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Incidence and reasons for biologic and targeted synthetic DMARD switching in juvenile idiopathic arthritis: a real- life stratified analysis

Daniel Clemente[1], Leticia Leon[2,3*], Juan Carlos Nieto-Gonzalez[4], Alina Lucica Boteanu[5], Laura Trives Folguera[6], Antía Asunción García-Fernández[5], Helena Amar Muñoz[4], Aliuska Palomeque[5], Juan Carlos López Robledillo[1] and Lydia Abasolo[3]

Abstract

Background Switching biologic and targeted synthetic DMARDs (b/tsDMARD) is common in juvenile idiopathic arthritis (JIA) patients, though information about how this switching is done is scarce. This study aimed to determine the incidence rate, reasons for switching, and risk factors associated with switching due to inefficacy across different JIA subtypes.

Methods A multi-hospital electronic health record (EHR) registry was used to identify JIA patients prescribed ≥ 1 b/tsDMARD between 2000 and 2024. Patients were categorized into four JIA subgroups: oligoarticular, polyarticular, juvenile spondyloarthritis (JSpA), and systemic JIA. The primary outcomes were switching rates and switching due to inefficacy. Incidence rates (IR) were calculated per 100 patients-year. Cox multivariate regression analyses were run to assess the risk of b/tsDMARDs switching due to inefficacy, expressed as hazard ratio (HR) and 95% CI.

Results In our JIA registry, a total of 213 patients received a b/tsDMARD, with a total of 321 courses. The mean age at onset was 6.03 ± 4.44 years and 66.20% were females. The oligoarticular course group included 69 patients (32.39%), the polyarticular group 76 patients (35.68%), the JSpA group 43 patients (20.19%), and the systemic group 25 patients (11.74%). We found a total of 100 b/tsDMARD switches, with 32.05% of patients switched at least once. The systemic JIA group was more likely to swapping ($p \leq 0.001$). Through the study period, the overall switching incidence rate was 7.32 [6.01–8.90] per 100 patients-year. In the stratified analysis across JIA groups, the systemic JIA group exhibited the highest incidence (IR:17.01 [11.20-25.84]). Regarding switching due to inefficacy, global incidence was 4.53 [3.53–5.82] and again systemic JIA was the group with the highest incidence (IR: 9.28 [5.27–16.34]). Still, the adjusted multivariate final model confirms that systemic JIA needed more switching due to inefficacy (2.43 [1.01–5.89], $p = 0.04$).

*Correspondence:
Leticia Leon
lleon.hcsc@salud.madrid.org

Full list of author information is available at the end of the article

Conclusion This real-life study provides data on different switch patterns in various subtypes of JIA, confirming that patients with systemic JIA needed more switching, did more swapping strategies, and had more risk for switching due to inefficacy.

Keywords Juvenile idiopathic arthritis, Biologic and targeted synthetic DMARDs, Switching, Incidence, Risk factors

Background

Juvenile Idiopathic Arthritis (JIA) is an umbrella term encompassing all forms of arthritis persisting for at least six weeks and with onset before 16 years of age, with other potential causes excluded [1]. During the last years, the management of JIA has substantially changed thanks to the availability of new treatment options, represented mainly by biological and targeted synthetic disease-modifying drugs (b/tsDMARDs) [2].

The current classification of JIA identifies different subtypes according to clinical manifestations and immunological criteria, reflecting distinct underlying pathogenic mechanisms. Each subtype requires different therapeutic approaches and determines the choice of biological therapy when needed [3, 4]. However, evidence has shown that the efficacy of distinct b/tsDMARDs is variable across and within JIA subtypes and may change during the patient's disease course [4–6]. Switches are common strategies used in managing JIA when the first-line biologic therapy fails. Main reasons for switching are primary failure (no initial response) and secondary failure (loss of response over time). When a patient does not respond to the initial b/tsDMARD, mainly a TNF inhibitor (TNFi), the patient may receive a second TNFi (cycling strategy) or a drug with a different mechanism of action (MoA) (swapping strategy), depending on the clinical manifestations and the reasons for changing treatment.

