anti-rheumatic drugs (bDMARDs) first approved in 1998 to treat adult arthritis have potential to help affected children improve mobility and decrease pain,[5,6] but with possible serious side-effects, including increased risk of serious infection, drug-induced lupus or psoriasis, and malignancies.[5,6,7]

Until 1999, available options for treatment of JIA were limited to non-steroidal anti-inflammatory medications (NSAIDs), conventional disease-modifying antirheumatic drugs (cDMARDs) and glucocorticoids. By the end of 2008, three bDMARDs had been approved by the U.S. Food and Drug Administration (FDA) for JIA (Supplemental Table 1).[8] In contrast to cDMARDs, which are typically small molecules with known chemical structure, bDMARDs are large, complex molecules derived from human or animal sources.[6] The advent of targeted therapy with bDMARDs has altered the range of JIA treatments available. Although there is no cure, the goal of treatment is inactive disease with eventual remission off medications.[9] Although bDMARDs have been shown to be efficacious for JIA treatment in clinical trials, less is known about the overall effects of increasing use of bDMARDs on JIA outcomes in real-world settings outside of clinical trials.

We investigated the general hypothesis that there were improved outcomes among children diagnosed with JIA in the time period after bDMARDs became an approved treatment compared to

outcomes among children diagnosed prior to their use in a real-world setting. Improvement was assessed as time to inactive disease status, and number of disease flares within 2 or 3 years of diagnosis. These medications suppress immune function, so we also hypothesized that children diagnosed more recently were more likely to be hospitalized for infection.

Methods

We conducted a single center (Seattle Children's Hospital - SCH) retrospective cohort study to assess outcomes identified during the three years post-diagnosis among children diagnosed during two different time periods of diagnosis generally representing periods that were pre- and post-biologic medication use/marketing. SCH is the major children's hospital in the region, drawing patients from Washington State, Idaho, and Alaska, and until recently, the sole institution with board-certified pediatric rheumatologists.

Data source

Institutional Review Board approvals were granted by SCH and the University of Washington. We accessed patient data from the SCH Pediatric Rheumatology Clinic. All patients <16 years of age diagnosed with JIA from 1995-2020 were identified from the electronic patient database using International Classification of Disease (ICD) -9 and ICD-10 codes indicating JIA diagnosis (ICD-9: 696.0, 714.3, 714.30-33, 720.0, 720.89; ICD-10: M08.0, M08.1, M08.2, M08.3, M08.4, M08.8, M08.9, L40.54, L40.59). Inclusion criteria were any JIA diagnosis and followed by the rheumatology clinic at SCH from two cohorts: 1) those diagnosed 1998-2000 with minimal opportunity for treatment with bDMARDs, and 2) those diagnosed 2015-2017 after multiple bDMARDs were approved for treatment for JIA.

Exposure

Our exposure of interest was the time period during which JIA diagnosis occurred. Dates of first visit and JIA diagnosis were confirmed through chart review, and those who were diagnosed January 1, 1998 – December 31, 2000 (N=194) and January 1, 2015 – December 31, 2017 (N=240) were included in this study.

Outcomes

Active or inactive disease status was assessed at each visit during the follow up period of 3 years post diagnosis. Inactive disease was defined as presence of either of the following: a) Physician Global Assessment (PGA) of Disease 0 (0-10 Likert scale),[10] b) documentation of quiet disease, no active joints, quiescent disease, no evidence of active arthritis, inactive, remission. Outcomes that were assessed were 1) inactive disease status (ever/never); 2) disease flare after inactive disease was achieved (ever/never); 3) time (days) to inactive disease; and (4) time (days) in inactive disease. The date of the first clinic visit at which inactive disease was noted was used as the event date for the outcome of time to inactive disease. For time in inactive disease, time accrued from the date inactive disease was noted in the chart and stopped at the next date when active disease was noted. All dates were noted. Time in inactive disease was summed to create a total time in inactive disease (days) for each subject during the 3 years of follow up post diagnosis.

We also measured infection-related hospitalizations; however too few children were hospitalized for infection during the three years to support analyses.

