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Title: Trends in New Use of Disease-Modifying Antirheumatic Drugs in Juvenile Idiopathic Arthritis Among Commercially Insured Children in the United States from 2001-2022

Running Head: Trends in New Use of DMARDs in JIA

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Abstract

Objective To describe recent trends in DMARD use for children with juvenile idiopathic arthritis (JIA) in the US.

Methods We used commercial claims data (2000-2022) to perform a serial cross-sectional utilization study of children ages 1-18 diagnosed with JIA. Initiations of conventional synthetic (cs), biologic (b), or targeted synthetic (ts) DMARDs were identified after a ≥12-month baseline and expressed as percentage of all new DMARD initiations per year, by category, class, and individual agent. Trends were evaluated using linear regression. Secondarily, we examined first b/tsDMARDs initiated after csDMARD monotherapy.

Results We identified 20,258 new DMARD use episodes among 13,696 individuals (median age 14 years, 67.5% female). csDMARDs, while most commonly used overall, declined from 89.5% of new use episodes to 43.2% (2001-2022, $p<0.001$ for trend). In contrast, bDMARD use increased (10.5-50.0%, $p<0.001$). For tumor necrosis factor inhibitors (TNFi), etanercept peaked at 28.3% (2006) and declined to 4.2% (2022) ($p=0.002$). Meanwhile, adalimumab use doubled (7.0-14.0%, 2007-2008) after JIA approval, increasing further following a less painful formulation release (20.5%, 2022, $p<0.001$). However, overall TNFi use has declined with increasing use of other b/tsDMARDs, particularly ustekinumab, secukinumab, and tofacitinib.

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By 2022, adalimumab was the most common b/tsDMARD initiated first after csDMARDs (77.8%).

Conclusion Among commercially insured children with JIA in the US, new b/tsDMARD use is rising while new csDMARD use declines. For b/tsDMARDs, adalimumab is most used and the predominant b/tsDMARD initiated first after csDMARDs. Patterns in DMARD use for JIA have evolved relative to multiple factors, including regulatory approvals and tolerability.

Keywords: juvenile idiopathic arthritis, disease-modifying antirheumatic drugs, drug utilization study

Introduction

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disorder, affecting approximately 16-150 per 100,000 children in North America.[1] The chronic inflammation, resultant damage, and burdens of treatment associated with JIA can impact patients' daily activities and productivity.[2] Important goals of treatment in patients with JIA are to eliminate active disease, normalize physical function, preserve normal vision and growth, prevent long-term damage, maximize quality of life, and minimize short- and long-term toxicity.[2] Disease-modifying antirheumatic drugs (DMARDs) collectively represent the most common and effective treatments used for JIA and JIA-associated eye inflammation (uveitis).[3] DMARDs include conventional synthetic DMARDs (csDMARDs) such as methotrexate; biologic DMARDs (bDMARDs) such as etanercept, adalimumab, and tocilizumab; and targeted synthetic DMARDs (tsDMARDs) such as tofacitinib and baricitinib.

Research on trends in DMARD utilization for children enable better understanding on how selection of therapies for JIA has evolved with increasing availability of effective agents.

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Nonetheless, most studies on DMARD utilization have focused on adults with inflammatory arthritis.[4] One retrospective study using United States (US) data from 2019-2020 found that tumor necrosis factor inhibitors (TNFi) were the most prescribed b/tsDMARDs for first and second-line treatment of rheumatoid arthritis (RA) in adults.[5] Among studies in populations with JIA, a retrospective cohort study from a single Canadian clinic (n=325) found that the most common DMARD used in 2011-2019 was methotrexate, followed by etanercept.[6] In a cross-sectional analysis of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry (2010-2011), approximately 75% of all enrolled children (median age 12 years) with JIA in the registry (N=2,748) received csDMARDs, and 25% received bDMARDs.[7] In a retrospective cohort study using commercial insurance claims data from US children with JIA from 2008-2016, etanercept was the most common first bDMARD used, followed by adalimumab.[8] However, this study focused on economic outcomes and did not consider trends across years. In another US retrospective cohort study of commercially insured children and young adults with JIA or RA from 2009-2013, etanercept was the most commonly used TNFi.[9] In a separate retrospective cohort study using national US commercial claims data from 2005-2012, use of TNFi for the treatment of JIA increased 2- to 3-fold.[10] However, trends in individual DMARD use were not compared across calendar years, and these older studies do not reflect potential changes from the availability of multiple new drugs, new formulations, and other more recent changes in the management of JIA. A more recent registry-based study showed increasing use of bDMARDs in Canada between 2005-2010 and 2017-2021, but analyses did not extend to specific DMARD types or classes.[11] Furthermore, most studies have not examined utilization specifically for JIA-associated uveitis, a common complication of JIA that influences choice of DMARD.

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There is little research evaluating trends in DMARD use in populations with JIA over the past decade, including research on specific DMARDs and first-line b/tsDMARDs. We evaluated national trends in new use of DMARDs from the last two decades among commercially insured children with JIA in the US. Inflection points in DMARD use were hypothesized to occur with JIA-specific approvals. We also hypothesized that bDMARD use has increased over time and that adalimumab has become the most commonly used bDMARD.

Patients and Methods

Study Design and Data Source

We performed a serial cross-sectional study in a cohort of commercially (privately) insured children in the US with JIA using Merative MarketScan Commercial Claims and Encounters data from 2000-2022 (the most recently available data at the time of analysis). This database contains administrative claims data with information about enrollment, inpatient and outpatient encounters, and prescription drug claims.[12] Medical encounters are coded using International Classification of Disease Ninth and Tenth Revision, Clinical Modification (ICD- 9-CM and ICD-10-CM) codes, Current Procedural Terminology Fourth Edition codes, Healthcare Common Procedure Coding System codes, and National Drug Codes.[13] This study of de-identified data was approved by the Rutgers University Institutional Review Board (Pro2023001171) with a waiver for informed consent and in accordance with existing data use agreements. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.[14]

Study Population

During each year of analysis from 2001-2022, we identified a cohort of children ages 1-18 years old with JIA diagnosis prior to age 18 who initiated a DMARD without prior use of the

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same DMARD in the prior 365 days. The index date was defined as the date of DMARD initiation for each DMARD of interest. Eligible individuals were required to have ≥365 days of continuous health care and pharmacy eligibility prior to the index date. JIA was defined by ≥1 diagnosis in an outpatient or inpatient encounter in any position (ICD-9-CM 696.0x, 714.xx, or 720.xx; ICD-10-CM L40.5x, M05.x, M06.x, M08.x, or M45.x).[15, 16] Patients with cancer, inflammatory bowel disease (IBD), lupus, and other systemic rheumatic diseases during the 365-day baseline period were excluded from the study since treatment for these patients is often dictated by these conditions rather than JIA. Subjects were eligible to have multiple initiations of distinct DMARDs each year if each initiation event met the eligibility criteria.