Lack or loss of efficacy may lead to immediate switching to control disease activity more quickly. Switching therapies in JIA can lead to sustained clinical improvements and disease control, particularly when the switch is managed carefully and tailored to the patient's specific needs. Studies have shown varying success rates with switching therapies. For instance, switching from one TNFi to another can be effective, especially in cases of secondary non-response [7] [8]. Besides, safety profiles are generally consistent across different b/tsDMARDs, but individual responses can vary. Monitoring for adverse events is crucial, especially when switching therapies. Swapping therapies can sometimes reduce adverse events experienced with the initial treatment, enhancing overall treatment tolerability and adherence.

Long-term follow-up studies have highlighted that JIA patients may require multiple switches throughout their treatment journey, underscoring the importance of personalized treatment plans and regular monitoring [9]. Current clinical guidelines recommend considering a switch in b/tsDMARDs if there is an inadequate response after a defined period, typically around 3 to 6 months of treatment [10, 11]. However, although recommendations by a task force have been reported defining a treat to target (T2T) strategy for JIA [12], the best choice of a second b/tsDMARD when the initial b/tsDMARD fails remains unclear, and data based on a randomised-controlled trial and real-life experience regarding switching patterns are limited [4, 13–15]. The choice of the next b/tsDMARDs should be based on the mechanism of action, patient history, and previous adverse events [7, 8]. In contrast to adult RA, the heterogeneity of JIA needed to be addressed and accounted for in the study of drug regimens, aimed to improve the management of these patients.

This proposal is framed in the study of switching between b/tsDMARDs in JIA patients. First, we aim to explore the incidence rate and causes of switching for the different JIA groups, and to assess the incidence rate of switching due to inefficacy. Finally, we want to analyze the role of other factors in the risk of switching due to inefficacy.

Methods

Setting, study design, patients and data sources

We designed a multicenter, observational, retrospective, and longitudinal study, focused on treatments. It was conducted at 3 different public hospitals of the National Health System, in Madrid, Spain. Patients attended by a pediatric rheumatologist, who met the ILAR classification criteria for JIA [3] with age < 18 years, under b/tsDMARDs, were included. We excluded patients with short-term follow-up (< 6 months from diagnosis), those with age > 18 years, and those lacking any clinical data. Inclusion period start on January 2020 and the end of study was on June 2024.

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Parents or legal guardians gave their consent to the data collection. Ethics Review Board approval was granted by the ethic committee of the Hospital Gregorio Marañon (Reuma-01-2021). This research was executed following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.

Data were retrieved by the revision of the electronic health records (EHR) of JIA patients treated with b/tsDMARDs and collected in an ad-hoc customized database. The collected data included patients' demographic

characteristics, JIA subtypes, present or previous uveitis; autoantibody positivity such as antinuclear antibody (ANA), rheumatoid factor (RF), or anticitrullinated cyclic peptide; HLA-B27 positivity, b/tsDMARDs used, duration of treatment, and reasons for switching.

Variables

Outcomes: To achieve the study objectives, two main outcomes were established:

1. Switching between b/tsDMARDs. Reasons for switching were recorded as: (a) inefficacy, including both: primary failure or loss of efficacy; (b) moderate and severe adverse events; (c) patient decision; (d) relapse following clinical remission off medication. Inefficacy and adverse events were registered according to rheumatologist´s criteria from the clinical chart. Switching variable included cycling and swapping: cycling was defined as switching from a first b/tsDMARD to a second b/tsDMARD with same mechanism of action (MoA), not including in the definition changes between original biologic to a biosimilar. Swapping was defined as switching from a first b/tsDMARD to another b/tsDMARD with a different MoA.
2. Switching between b/tsDMARDs due to inefficacy. It was defined by the clinical presentation of one or more active joints or by active uveitis.

Independent variable JIA diagnostic groups. JIA patients were classified according to 4 groups in order to obtain clinically homogeneous groups [16, 17]. Group 1 included patients with an oligoarticular disease course, including only persistent oligoarticular JIA; group 2 included those patients who presented a polyarticular course, including extended oligoarticular JIA and both RF-negative and RF-positive polyarticular JIA; group 3 included patients with juvenile spondyloarthritis (JSpA), including enthesitis-related JIA and psoriatic JIA; and the last group 4 included patients diagnosed with systemic JIA or Still´s disease.