Data collection

Based on relevant ICD-9 and ICD-10 codes, we identified for each cohort: date of first rheumatology appointment, which we used as an the "diagnosis" date; dates of hospital admissions/discharges with discharge diagnosis codes; and demographic information, including date of birth, sex assigned at birth, caregiver- or self-reported race/ethnicity, and zip code of residence. Because

of small numbers, race/ethnicity categories used in analyses were Non-Hispanic White/Other, and White/Nonwhite. Any data that was not available electronically was abstracted through chart review. Date of first rheumatology appointment was confirmed through chart review for both time periods. Other information obtained through chart review for both cohorts were disease status at each rheumatology clinic visit, JIA category, and medications prescribed to treat JIA.

Data analysis

Analyses were conducted using Stata version 14.[11] The demographic and disease characteristics were described for each cohort. Relative risks (RR) and 95% confidence intervals (CI) for the outcomes of active/inactive disease and disease flare (ever/never) were initially estimated using Mantel-Haenszel stratified analysis and subsequently by multivariable Poisson regression with robust standard errors to account for common outcomes. Analyses were conducted for children with a full 3 years of follow up, and repeated for the larger group of children with 2 full years of follow up. Results were stratified by sex, race/ethnicity, and JIA category, categorized as: a) polycourse disease, which includes polyarticular arthritis, extended oligoarthritis, psoriatic arthritis, and enthesitis related arthritis; b) persistent oligoarthritis; and c) systemic arthritis.

Mean days to inactive disease and mean days in inactive disease for those with at least 2 full years of follow up, and for those with 3 full years of follow up were calculated and compared using t-tests.

For estimation of RRs, child's age at diagnosis was included *a priori* in all models. Other potential confounders assessed were sex, occurrence of one or more intraarticular glucocorticoid injections (yes/no), and JIA course (polycourse, persistent oligoarthritis, and systemic). RRs are presented adjusted only for age at diagnosis, and also adjusted for age at diagnosis, JIA course, and whether intraarticular glucocorticoid injection(s) were received during follow up. Because our exposure (time period of

diagnosis) was used as a proxy for bDMARD exposure, we subsequently reassessed RR estimates after excluding 12 children identified in the first cohort as having received any bDMARDs.

Results

In both cohorts, children diagnosed with JIA were more likely to be female, but the proportion was greater in the earlier (71%) vs. the later (61%) cohort (Table 1). Children in the earlier cohort were more likely to be diagnosed at a younger age and were more likely to be identified as white. Twelve children (6%) in the earlier cohort and 139 (58%) in the later cohort were prescribed at least one bDMARD during the follow up period. More than 90% of children in each cohort with a complete three years of follow up achieved inactive disease at least once during the follow up period (Table 2).

Among children with 3 full years of follow up, the RR for achieving inactive disease was 1.01 (95% CI: 0.94-1.07). Results did not vary by sex, and there was little change when stratified by race/ethnicity or JIA course. Among those who achieved inactive disease status, the relative occurrence of a disease flare was modestly increased for children in the later cohort (RR 1.21, 95%CI: 0.99-1.50 in the fully adjusted model), although the CI included one. The RRs for disease flares in the later vs. early cohorts were modestly, but not statistically significantly increased in both males (RR 1.26, 95% CI: 0.85-1.88) and females (RR 1.19, 95% CI: 0.93-1.51), and greatest among children with oligoarticular-persistent disease (RR 1.37, 95% CI: 0.96-1.96). The RR for disease flare occurrence among white children was 1.18 (95%CI: 0.93-1.51); among non-white children it was 0.89 (95% CI: 0.58-1.35).

When analyses were restricted to the larger groups of children with 2 or more years of follow up, the RRs for achievement of inactive disease during follow up were essentially the same as those for the children with 3 years of follow up. However, among children who had achieved inactive status, the RR for flare occurrence in the later vs. earlier cohorts was 1.50 (95% CI: 1.13-2.00), with slight variation by sex (RR 1.31, 95% CI: 0.80-2.14 in males; RR 1.52, 95% CI: 1.07-2.16 in females), and race (RR 1.57,

95% CI: 1.31-2.18 in white, RR 0.81, 95% CI: 0.40-1.61 in non-white children). Among children with oligoarticular-persistent JIA, the RR was 1.55 (95% CI: 0.98-2.42).

Regardless of length of follow up period, children in the later cohort had fewer mean days to inactive disease status (234 days, sd 233 in later cohort vs. 303 days, sd 234 in early cohort, p=0.01, Table 3). Children in the later cohort also had a greater mean number of days in inactive disease than did those in the early cohort, however these results did not reach the level of statistical significance.