DMARDs

The DMARDs evaluated in this study were csDMARDs (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide), bDMARDs (etanercept, adalimumab, golimumab, infliximab, certolizumab, abatacept, tocilizumab, sarilumab, canakinumab, anakinra, rilonacept, secukinumab, ustekinumab, rituximab), and tsDMARDs (tofacitinib, ruxolitinib, baricitinib, upadacitinib) (**Table S1**). DMARDs were characterized by category (csDMARD, bDMARD, or tsDMARD), class (tumor necrosis factor inhibitors (TNFi), interleukin-6 (IL-6) inhibitors, interleukin-1 (IL-1) inhibitors, or Janus kinase (JAK) inhibitors), and specific drug. DMARDs were identified from inpatient records, outpatient records, and dispensing records.

Covariates

The covariates evaluated in this study were age, sex, region, and inpatient or outpatient diagnoses of select comorbidities at baseline, namely, chronic pain disorders, psoriasis, celiac disease, and uveitis.

Statistical Analysis

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To describe the study population, baseline characteristics of all eligible subjects were assessed prior to or on the index date for each new use episode. We calculated the percentage of DMARD initiations per calendar year, classified by specific DMARD, DMARD class, or DMARD category; the denominator was represented by the number of all eligible DMARD initiations in that calendar year. To assess for statistically significant changes in DMARD use over the entire study period, we used linear regression with calendar year as the independent variable. Trends in DMARD use were also described visually based on comparison with key dates (e.g., regulatory approvals, changes in formulation) (**Tables S1-S2**)[17, 18, 19, 20, 21, 22, 23, 24], hypothesizing inflection points with Food and Drug Administration (FDA) approvals for JIA. Additional exploratory inflection points of interest corresponded to published American College of Rheumatology (ACR) guidelines for JIA management in 2011, 2013, and 2019[25, 26, 27], changes in formulations, and the start of the US COVID-19 pandemic in 2020.

Given that b/tsDMARDs are more expensive and frequently follow initial treatment with csDMARDs based on treatment recommendations[25, 26, 27], in a secondary analysis, we assessed the first bDMARD or tsDMARD used ≥30 days after the use of csDMARD monotherapy. bDMARDs and tsDMARDs were not included in this secondary analysis if their use was within 30 days of csDMARD initiation since this could constitute combination therapy. Secondary subgroup analyses were stratified by age group (<12 or ≥12 years) and sex (male, female). We also conducted secondary subgroup analyses for patients with uveitis diagnosis and, separately, for patients without psoriasis diagnosis.

To assess whether utilization patterns differed based on the timing of DMARD use or definition of the study population, two sensitivity analyses were performed: 1) evaluation of any DMARD use (incident or prevalent) within each calendar year; and 2) eligibility based on ≥2 JIA

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diagnosis codes 30-365 days apart. All data analyses were conducted using SAS version 9.4 (SAS Institute). P-values less than 0.05 were considered statistically significant and were not adjusted for multiple testing as analyses were intended to be descriptive.

Results

Baseline Characteristics

We identified 20,258 new episodes among 13,696 children diagnosed with JIA who newly initiated at least one DMARD between 2001 and 2022. The median age was 14 (interquartile range [IQR], 10-16) years; most subjects were between the ages of 12-18 years (65.5%) and female (67.5%) (**Table 1**). Of the four comorbidities assessed, subjects most commonly had diagnoses of psoriasis (21.2%), followed by uveitis (7.5%), chronic pain disorders (5.1%), and celiac disease (0.7%).

Trends in DMARD Use in Children with JIA

Of the DMARD categories, csDMARDs were most common early in the study period until 2018, when their use was surpassed by bDMARDs (**Figure 1**, **Table S3**). Between 2001 and 2022, use of csDMARDs declined from 89.5% to 43.2% of all DMARD initiations ($p<0.001$ for trend). During this same period, bDMARD use increased from 10.5% to 50.0% ($p<0.001$). For TNFi specifically, use of etanercept (first-in-class) peaked at 28.3% of all DMARD initiations in 2006 and subsequently declined to 4.2% by 2022 ($p=0.002$) (**Figure 2, Table S4**). Another TNFi, adalimumab, doubled in use from 7.0% in 2007 to 14.0% in 2008 (year of FDA approval for JIA). Adalimumab initiations increased even further following the 2018 approval of a citrate-free formulation to reduce burning, reaching 20.5% by 2022 ($p<0.001$).

Despite the increases in individual TNFi over time, overall TNFi use declined in recent years as use of other b/tsDMARD has increased (**Figure S1**). Two bDMARDs initially approved for

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psoriasis increased in recent years: ustekinumab, increasing from 0.1% of all DMARD initiations in 2009 (year of FDA approval for adults with psoriasis) to 2.4% in 2017 (year of FDA approval for pediatric psoriasis) to 10.5% in 2022 (year of FDA approval for pediatric psoriatic arthritis) ($p<0.001$); and secukinumab, increasing from 0.2% of all DMARD initiations in 2015 (year of FDA approval for adults with psoriasis) to 3.0% in 2021 (year of FDA approval for pediatric psoriatic arthritis) and 4.8% in 2022 ($p<0.001$) (**Figure 3, Table S4**). Initiations of tofacitinib increased following approval from 2.9% of all DMARD initiations in 2020 to 5.2% in 2021 before dipping to 3.7% in 2022 ($p<0.001$). Of all DMARDs assessed, methotrexate (csDMARD) was the most commonly used DMARD throughout the entire study period but declined in use relative to all DMARDs (42.1% in 2001, 21.5% in 2022, $p<0.001$) (**Figure 4, Table S4).**

Secondary and Sensitivity Analyses

In the secondary analysis of the first b/tsDMARD used after csDMARDs, etanercept use went from 100% in 2001-2002 to 6.5% by 2022 ($p<0.001$) (**Figure 5, Table S5**). In contrast, adalimumab use went from 0% in 2001-2002 to 77.8% by 2022 ($p<0.001$).