Covariables (1) Demographic (age and sex at birth). (2) Baseline disease-related (date of symptoms, laboratory parameters [anticitrullinated cyclic peptide (Anti-CCP), antinuclear antibody (ANA), rheumatoid factor (RF) and HLA B27]). (3) Exposure to b/tsDMARDs during follow-up, encompassing the following groups: (a) Tumor necrosis factor (TNF)-alpha inhibitors (TNFi) (Infliximab, Adalimumab, Etanercept, Golimumab); (b) anti-interleukin agents: anti-IL-1 (Anakinra and Canakinumab); anti-IL-6 (Tocilizumab, Sarilumab); (c) selective immunosuppressant (SI) (Abatacept); (d) JAKi (Tofacitinib, Baricitinib). 4) Other concomitant therapy (methotrexate, considered exposed if the patient were using for at least 6 months); and 5) calendar time: dividing the starting time of each b/tsDMARDs in time period intervals based on treatment strategies (2000–2010; 2010–2019; 2019–2024).

Statistical analysis

The statistical analysis included descriptive assessments of the sociodemographic factors, clinical characteristics and treatment details for all patients included in the study. A detailed description of the clinical course, treatment switches to b/tsDMARDs, and causes was carried out, both globally and stratified by JIA groups. Frequency distributions were used for qualitative variables, while means and standard deviations or medians and percentiles were reported for quantitative variables. For the study of bivariate associations, the student's t-test were used for the analysis of continuous variables with normal distribution. Continuous variables with non-normal distribution were analyzed with the Mann-Whitney test or the Kruskal-Wallis test if there are more than 2 categories. The categorical variables were analyzed with Chi-square or the Fisher Test.

To explore switching between b/tsDMARDs, we included all the patients with JIA. The study exposure period was defined as the time from the baseline visit (the start date of the first b/tsDMARD therapy) until the occurrence of any of the following events: loss to follow-up, b/tsDMARD switching, transition to adulthood (18 years), or the end of the study. Kaplan–Meier curves were set to account for switching over time. Incidence rates (IR) of total switching and switching due to inefficacy were estimated by survival techniques (allowing for multiple-failure per patient), expressing the IR per 100 patient-years with their respective 95% Confidence Interval (CI). Cox bivariate analyses were conducted to assess the differences between demographic, clinical covariates and the risk of switching due to inefficacy. Cox multivariate regression analyses were run to assess the role of the different groups of b/tsDMARDs in switching due to inefficacy. Other covariates were also investigated. In the multivariate analysis, we included age, sex, calendar time, other related factors previously identified, and all variables with a p-value < 0.2 in the bivariate analysis. It is important to note that the way in which b/tsDMARDs prescription was done in real-life conditions, shaped the analysis. Patients were divided into periods according to the retention rate of each b/tsDMARDs that determined the presence or not of an event in that time frame. The analysis was run considering a patient-level clustering approach. Variables such as MTX and calendar time were analysed in a time dependent manner. The results of the regression models were expressed by hazard ratio (HR) and 95% CI. We limited the number of variables in the multivariate model following the rule of Freeman [18] and the value of 10 events per variable [19, 20]. Variables

with more than 10% of missing values were not used in the multivariate analysis. Proportional hazard assumption was tested using Schoenfeld residuals and the scaled Schoenfeld residuals. A two-tailed *p*-value under 0.05 was considered to indicate statistical significance. Statistical analyses were performed using STATA software (Stata Corp, College Station, TX, USA).

Results

In our JIA patient's registry, a total of 213 patients received a b/tsDMARD, with a total of 321 courses. The total study follow up was 1,366.1 patients-year, with a median of 7.5 [4.9–11.1] years and a maximum of 17 years. The mean age of patients at diagnosis was 6.03 ± 4.44 years and 66.20% were females. The mean age at b/tsDMARD onset was 8.35 ± 4.84 years. The oligoarticular course group consisted of 69 patients (32.39%), the polyarticular group 76 patients (35.68%), the JSpA (10.9%) group 43 patients (20.19%), and the systemic group 25 patients (11.74%). The demographic characteristics are shown in Table 1. As expected, there were some clinical differences between the JIA groups, including age at disease onset, sex, treatment received, and the prevalence of uveitis or autoimmunity.

As first-line b/tsDMARDs therapy, TNFi were the most used b/tsDMARDs, representing almost 90% of the choices, although in systemic JIA, as expected, anti-IL1 and anti-IL6 were most used. Regarding other therapies, a large majority of patients were also on concomitant methotrexate (Table 1).