Results of analyses were essentially unchanged after exclusion of the 12 children in the early cohort who were known to have received bDMARDs (Table 4, Table 5).

Discussion

We did not observe strong evidence of better disease outcomes (achievement of inactive disease, reduction in flare occurrence) in the later cohort when bDMARDS were more available. This is consistent with recent findings by Kimura, et al. who reported that achievement of inactive disease did not differ significantly at 12 months with use of bDMARDs among children with polycourse JIA.[12] However, we did find that the mean number of days to inactive disease was less and the mean number of days in inactive disease was greater in the later cohort, lending support to the hypothesis that bDMARDs improve disease outcomes outside of a clinical trial environment.

Our data suggests that girls may be more likely to experience a disease flare and be slightly less likely to achieve inactive disease status, consistent with earlier studies.[13]

Little is known about the association between race/ethnicity and JIA outcomes. In our study, there was modest evidence that white children in the later cohort had greater occurrence of disease flare than non-white children. This should be interpreted with caution given the amount of missing data

for race/ethnicity variables in the early cohort. If the distribution of the missing race/ethnicity data differs from the data that is present, these findings may be biased.

Strengths of this study include our ability to examine outcomes in JIA in a real world setting leveraging existing electronic medical records and confirming all diagnoses with chart review (AS). Thus, there are no erroneous ICD-9/10 diagnoses in this dataset. Other strengths include capturing most JIA in Washington State as SCH was the only pediatric rheumatology service for the majority of the time periods studied.

This study has several limitations. Our sample size was small, limiting our ability to detect differences between the two cohorts. Due to sample size limitations, we were unable to examine the disease outcomes in children diagnosed with systemic JIA which may have shown the greatest association between bDMARD availability and disease outcomes as children with systemic JIA are often prescribed a bDMARD soon after diagnosis, whereas those with other JIA types typically are offered other regimens before moving to bDMARDS.[14] Small sample size restricted our ability to identify JIA category-specific associations that could plausibly exist as JIA is a heterogeneous group of discrete categories. Examining these category-specific associations should be attempted in future studies.

Our data may have not captured all disease flares because of the possibility that only flares severe enough to necessitate an urgent visit to the rheumatologist or detected during routine visits would have been included. This is likely nondifferential misclassification as this would have been an issue in both cohorts and would have biased results toward the null. However, flares may have been detected more frequently and more accurately among children in the later cohort due to the increasing use of MRIs and ultrasound, which would have caused differential assessment across time periods[15] biasing results away from null with increased flare occurrence in recent years. This could also affect the outcome of time to inactive disease in the same way as children in the earlier cohort with mild active

disease that would have been seen on ultrasound exam or MRI in the later cohort may have been misclassified as having inactive disease.

Loss to follow up is a concern, as the later cohort had a greater proportion of individuals with complete follow up at 3 years and 2 years post diagnosis. If the loss to follow up was differential, this would introduce selection bias to our study. If those in the earlier cohort were followed for less time after achieving inactive disease and only returned to clinic if they had a flare, that would lead to an overestimation of the proportion of children with active disease in the later cohort which would lead to an underestimation of RR of negative outcomes between the two cohorts. However, if those in the earlier cohort were lost to follow up because available treatment options had too many side effects (e.g., long-term glucocorticoid use may have been more prevalent in the earlier cohort[16]) or were ineffective, this could lead to an underestimate of the risk of negative outcomes in the earlier cohort, thereby overestimating the RR of negative outcomes in the later cohort compared with the earlier cohort. An analysis of disease status at the last visit among those lost to follow up may provide some insight regarding these issues.

This study raises important questions for future research. Our findings regarding race/ethnicity should be further examined in other cohorts/datasets to further elucidate the relationship between race/ethnicity and JIA outcomes as there have been few studies that have examined this in the US.[17] In addition, the timing of bDMARD administration (e.g. immediately after diagnosis vs. later) may be an important factor and should be studied further. As bDMARDs become increasingly available and there is increased marketing of these medications directly to the patients, it is important to study these medications and their long-term outcomes in order to understand how best to use them to improve outcomes in children with JIA.