In the subgroup of those diagnosed with uveitis, the top six commonly used DMARDs were adalimumab, etanercept, hydroxychloroquine, infliximab, methotrexate, and sulfasalazine (**Figure S2, Table S6**). Among those diagnosed with JIA and uveitis, the percentage of methotrexate initiations declined from 54.8% in 2005 to 20.0% in 2006 ($p<0.001$) as relative use of bDMARDs in this subpopulation increased; infliximab and etanercept were more common in earlier years, and adalimumab, in later years. In the subgroup of those without psoriasis, we found much lower ustekinumab use compared to the general JIA population (**Figure S3, Table S7**). Users of ustekinumab or secukinumab had a similar or larger number of baseline JIA diagnoses compared with psoriasis diagnoses across most years (**Table S8**).

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DMARD trends in subgroup analyses stratified by age group (**Figure S4**) and sex (**Figure S5**) were mostly consistent with the main analyses. However, methotrexate use was relatively more common in children under age 12 than older children. Adalimumab, etanercept, hydroxychloroquine, methotrexate, and sulfasalazine were most commonly used by children of both sexes. Use of ustekinumab was higher among older children (≥12) and male patients, while use of infliximab was higher among younger children (<12) and female patients.

The results of the sensitivity analyses were consistent when assessing any DMARD use (**Figure S6, Table S9**) and including those with at least two JIA diagnosis codes in the prior year (**Figure S7, Table S10**).

Discussion

Among commercially insured children with JIA in the US, methotrexate remains the most commonly initiated DMARD for JIA. However, as with other csDMARDs, new methotrexate use has been declining as b/tsDMARD use has been steadily increasing over time. In recent years, adalimumab has been the most commonly used b/tsDMARD and the predominant b/tsDMARD initiated first after csDMARDs. Use of other b/tsDMARDs, particularly ustekinumab and secukinumab, which are indicated for psoriatic arthritis, have sharply risen in recent years.

The findings from our study expand on the available literature on DMARD use for patients with JIA. In a prior retrospective study of patients with systemic JIA using the German National Pediatric Rheumatologic Database, use of csDMARDs predominated in 2003-2005, but bDMARD use in this population increased, exceeding csDMARDs by 2011-2013.[28] Our larger study including all types of JIA in the US showed a similar if delayed trend, with bDMARD initiations surpassing csDMARD initiations by 2018. In a prospective cohort of young adults

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with JIA in Germany from 2007-2019, the most frequently used DMARD was etanercept, followed by methotrexate, and adalimumab.[29] However, the study did not focus on children and had a small sample size. In another retrospective cohort study using MarketScan data from 2008-2016, etanercept was the most common first bDMARD used in children with JIA, although trends over time were not evaluated.[8] In contrast to these smaller studies using older data, we found that, by 2022, adalimumab was by far the most commonly started b/tsDMARD (20.5%), while etanercept only represented 4.2% of initiations. Our findings also extend the findings of a prior single-center study, in which adalimumab was the most frequently prescribed bDMARD by 2018.[30]

In the early 2000s, methotrexate, hydroxychloroquine, and sulfasalazine represented the vast majority of DMARD initiations for JIA. However, as hypothesized, relative csDMARD use steadily fell over time as b/tsDMARDs became available. While b/tsDMARDs are more expensive for patients, they are more targeted than csDMARDs and frequently better tolerated than methotrexate. While methotrexate and adalimumab both had changes in formulation during the study period, only adalimumab showed an increase in initiations, following a new, less painful formulative release in 2018. That same year also represented an inflection point after which adalimumab became the preferred b/tsDMARD following csDMARDs. The rising use of adalimumab initiations compared to etanercept could also relate to other conveniences of administration, including fixed-dose formulations for children and the every-other-week dosing regimen.[31] Throughout the study period, we observed off-label use of novel b/tsDMARDs for JIA after their initial FDA approval for adults with inflammatory arthritis or psoriasis and before approval for JIA. Use of many b/tsDMARDs noticeably increased following their approval in children, including adalimumab, golimumab, tocilizumab, canakinumab, abatacept, ustekinumab,

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secukinumab, and tofacitinib, suggesting that labeling and corresponding marketing does influence prescribing and use of DMARDs for JIA.

Of note, nearly a quarter of patients in this cohort had a documented diagnosis of psoriasis, which is higher than the expected prevalence of psoriatic arthritis in JIA.[32] This could in part relate to dual use of b/tsDMARDs for JIA and psoriasis, including agents specifically approved specifically for psoriatic arthritis in adults and children, such as ustekinumab. Notably, ustekinumab increased considerably in use over time, becoming the second most common b/tsDMARD (after adalimumab) used in the study population by the end of the study period. Ustekinumab was predominantly prescribed for patients diagnosed with both JIA and psoriasis rather than patients with psoriatic arthritis *without* psoriasis diagnosis. While the reasons for the rise in ustekinumab use are unclear, some potential explanations include: patients with psoriatic arthritis frequently have chronically uncontrolled disease, which may require additional therapy with agents such as ustekinumab[33]; preferential prescribing of ustekinumab by dermatologists who see patients with psoriasis and arthritis; or misclassified coding of JIA in patients who may have had psoriasis and joint pain without frank arthritis, though few patients had more baseline psoriasis diagnoses than JIA diagnoses. Additionally, TNFi have been associated with the development of psoriasis in some children[34], and given the broad use of TNFi in the population with JIA, diagnosis of this potential treatment complication may also have contributed to the unexpectedly high prevalence of psoriasis.

We did not observe a major impact of the US COVID-19 pandemic on DMARD prescribing except perhaps a reversal of a downward trend of hydroxychloroquine use starting in 2020, following its brief emergency use authorization for COVID-19 before its effectiveness was disproven. In one recent study, commercially insured children with acute COVID-19 were

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observed to have higher rates of non-recommended prescriptions, including hydroxychloroquine.[35]

In the subpopulation of JIA diagnosed with uveitis, we found greater use of adalimumab and infliximab and lower use of etanercept than in the general JIA population, consistent with the relative effectiveness of these respective agents in treating uveitis as well as the 2019 guidelines for JIA-associated uveitis which recommend monoclonal TNFi over etanercept.[36, 37] Notably, use of etanercept declined steeply after the publication of a negative clinical trial for JIA-associated uveitis by Smith et al.[38] It is possible that some DMARDs that are not recommended for uveitis were used to treat other aspects of JIA, such as etanercept for arthritis or sulfasalazine for enthesitis.