During the study period, patients received 312 courses of b/tsDMARDs therapy. Only a course was prescribed in 145 patients, while 68 and 18 patients received two and three consecutive b/tsDMARDs respectively. Thus, 13 patients had more than four courses of b/tsDMARDs (Fig. 1). Most frequent drugs used in all courses were TNFi with 244 (78.2%) courses (mainly adalimumab and etanercept), followed by anti-IL-6, with 37 courses (mainly tocilizumab), and anti-IL-1, with 26 courses (mainly anakinra).

There were 168 b/tsDMARDs discontinuations. The main reason for discontinuation was improvement (43.45%), followed by inefficacy (33.93%), and by the occurrence of an adverse event (10.71%). The remaining courses were discontinued due to patient decision. Regarding adverse events, most of them were moderate mainly related to skin reactions. Concerning the eight discontinuations due to severe adverse events, we recorded infections, laboratory alterations, one severe anaphylaxis and two cancers. No deaths were in our patients.

Most of these discontinuations led to treatment switches, with a total of 100 ts/bDMARD switches recorded. A 32.05% of patients switched bDMARDs at least once. Differences in switching patterns were observed across JIA groups. Figure 2 provides a detailed breakdown of the reasons for switching, stratified by JIA group. The primary reasons for switching were lack of efficacy (62%) and the need to restart treatment due to relapse after clinical remission off medication (26%).

Regarding type of switching, most of them were related to cycling (59%). Specifically by groups of diagnosis, the oligoarticular group, the polyarticular group and the JSPA group were more likely to cycling, while the systemic group was more likely to swapping ($p \leq 0.001$) (Fig. 3). Moreover, we found differences between the cycling and swapping strategies attending the reason for switching, with more swapping due to inefficacy, and

Table 1 Baseline characteristics of JIA patients included in the study, globally and according to JIA group

	Total ***n*** **= 213**	**Oligoarticular course,** ***n*** **= 69**	**Polyarticular course,** ***n*** **= 76**	**Juvenile Spondyloarthritis,** ***n*** **= 43**	**Systemic JIA,** ***n*** **= 25**	***p***
Female sex; n (%)	141 (66.20)	51 (73.91)	60 (78.95)	14 (32.56)	16 (64)	**< 0.001**
Age at diagnosis; mean ± SD (years)	6.03 ± 4.44	3.93 ± 2.79	5.89 ± 4.64	9.75 ± 3.60	5.88 ± 4.44	**< 0.001**
Age at first b/tsDMARD; mean ± SD (years)	8.35 ± 4.34	6.96 ± 3.92	7.97 ± 4.76	11.69 ± 4.33	7.64 ± 5.67	0.11
Presence of uveitis; n (%)	57 (26.76)	35 (50.72)	14 (18.42)	8 (18.60)	0	**< 0.001**
ANAS; n (%) (*n* = 209)	86(41.15)	44(63.77)	35(47.30)	6(14.63)	1(4)	**< 0.001**
RF; n (%)(*n* = 206)	16(7.77)	0	15(20.27)	0	1(4.35)	**< 0.001**
Anti-CCP; n (%)(*n* = 146)	10 (6.85)	1(2.33)	9 (16.07)	0	0	**0.006**
HLA-B27; n (%) (*n* = 172)	33(19.19)	2(3.64)	8(13.11)	23(54.76)	0	**< 0.001**
Concomitant Methotrexate; n (%)	197 (92.49)	69 (100)	75 (98.68)	33 (76.74)	20(80)	**< 0.001**
ts/bDMARDs; n (%)	191 (89.67)	69 (100)	73 (96.05)	43 (100)	6 (24)	**< 0.001**
TNFi	7 (3.29)	0	2 (2.63)	0	5 (20)	
Anti-IL6	0	0	0	0	0	
SI	15(7.04)	0	1 (1.32)	0	14 (56)	
Anti-IL1	0	0	0	0	0	
JAKi						

Values in bold are statistically significant. JIA: juvenile idiopathic arthritis; SD: standard deviation; Anti-CCP: anticitrullinated cyclic peptide; ANA: antinuclear antibody; bDMARD: biologic disease-modifying antirheumatic drug; JIA: juvenile; SI: selective inhibitor