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Table 1: Characteristics of children diagnosed with Juvenile Idiopathic Arthritis (JIA) at Seattle Children's Hospital by cohort [1]

Characteristics	Pre-bDMARD Cohort: 1998-2000 (N=194)		bDMARD Cohort: 2015-2017 (N=240)	
	n	%	n	%
Sex				
Male	56	28.9	94	39.2
Female	138	71.1	146	60.8
Age at diagnosis				
0-5 years	*79*	40.7	72	30.0
6-10 years	66	34.0	60	25.0
11+ years	49	25.2	108	45.0
Race/Ethnicity				
White	128	87.1	162	73.6
Non-white	19	12.9	58	26.4
Non-Hispanic White	30	71.4	145	66.5
Other	12	28.6	73	33.5
Washington State Residents	154	94.5	230	90.2
JIA Categories				
Oligoarticular				
Persistent	86	44.3	78	32.5
Extended	20	10.3	6	2.5

Polyarticular				
RF+	7	3.6	13	5.4
RF-	33	17.0	58	24.2
RF unknown	16	8.2	1	0.4
Systemic	13	6.7	11	4.6
Psoriatic	5	2.6	28	11.7
Enthesitis-related	14	7.2	42	17.5
Undifferentiated	0	0	3	1.3
JIA categories				
Polycourse[b]	95	49.0	148	62.5
Persistent Oligoarticular	86	44.3	78	32.9
Systemic	13	6.7	11	4.6
Medications[c]				
NSAIDs	178	91.8	218	90.8
Conventional DMARDs	92	47.4	170	70.8
Glucocorticoids	43	22.6	109	45.4
Intraarticular glucocorticoid injections	126	65.0	128	53.3
Biologic DMARDs	12	6.2	139	57.9

[a] Numbers may not sum to totals due to missing data
[b] Includes polyarticular, extended oligoarticular, psoriatic, and enthesitis-related
[c] A child may have used >1 medication.

Table 2: Selected outcomes of children diagnosed with juvenile idiopathic arthritis (JIA) at Seattle Children's by cohort

	Cohort 1[a] N=194		Cohort 2[b] N=240					
	n	**%**	**n**	**%**	**RR[c]**	**95% CI**	**RR[d]**	**95% CI**
Inactive disease among those with 3 full years of follow up	107	93.9	165	93.2	1.01	0.95, 1.07	1.01	0.94, 1.07
Stratified by sex								
Female	81	93.1	95	91.3	1.00	0.92, 1.09	1.00	0.91, 1.09
Male	26	96.3	70	95.9	1.00	0.93, 1.08	1.00	0.93, 1.07
Stratified by JIA course								
Polycourse	62	91.2	104	92.0	1.04	0.94, 1.14	1.03[e]	0.93, 1.14
Oligoarticular - persistent	39	100	50	94.3	0.95	0.90, 1.01	0.95[e]	0.90, 1.01
Systemic	6	85.7	10	100	1.18	0.86, 1.63	1.18[e]	0.85, 1.64
Stratified by ethnicity								
Non-Hispanic White	25	96.2	102	96.2	1.03	0.94, 1.12	1.00	0.91, 1.09
Other ethnicity	8	88.9	49	87.5	1.10	0.86, 1.40	1.09	0.86, 1.38
Stratified by white/non-white								
White	85	95.5	114	95.8	1.01	0.95, 1.07	1.01	0.95, 1.07
Non-white	13	86.7	39	86.7	1.10	0.88, 1.38	1.11	0.88, 1.39
Disease flare among those with 3 full years of follow up	60	56.1	101	61.2	1.16	0.94, 1.43	1.21	0.99, 1.50

Stratified by sex								
Female	47	58.0	60	63.2	1.15	0.90, 1.46	1.19	0.93, 1.51
Male	13	50.0	41	58.6	1.22	0.80, 1.88	1.26	0.85, 1.88
Stratified by JIA course								
Polycourse	38	61.3	57	54.8	0.99	0.76, 1.29	1.08[e]	0.83, 1.41
Oligoarticular - persistent	20	51.3	35	70.0	1.37	0.96, 1.96	1.37[e]	0.96, 1.97
Systemic[f]								
Stratified by ethnicity								
Non-Hispanic White	19	76.0	60	58.8	1.03	0.94, 1.12	1.03	0.76, 1.40
Other ethnicity	8	62.5	31	63.3	1.10	0.86, 1.40	0.99	0.55, 1.79
Stratified by white/non-white								
White	47	55.3	66	57.9	1.11	0.87, 1.41	1.18	0.93, 1.51
Non-white	10	76.9	27	69.2	0.91	0.61, 1.35	0.89	0.58, 1.35
Number of disease flares among those who achieved inactive disease within 3 years with 3 years of follow up								
No flares	47	43.9	64	38.8	0.80	0.60, 1.07	0.75	0.57, 1.01
One flare	41	38.3	66	40.0	1.11	0.82, 1.51	1.14	0.83, 1.56
Two or more flares	19	17.8	35	21.2	1.26	0.76, 2.10	1.38	0.84, 2.27