Evaluation of individual agents in other subgroups also revealed important insights. Methotrexate use was relatively more common in children under age 12 than older children, possibly since younger children may be less likely to experience methotrexate-associated gastrointestinal side effects or more likely to respond to methotrexate monotherapy.[39, 40] Another possibility is that relatively more subjects in the younger age group were newly diagnosed and started on methotrexate as first-line therapy. To our surprise, hydroxychloroquine was commonly used by children of both sexes and in both age groups, despite a negative landmark trial and lack of approval for JIA.[41] Additionally, use of ustekinumab was higher among older children (≥12) and male patients, while use of infliximab was higher among younger children (<12) and female patients. This could be due to the higher incidence of uveitis in younger children and higher incidence of psoriatic disease in older children.[42] Older children with psoriatic arthritis are also more likely to be male than younger children.[43]

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Our study had several strengths, including the analysis of a large national population of commercially insured children in the US, providing more generalizable findings than in prior single-center and registry-based populations. Our inclusion of data spanning the last two decades enabled us to describe trends over a period of dramatic expansion in the market availability of treatments for JIA, particularly b/tsDMARDs. We also present novel findings on the recent dominance of adalimumab as a first-line b/tsDMARD for JIA as well the recent increases in the use of ustekinumab, tofacitinib (first targeted oral agent FDA-approved for JIA, 2020), and secukinumab in this population, making this study timely and informative to understanding real-world treatment patterns for JIA.

This study also had certain limitations. Our findings from a privately insured population may not be generalizable to other populations, as DMARD prescribing and use may differ in patients with public insurance, patients without insurance, or patients outside of the US. Additionally, we did not have access to data on race, ethnicity, or socioeconomic status to investigate the presence of disparities in DMARD use. We also lacked clinical details about the population with JIA, including JIA type (e.g., systemic JIA, polyarticular JIA), disease severity, prescribers' specialty, and other factors that could impact patterns of DMARD prescribing and use. There was also the potential of diagnostic misclassification of JIA and comorbidities, such as uveitis or psoriasis. These utilization data also do not reveal the reasons behind the observed patterns of DMARD use, including the high recent uptake of ustekinumab.

In summary, in a large population of commercially insured children with JIA in the US, we found a steady decrease in initiations of csDMARDs and a corresponding increase in initiations of b/tsDMARDs from 2001 to 2022. Adalimumab has become the most widely used b/tsDMARD, particularly as a first-line agent after csDMARDs. Use of ustekinumab,

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secukinumab, and tofacitinib has also increased in recent years. These real-world treatment patterns give us insight into how selection of therapies for JIA has evolved with increasing availability of effective agents and help prepare for future studies on comparative DMARD safety and effectiveness.

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References

1. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. Lancet. 2011; 377(9783):2138-49. doi:10.1016/s0140-6736(11)60244-4
2. Barut K, Adrovic A, Şahin S, et al. Juvenile idiopathic arthritis. Balkan medical journal. 2017; 34(2):90-101. doi:10.4274/balkanmedj.2017.0111
3. Chen JL, Abiri P, Tsui E. Recent advances in the treatment of juvenile idiopathic arthritis-associated uveitis. Therapeutic advances in ophthalmology. 2021; 13:2515841420984572. doi:10.1177/2515841420984572
4. Schmajuk G, Solomon DH, Yazdany J. Patterns of disease-modifying antirheumatic drug use in rheumatoid arthritis patients after 2002: a systematic review. Arthritis Care Res. (Hoboken). 2013; 65(12):1927-35. doi:10.1002/acr.22084
5. Holdsworth EA, Donaghy B, Fox KM, et al. Biologic and targeted synthetic DMARD utilization in the United States: Adelphi real world disease specific programme for rheumatoid arthritis. Rheumatology and Therapy. 2021; 8(4):1637-49. doi:10.1007/s40744-021-00357-1
6. Grazziotin LR, Currie G, Twilt M, et al. Real-world data reveals the complexity of disease modifying anti-rheumatic drug treatment patterns in juvenile idiopathic arthritis: an observational study. Pediatric Rheumatology. 2022; 20(1):25. doi:10.1186/s12969-022-00682-x
7. Beukelman T, Ringold S, Davis TE, et al. Disease-modifying antirheumatic drug use in the treatment of juvenile idiopathic arthritis: a cross-sectional analysis of the CARRA Registry. J. Rheumatol. 2012; 39(9):1867-74. doi:10.3899/jrheum.120110

Accepted Article

8. Marshall A, Gupta K, Pazirandeh M, et al. Treatment patterns and economic outcomes in patients with juvenile idiopathic arthritis. ClinicoEconomics and outcomes research : CEOR. 2019; 11:361-71. doi:10.2147/ceor.S197117

9. Lee WJ, Briars L, Lee TA, et al. Use of tumor necrosis factor-alpha inhibitors in children and young adults with juvenile idiopathic arthritis or rheumatoid arthritis. Pharmacotherapy. 2016; 36(12):1201-9. doi:10.1002/phar.1856

10. Mannion ML, Xie F, Curtis JR, et al. Recent trends in medication usage for the treatment of juvenile idiopathic arthritis and the influence of tumor necrosis factor inhibitors. J. Rheumatol. 2014; 41(10):2078-84. doi:10.3899/jrheum.140012

11. Nguyen K, Barsalou J, Basodan D, et al. A decade of progress in juvenile idiopathic arthritis treatments and outcomes in Canada: results from ReACCh-Out and the CAPRI registry. Rheumatology. 2023. doi:10.1093/rheumatology/kead560

12. Kulaylat AS, Schaefer EW, Messaris E, et al. Truven Health Analytics MarketScan Databases for Clinical Research in Colon and Rectal Surgery. Clin. Colon Rectal Surg. 2019; 32(1):54-60. doi:10.1055/s-0038-1673354

13. IBM MarketScan research databases for life sciences researchers. IBM Watson Health. https://www.ibm.com/downloads/cas/0NKLE57Y. Accessed 24 December 2023.

14. von Elm E, Altman DG, Egger M, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007; 335(7624):806-8. doi:10.1136/bmj.39335.541782.AD

15. Horton DB, Xie F, Chen L, et al. Oral glucocorticoids and incident treatment of diabetes mellitus, hypertension, and venous thromboembolism in children. Am. J. Epidemiol. 2021; 190(3):403-12. doi:10.1093/aje/kwaa197

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16. Horton DB, Yang Y, Neikirk A, et al. Impact of the COVID-19 pandemic on the management of juvenile idiopathic arthritis: Analysis of United States commercial insurance data. J. Clin. Rheumatol. 2023; 29(8):388-95. doi:10.1097/rhu.0000000000002035
17. Novartis drug Ilaris® approved by FDA to treat active systemic juvenile idiopathic arthritis, a serious form of childhood arthritis. https://www.fiercepharma.com/pharma/novartis-drug-ilaris%C2%AE-approved-by-fda-to-treat-active-systemic-juvenile-idiopathic-arthritis.
18. Johns Hopkins Arthritis News on FDA Approval of Sulfasalazine for treament of Juvenile Rheumatoid Arthritis (JRA). https://www.hopkinsarthritis.org/arthritis-news/johns-hopkins-arthritis-news-on-fda-approval-of-sulfasalazine-for-treament-of-juvenile-rheumatoid-arthritis-jra/
19. CenterWatch. https://www.centerwatch.com/
20. FDA Approves Expanded Use Of ENBREL® (etanercept) To Treat Children With Chronic Moderate-To-Severe Plaque Psoriasis. https://www.amgen.com/newsroom/press-releases/2016/11/fda-approves-expanded-use-of-enbrel-etanercept-to-treat-children-with-chronic-moderatetosevere-plaque-psoriasis.
21. U.S. FDA approves Pfizer's XELJANZ® (tofacitinib) for the treatment of active polyarticular course juvenile idiopathic arthritis. News release. Pfizer. 2020. https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-pfizers-xeljanzr-tofacitinib-treatment. Accessed 24 March 2023.