Oligoarticular group (n=69) N (%)	Polyarticular group (n=76) N (%)	JSpA group (n=43) N (%)	Systemic group (n=25) N (%)	
1st ts/bDMARD •Anti-TNF: 69 (100)	**1st ts/bDMARD** •Anti-TNF: 73 (96.05) •IL-6: 2 (2.63) •IL-1: 1 (1.32)	**1st ts/bDMARD** •Anti-TNF : 43 (100)	**1st ts/bDMARD** •Anti-TNF: 6 (24) •IL-6: 5 (20) •IL-1: 14 (56)	
2nd ts/bDMARD •Anti-TNF: 17 (77.27) •IL-6: 4 (18.18) •SI: 1 (4.55)	**2nd ts/bDMARD** •Anti-TNF : 19 (70.37) •IL-6: 7 (25.93) •SI: 1 (3.70)	**2nd ts/bDMARD** •Anti-TNF : 7 (87.50) •IL-6: 1 (12.50)	**2nd ts/bDMARD** •Anti-TNF: 1 (9.09) •IL-6: 8 (72.73) •IL-1: 2 (18.18)	**1th switch or 2nd course (n=68)**
3nd ts/bDMARD •Anti-TNF: 2 (50) •IL-6: 1 (25) •JAKi: 1 (25)	**3nd ts/bDMARD** •Anti-TNF : 4 (57.14) •IL-6: 2 (28.57) •SI: 1 (14.29)	**3nd ts/bDMARD** •Anti-TNF : 1 (50) •IL-6: 1 (50)	**3nd ts/bDMARD** •IL-1: 5 (100)	**2nd switch or 3rd course (n=18)**
4nd ts/bDMARD •IL-6: 1 (100)	**4nd ts/bDMARD** •IL-6: 1 (100)	**4nd ts/bDMARD** •IL-6: 2 (100)	**4nd ts/bDMARD** •Anti-TNF: 1 (25) •IL-6: 1 (25) •IL-1: 2 (50)	**3rd switch or 4th course (n=8)**
5nd ts/bDMARD •IL-6: 1 (100)			**5nd ts/bDMARD** •IL-1: 2 (100)	**4th switch or 5th course (n=3)**
6nd ts/bDMARD •Anti-TNF:1 (100)				**5th switch or 6th course (n=1)**
7nd ts/bDMARD •JAKi: 1 (100)				**6th switch or 7th course (n=1)**