Inactive disease within 2 years with 2 full years of follow up	112	92.6	165	90.7	1.00	0.94, 1.07	1.00	0.93, 1.07
stratified by sex								
Female	88	92.6	94	88.7	0.99	0.90, 1.08	0.98	0.90, 1.08
Male	24	92.3	71	93.4	1.02	0.91, 1.13	1.01	0.90, 1.13
stratified by JIA course								
Polycourse	66	91.7	111	90.2	1.02	0.92, 1.14	1.02[e]	0.91, 1.13
Oligoarticular - persistent	48	96.0	53	91.4	0.96	0.88, 1.05	0.96[e]	0.87, 1.05
Systemic	6	85.7	10	100	1.22	0.83, 1.78	1.22[e]	0.83, 1.80
Stratified by ethnicity								
Non-Hispanic White	28	96.6	102	92.7	1.02	0.93, 1.11	1.00	0.92, 1.09
Other ethnicity	8	88.9	51	86.4	1.10	0.87, 1.41	1.12	0.87, 1.43
Stratified by white/non-white								
White	87	93.5	115	92.7	1.00	0.93, 1.07	1.00	0.93, 1.08
Non-white	13	86.7	40	85.1	1.11	0.89, 1.38	1.10	0.87, 1.39
Disease flare in first 2 years among those with 2 full years of follow-up	43	35.8	87	49.7	1.42	1.07, 1.89	1.50	1.13, 2.00
Stratified by sex								
Female	32	34.4	50	50.0	1.49	1.05, 2.10	1.52	1.07, 2.16
Male	11	40.7	37	49.3	1.24	0.74, 2.07	1.31	0.80, 2.14
Stratified by JIA course								

Polycourse	25	37.9	50	45.0	1.24	0.84, 1.82	1.35[e]	0.92, 1.97
Oligoarticular - persistent	17	35.4	29	54.7	1.54	0.97, 2.42	1.55[e]	0.98, 2.45
Systemic[f]								
Stratified by ethnicity								
Non-Hispanic White	12	42.9	54	50.9	1.47	0.90, 2.40	1.61	1.01, 2.57
Other ethnicity[f]								
Stratified by white/non-white								
White	33	35.1	58	48.3	1.44	1.03, 2.01	1.57	1.13, 2.18
Non-white	7	50.0	23	53.5	0.89	0.46, 1.74	0.81	0.40, 1.61
Number of disease flares among those who achieved inactive disease within 2 years with 2 years of follow up								
No flares	77	64.2	88	50.3	0.76	0.63, 0.94	0.73	0.60, 0.90
One flare	32	26.7	68	38.9	1.49	1.04, 2.13	1.55	1.08, 2.23
Two or more flares	11	9.2	19	10.6	1.22	0.61, 2.48	1.36	0.68, 2.70

[a] Pre-bDMARD cohort: 1998-2000

[b] bDMARD cohort: 2015-2017

[c] Relative risk (RR) adjusted for age at diagnosis

[d] Adjusted for age at diagnosis, JIA course, and intraarticular glucocorticoid injections

[e] Adjusted for age at diagnosis and intraarticular glucocorticoid injections

[f] Results suppressed because variable contains cell sizes < 5

Table 3: Mean days to inactive disease and time in active disease among children with juvenile idiopathic arthritis (JIA) at Seattle Children's Hospital, by cohort.