Accepted Article

23265205, ja, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/art.43041, Wiley Online Library on [12/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

22. Goldzweig O, Hashkes PJ. Abatacept in the treatment of polyarticular JIA: development, clinical utility, and place in therapy. Drug Des. Devel. Ther. 2011; 5:61-70. doi:10.2147/dddt.S16489

23. Marzan KA. Role of adalimumab in the management of children and adolescents with juvenile idiopathic arthritis and other rheumatic conditions. Adolescent health, medicine and therapeutics. 2012; 3:85-93. doi:10.2147/ahmt.S22607

24. Yokota S, Tanaka T, Kishimoto T. Efficacy, safety and tolerability of tocilizumab in patients with systemic juvenile idiopathic arthritis. Ther. Adv. Musculoskelet. Dis. 2012; 4(6):387-97. doi:10.1177/1759720x12455960

25. Beukelman T, Patkar NM, Saag KG, 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. (Hoboken). 2011; 63(4):465-82. doi:10.1002/acr.20460

26. Ringold S, Angeles-Han ST, Beukelman T, 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 Care Res. (Hoboken). 2019; 71(6):717-34. doi:10.1002/acr.23870

27. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013; 65(10):2499-512. doi:10.1002/art.38092

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28. Klotsche J, Raab A, Niewerth M, et al. Outcome and trends in treatment of systemic juvenile idiopathic arthritis in the German national pediatric rheumatologic database, 2000-2013. Arthritis & rheumatology (Hoboken, N.J.). 2016; 68(12):3023-34. doi:10.1002/art.39796

29. Montag LJ, Horneff G, Hoff P, et al. Medication burden in young adults with juvenile idiopathic arthritis: data from a multicentre observational study. RMD open. 2022; 8(2). doi:10.1136/rmdopen-2022-002520

30. Yue X, Huang B, Hincapie AL, et al. Prescribing patterns and impact of factors associated with time to initial biologic therapy among children with non-systemic juvenile idiopathic arthritis. Paediatr. Drugs. 2021; 23(2):171-82. doi:10.1007/s40272-021-00436-4

31. HUMIRA® (adalimumab) injection, for subcutaneous use. United States Food and Drug Administration. 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125057s410lbl.pdf. Accessed 30 April 2024.

32. Naddei R, Rebollo-Giménez A, Burrone M, et al. Juvenile Psoriatic Arthritis: Myth or Reality? An Unending Debate. J Clin Med. 2023 Jan 3;12(1):367. doi: 10.3390/jcm12010367

33. Brunner HI, Schanberg LE, Kimura Y, et al. New Medications Are Needed for Children With Juvenile Idiopathic Arthritis. Arthritis Rheumatol. 2020;72(11):1945-1951. doi:10.1002/art.41390

34. Zhao Y, Sullivan E, Son MB, et al. Psoriasis rate is increased by the exposure to TNF inhibition in children with JIA. Ann. Rheum. Dis. 2022; 81(5):662-5. doi:10.1136/annrheumdis-2021-221694

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23265205, ja, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/art.43041, Wiley Online Library on [12/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

35. Burns JE, Dahlen A, Bio LL, et al. Prescribing patterns of nonrecommended medications for children with acute COVID-19. Pediatrics. 2024. doi:10.1542/peds.2023-065003

36. Angeles-Han ST, Ringold S, Beukelman T, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the screening, monitoring, and treatment of juvenile idiopathic arthritis-associated uveitis. Arthritis Care Res. (Hoboken). 2019; 71(6):703-16. doi:10.1002/acr.23871

37. Simonini G, Druce K, Cimaz R, et al. Current evidence of anti-tumor necrosis factor α treatment efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach of individual drugs. Arthritis Care Res. (Hoboken). 2014; 66(7):1073-84. doi:10.1002/acr.22214

38. Smith JA, Thompson DJ, Whitcup SM, et al. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. Arthritis Rheum. 2005; 53(1):18-23. doi:10.1002/art.20904

39. Albarouni M, Becker I, Horneff G. Predictors of response to methotrexate in juvenile idiopathic arthritis. Pediatr. Rheumatol. Online J. 2014; 12:35. doi:10.1186/1546-0096-12-35

40. Kearsley-Fleet L, Vicente González L, Steinke D, et al. Methotrexate persistence and adverse drug reactions in patients with juvenile idiopathic arthritis. Rheumatology (Oxford). 2019; 58(8):1453-8. doi:10.1093/rheumatology/kez048

41. Brewer EJ, Giannini EH, Kuzmina N, et al. Penicillamine and hydroxychloroquine in the treatment of severe juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind placebo-controlled trial. N. Engl. J. Med. 1986; 314(20):1269-76. doi:10.1056/nejm198605153142001

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42. van Straalen JW, Kearsley-Fleet L, Klotsche J, et al. Development and external validation of a model predicting new-onset chronic uveitis at different disease durations in juvenile idiopathic arthritis. Arthritis & rheumatology (Hoboken, N.J.). 2023; 75(2):318-27. doi:10.1002/art.42329

43. Stoll ML, Zurakowski D, Nigrovic LE, et al. Patients with juvenile psoriatic arthritis comprise two distinct populations. Arthritis Rheum. 2006; 54(11):3564-72. doi:10.1002/art.22173

44. United States population growth by region. United States Census Bureau. https://www.census.gov/popclock/data_tables.php?component=growth. Accessed 14 February 2024.