	Pre-bDMARD Cohort: 1998-2000 (N=194)		bDMARD Cohort: 2015-2017 (N=240)		
	mean	**sd**	**mean**	**sd**	**t-test p-value**
Days to inactive disease					
With two full years of follow up[a]	*303*	234	234	233	0.01
With three full years of follow up[b]	*306*	239	238	237	0.02
Days in inactive disease					
With two full years of follow up[c]	*595*	284	629	316	0.32
With three full years of follow up[d]	*621*	281	652	306	0.39

[a] Pre-bDMARD cohort n=120; bDMARD Cohort n=175
[b] Pre-bDMARD cohort n=107; bDMARD Cohort n=165
[c] Pre-bDMARD cohort n=129; bDMARD Cohort n=192
[d] Pre-bDMARD cohort n=114; bDMARD Cohort n=177

Table 4: Subanalysis of selected outcomes of children diagnosed with Juvenile Idiopathic Arthritis (JIA) at Seattle Children's Hospital by cohort with those using bDMARDs excluded from the early cohort

	Cohort 1[a] N=182		Cohort 2[b] N=240					
	n	**%**	**n**	**%**	**RR[c]**	**95% CI**	**RR[d]**	**95% CI**
Inactive disease among those with 3 full years of follow up	99	95.2	165	93.2	1.00	0.94, 1.05	0.99	0.93, 1.06
Stratified by sex								
Female	76	95.0	95	91.3	0.98	0.91, 1.06	0.98	0.90, 1.06
Male	23	95.8	70	95.9	1.01	0.93, 1.09	1.00	0.93, 1.08
Stratified by JIA course								
Polycourse	55	93.2	104	92.0	1.01	0.92, 1.11	1.01[e]	0.91, 1.11
Oligoarticular -persistent	39	100.0	50	94.3	0.95	0.90, 1.01	0.95[e]	0.90, 1.01
Systemic	5	83.3	10	100.0	1.19	0.84, 1.68	1.19[e]	0.85, 1.67
Stratified by ethnicity								
Non-Hispanic White	24	96.0	102	96.2	1.03	0.94, 1.12	1.00	0.91, 1.10
Other ethnicity	7	100.0	49	87.5	0.98	0.93, 1.04	1.00	0.90, 1.10
Stratified by white/non-white								
White	78	95.1	114	95.8	1.01	0.96, 1.08	1.02	0.95, 1.08
Non-white	13	92.9	39	86.7	1.03	0.86, 1.23	1.04	0.86, 1.26
Disease flare among those with 3 full years of follow up	54	54.5	101	61.2	1.21	0.97, 1.50	1.26	1.02, 1.57
Stratified by sex								

Female	43	56.6	60	63.2	1.18	0.92, 1.52	1.21	0.94, 1.56
Male	11	47.8	41	58.6	1.31	0.84, 2.06	1.38	0.91, 2.09
Stratified by JIA course								
Polycourse	33	60.0	57	54.8	1.02	0.77, 1.35	1.11[e]	0.84, 1.47
Oligoarticular -persistent	20	51.3	35	70.0	1.37	0.96, 1.96	1.37[e]	0.96, 1.97
Systemic[f]								
Stratified by ethnicity								
Non-Hispanic White	18	75.0	60	58.8	0.99	0.74, 1.33	1.04	0.77, 1.42
Other ethnicity[f]								
Stratified by white/non-white								
White	42	53.8	66	57.9	1.15	0.90, 1.49	1.23	0.96, 1.58
Non-white	10	76.9	27	69.2	0.91	0.61, 1.35	0.89	0.58, 1.35
Number of disease flares among those who achieved inactive disease within 3 years with 3 full years of follow up								
No flares	45	45.5	64	38.8	0.76	0.57, 1.02	0.72	0.54, 0.96
One flare	37	37.4	66	40.0	1.16	0.84, 1.60	1.19	0.86, 1.64
Two or more flares	17	17.2	35	21.2	1.30	0.77, 2.22	1.42	0.84, 2.38
Inactive disease within 2 years among those with 2 years of follow up	104	93.7	165	90.7	0.99	0.93, 1.06	0.99	0.92, 1.06
Stratified by sex								

Female	83	94.3	94	88.7	0.97	0.89, 1.05	0.97	0.89, 1.05
Male	21	91.3	71	93.4	1.03	0.91, 1.16	1.02	0.90, 1.15
Stratified by JIA course								
Polycourse	54	93.1	101	89.4	1.00	0.91, 1.10	1.00[e]	0.90, 1.11
Oligoarticular -persistent	46	95.8	53	91.4	0.96	0.88, 1.05	0.96[e]	0.87, 1.05
Systemic[f]								
Stratified by ethnicity								
Non-Hispanic White	27	96.4	102	92.7	1.02	0.93, 1.11	1.00	0.92, 1.10
Other ethnicity	7	100.0	51	86.4	0.99	0.93, 1.05	1.02	0.90, 1.16
Stratified by white/non-white								
White	80	93.0	115	92.7	1.01	0.94, 1.08	1.01	0.94, 1.09
Non-white	13	92.9	40	85.1	1.03	0.86, 1.23	1.03	0.85, 1.26
Disease flare in first 2 years of follow up among those with 2 full years of follow up	39	34.8	87	49.7	1.48	1.10, 1.99	1.55	1.16, 2.09
Stratified by sex								
Female	30	34.1	50	50.0	1.50	1.05, 2.14	1.53	1.07, 2.19
Male	9	37.5	37	49.3	1.38	0.79, 2.41	1.48	0.87, 2.53
Stratified by JIA course								
Polycourse	21	35.6	50	45.0	1.34	0.89, 2.02	1.53[e]	1.07, 2.19
Oligoarticular -persistent	17	35.4	29	54.7	1.54	0.97, 2.42	1.48[e]	0.87, 2.53
Systemic[f]								
Stratified by ethnicity								

Non-Hispanic White	12	44.4	54	50.9	1.42	0.88, 2.30	1.56	0.99, 2.46
Other ethnicity[f]								
Stratified by white/non-white								
White	30	34.5	58	48.3	1.48	1.05, 2.10	1.62	1.16, 2.28
Non-white	7	50.0	23	53.5	0.89	0.46, 1.74	0.81	0.40, 1.61
Number of disease flares among those who achieved inactive disease within 2 years with 2 years of follow up								
No flares	73	65.2	88	50.3	0.75	0.61, 0.92	0.72	0.58, 0.88
One flare	29	25.9	68	38.9	1.54	1.06, 2.24	1.60	1.10, 2.33
Two or more flares	10	8.9	19	10.9	1.28	0.62, 2.63	1.47	0.69, 2.84

[a] Pre-bDMARD cohort: 1998-2000
[b] bDMARD cohort: 2015-2017
[c] Relative risk (RR) adjusted for age at diagnosis
[d] Adjusted for age at diagnosis, JIA course, and intraarticular glucocorticoid injections
[e] Adjusted for age at diagnosis and intraarticular glucocorticoid injections
[f] Results suppressed because variable contains cell sizes < 5

Table 5: Mean days to inactive disease and time in active disease among children with juvenile idiopathic arthritis (JIA) at Seattle Children's Hospital, by cohort, excluding those from the early cohort using bDMARDs

	Pre-bDMARD Cohort: 1998-2000 (N=182)		bDMARD Cohort: 2015-2017 (N=240)		
	mean	**sd**	**mean**	**sd**	**t-test p-value**
Days to inactive disease					
With two full years of follow up[a]	*301*	239	238	233	0.02
With three full years of follow up[b]	*303*	244	238	237	0.03
Days in inactive disease					
With two full years of follow up[c]	*607*	283	629	316	0.53
With three full years of follow up[d]	*638*	278	652	306	0.69

[a] Pre-bDMARD cohort n=112; bDMARD Cohort n=175
[b] Pre-bDMARD cohort n=99; bDMARD Cohort n=165
[c] Pre-bDMARD cohort n=119; bDMARD Cohort n=192
[d] Pre-bDMARD cohort n=104; bDMARD Cohort n=177

Supplemental Table 1. Dates of U. S. Food and Drug Administration approval of biologic medications for arthritis patients.[8]

	Adults	Children
Etanercept (Enbrel)	11/2/1998	5/1999 (poly JIA course)
Infliximab (Remicade)	11/10/1999	Off label use
Anakinra (Kineret)	11/14/2001	Off label use
Adalimumab (Humira)	12/31/2002	2/2008 (poly JIA course)
Abatacept (Orencia)	12/23/2005	4/2008 (poly JIA course)
Rituximab (Rituxan)	3/1/2006	Off label use
Tocilizumab (Actemra)	1/8/2010	4/2011 (systemic) 4/2013 (poly JIA course)
Canakinumab (Ilaris)	6/17/2009	5/2013 (systemic)
Golimumab (Simponi)	4/24/2009	9/2020 (poly JIA course, psoriatic)
Certolizumab (Cimzia)	5/13/2009	Off label use
Tofacitinib (Xeljanz)	11/6/2012	9/2020 (poly JIA course)
Ustekinumab (Stelara)	10/23/2013	Off label use