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23265205, ja, Downloaded from https://acrjournals.onlinelibrary.wiley.com/doi/10.1002/art.43041, Wiley Online Library on [12/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

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Figure Legends

Figure 1. Initiation of DMARDs by drug class or category in children with JIA, 2001-2022

This figure displays the percentage of total new episodes per year of each DMARD class or category in children with JIA in MarketScan between the years 2001 and 2022. A DMARD claim was considered a new episode if a patient had no claim for the same DMARD within 365 days prior to the current DMARD claim. Each patient could contribute more than one eligible new DMARD episode. csDMARDs included methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine; bDMARDs included etanercept, adalimumab, infliximab, certolizumab, golimumab, tocilizumab, anakinra, canakinumab, rilonacept, abatacept, ustekinumab, secukinumab, and rituximab; TNF inhibitors included etanercept, adalimumab, infliximab, certolizumab, and golimumab; IL-6 inhibitors included tocilizumab; IL-1 inhibitors included anakinra, canakinumab, and rilonacept; JAK inhibitors included tofacitinib, baricitinib, and ruxolitinib; and other bMDARDs included abatacept, ustekinumab, secukinumab, and rituximab.

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Figure 2. Initiation of TNFi in children with JIA, 2001-2022

ADA, adalimumab; CER, certolizumab; ETA, etanercept; GOL, golimumab; INF, infliximab; JIA, juvenile idiopathic arthritis; TNFi, tumor necrosis factor inhibitors.

This figure displays the percentage of total new episodes per year of each TNFi in children with JIA in MarketScan between the years 2001 and 2022. A DMARD claim was considered a new episode if a patient had no claim for the same DMARD within 365 days prior to the current DMARD claim. Each patient could contribute more than one eligible new DMARD episode. Select relevant events in the timeline are marked by vertical lines and corresponding labels.

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Figure 3. Initiation of non-TNFi b/tsDMARDs in children with JIA, 2001-2022

ABA, abatacept; BAR, baricitinib; bDMARDs, biologic disease-modifying antirheumatic drugs; JIA, juvenile idiopathic arthritis; RTX, rituximab; RUX, ruxolitinib; SAR, sarilumab; SEC, secukinumab; TNFi, TNF inhibitors; TOC, tocilizumab; TOF, tofacitinib; tsDMARDs, targeted synthetic disease-modifying antirheumatic drugs; UPA, upadacitinib; UST, ustekinumab.

This figure displays the percentage of total new episodes per year of b/tsDMARDs besides TNFi and IL-1 inhibitors in children with JIA in MarketScan between the years 2001 and 2022. A DMARD claim was considered a new episode if a patient had no claim for the same DMARD within 365 days prior to the current DMARD claim. Each patient could contribute more than one eligible new DMARD episode. Select relevant events in the timeline are marked by vertical lines and corresponding labels.

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Figure 4. Initiation of csDMARDs in commercially insured children with JIA, 2001-2022

csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; HCQ, hydroxychloroquine; JIA, juvenile idiopathic arthritis; LEF, leflunomide; MTX, methotrexate; SSZ, sulfasalazine.

This figure displays the percentage of total new DMARD episodes per year of each csDMARD in children with JIA in MarketScan between the years 2001 and 2022. A DMARD claim was considered a new episode if a patient had no claim for the same DMARD within 365 days prior to the current DMARD claim. Each patient could contribute more than one eligible new DMARD episode.

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Figure 5. Initiation of first b/tsDMARD used after csDMARDs in children with JIA, 2001-2022

ABA, abatacept; ADA, adalimumab; bDMARD, biologic disease-modifying antirheumatic drug; csDMARDs, conventional synthetic disease-modifying antirheumatic drug; ETA, etanercept; JIA, juvenile idiopathic arthritis; TOC, tocilizumab; tsDMARD, targeted synthetic disease-modifying antirheumatic drug; UST, ustekinumab.

This figure displays the percentage of total new episodes per year of each first b/tsDMARD used after csDMARDs in children with JIA in MarketScan between the years 2001 and 2022, only including DMARDs that reached 5% in a given year. Each patient could contribute more than one eligible new DMARD episode.

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Table 1. Baseline characteristics of children with JIA who newly initiated at least one DMARD between 2001 and 2022

	N=20,258	%
Total number of new episodes	20,258	-
Total number of distinct patients with new episodes	13,696	-
Age, years, median (IQR)	14 (10, 16)	-
Age, years		
<6	2,168	10.7%
6-11	4,816	23.8%
12-18	13,274	65.5%
Sex		
Male	6,580	32.5%
Female	13,678	67.5%
Comorbidities[a]		
Psoriasis	4,287	21.2%
Uveitis	1,524	7.5%
Chronic pain disorders	1,028	5.1%
Celiac disease	143	0.7%
Region[b]		
Northeast	3,439	17.0%
North Central/Midwest	5,181	25.6%
South	7,505	37.0%
West	3,885	19.2%
Unknown	248	1.2%

DMARD, disease-modifying antirheumatic drug; IQR, interquartile range; JIA, juvenile idiopathic arthritis.

[a] Code lists are provided in Table S11.

[b] Based on United States Census data from 2020, the geographic breakdown of the overall United States population is: Northeast (17.3%), Midwest (20.8%), South (38.1%), and West (23.7%).[44]

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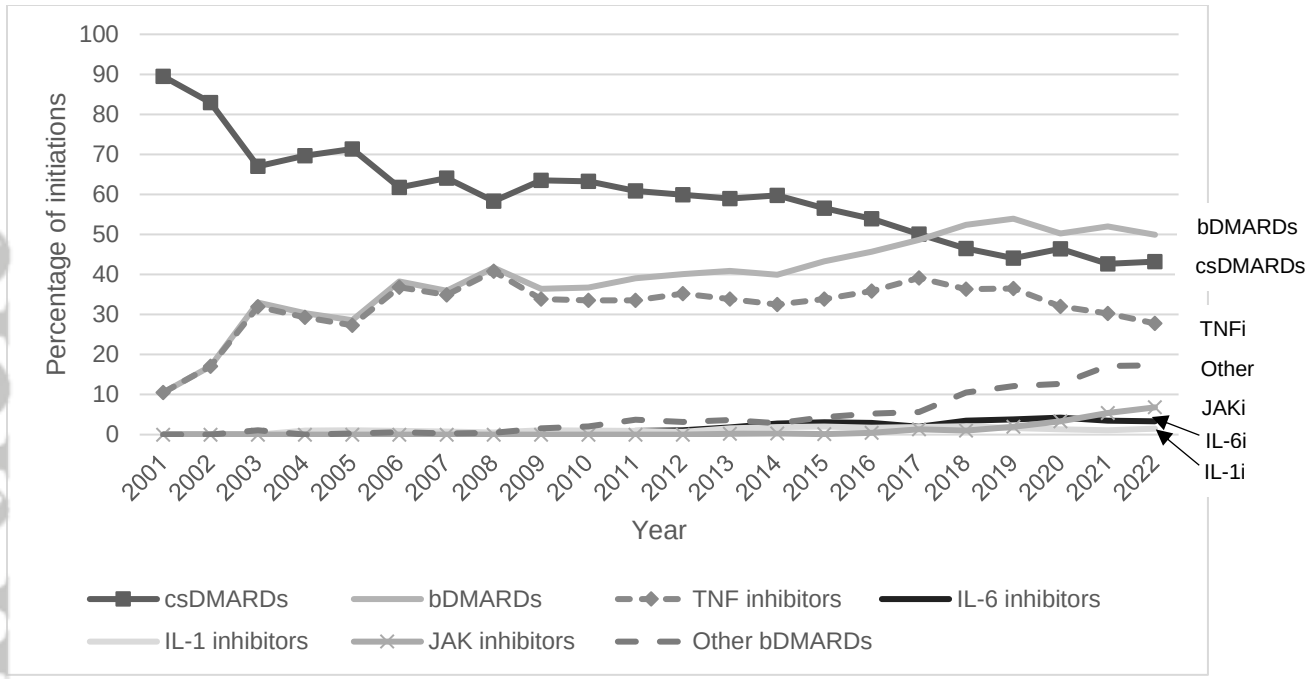

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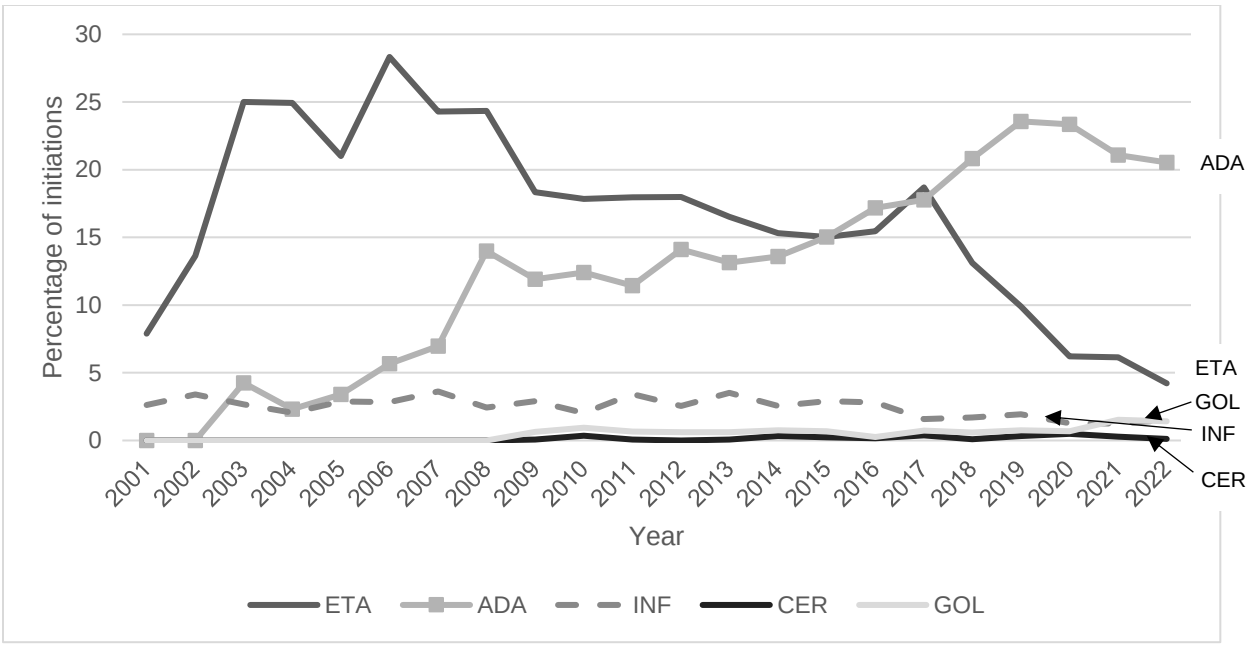

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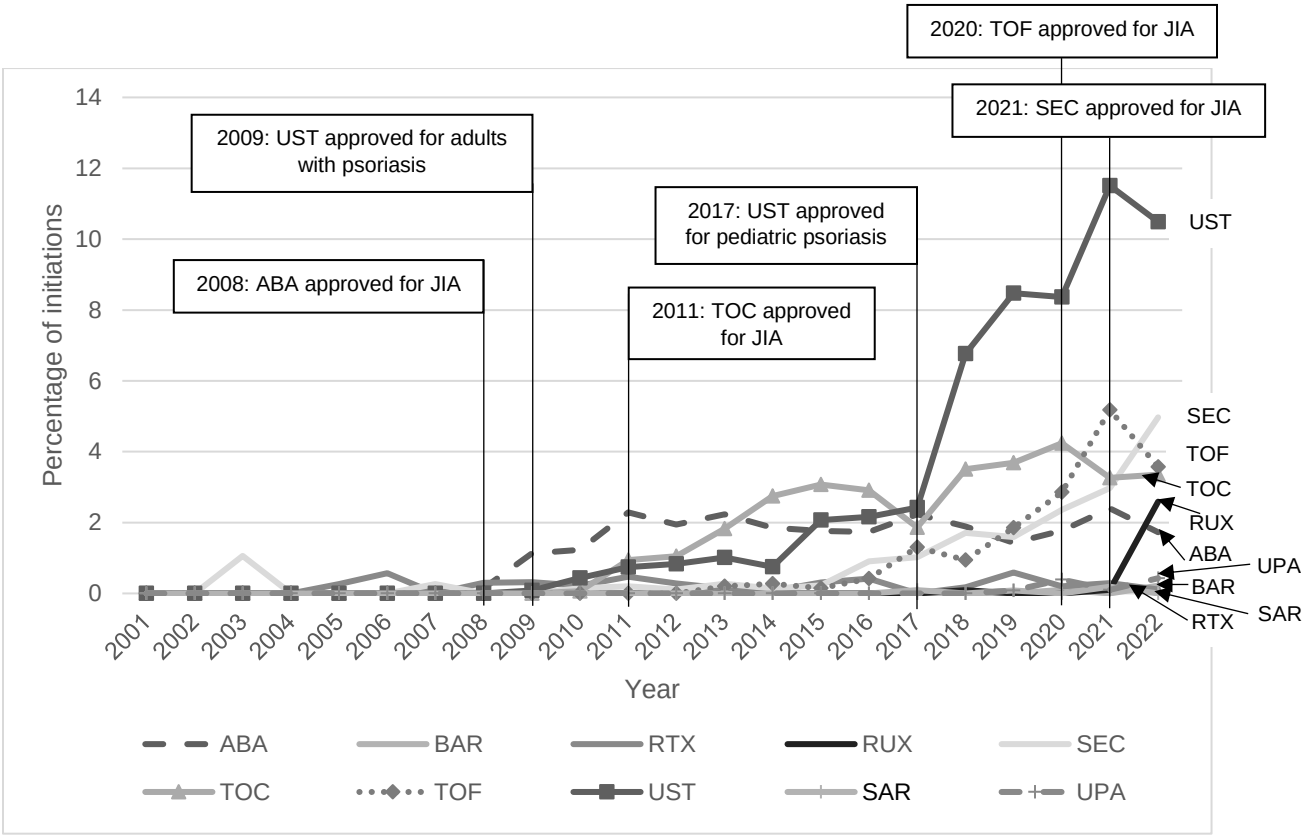

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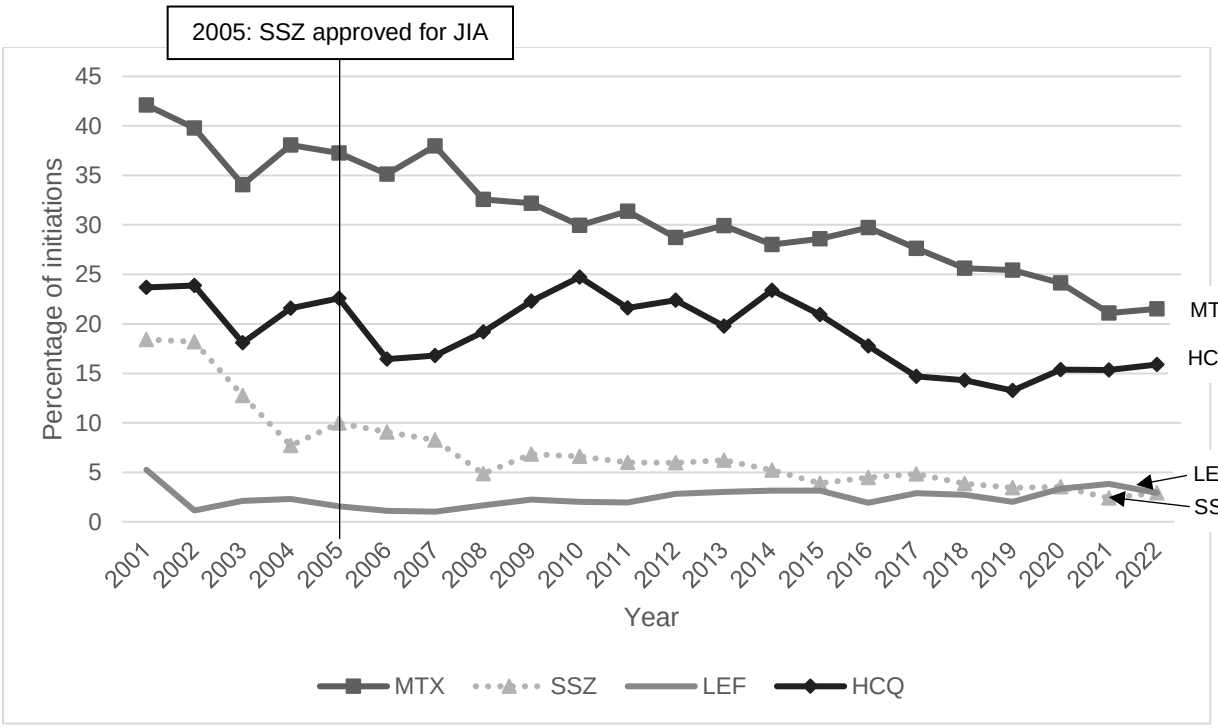

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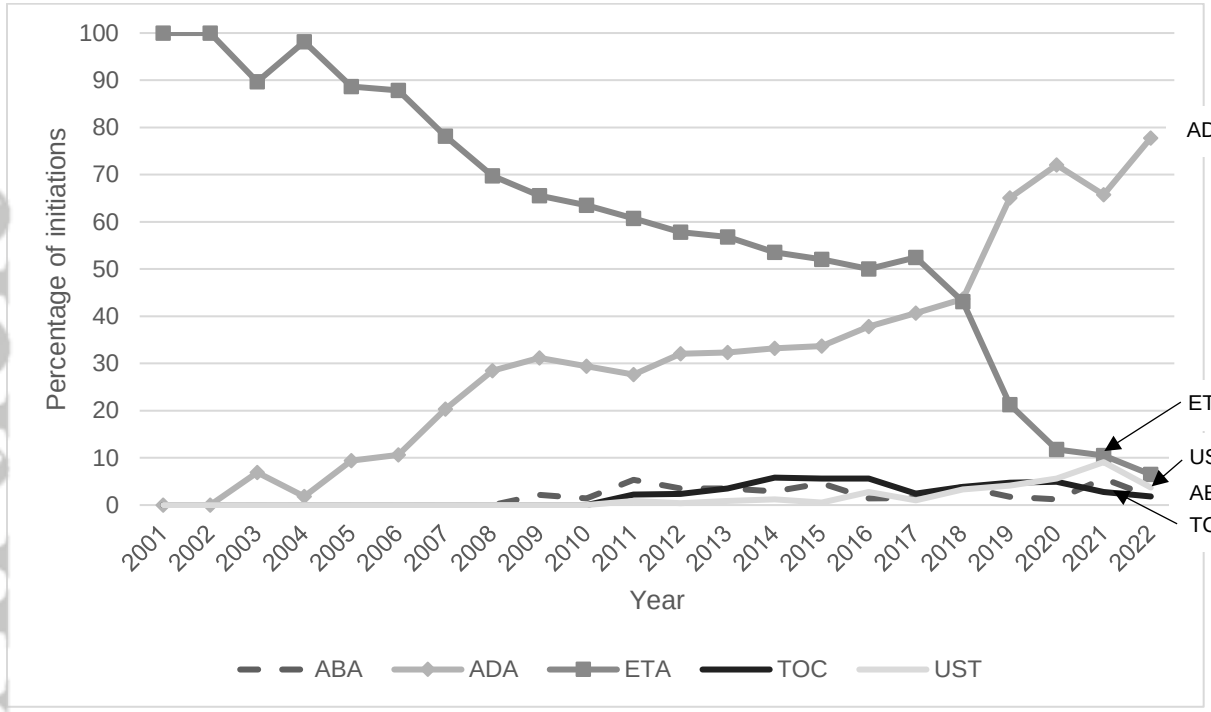

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