Fig. 1 Treatment courses across JIA groups

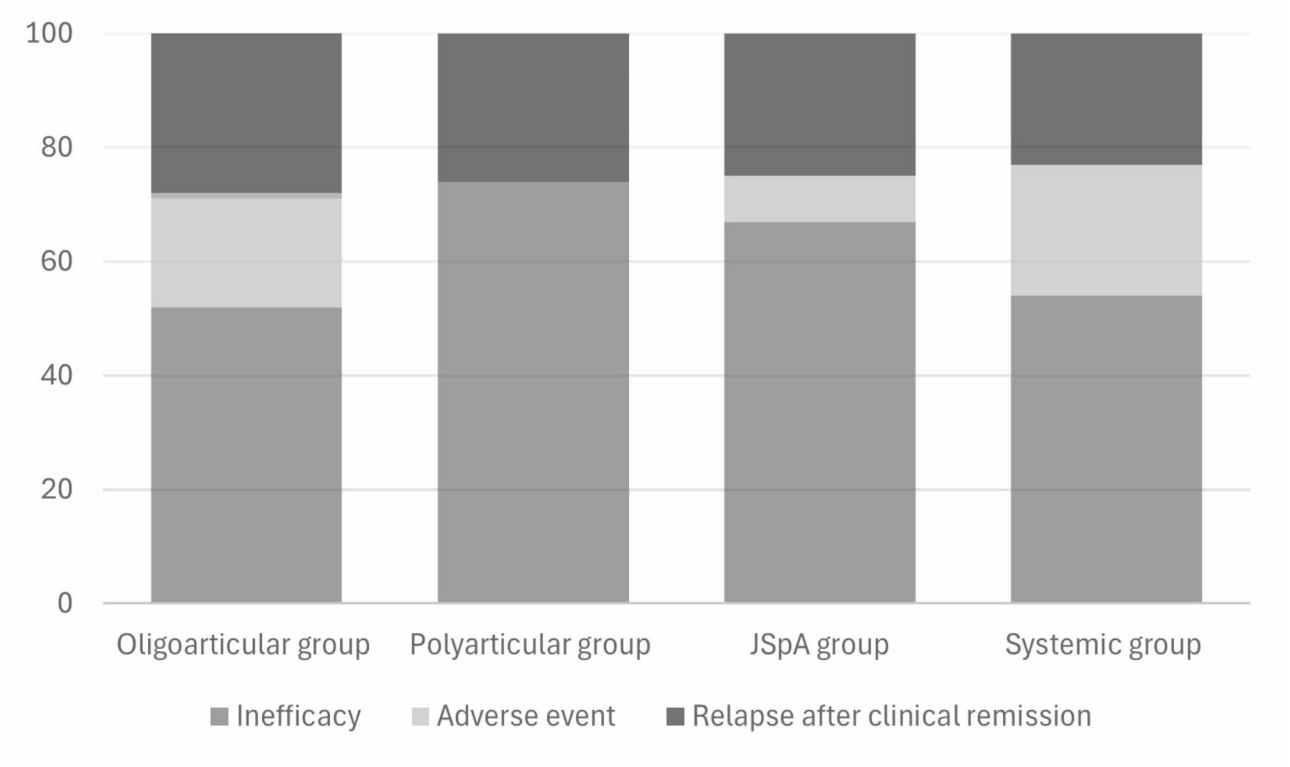

Fig. 2 Main causes for switching by JIA groups

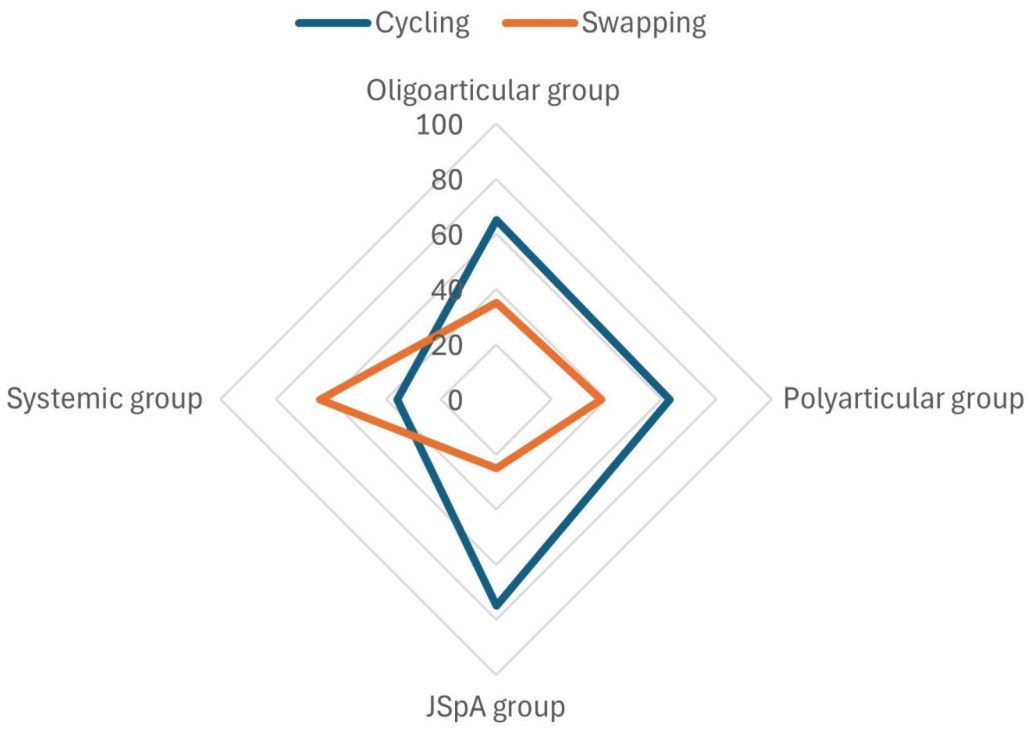

Fig. 3 Switching strategies by JIA groups

more cycling due to uveitis or new course after a remission period ($p \leq 0.001$).

Through the study period, the IR of total switching was estimated in 7.32 [6.01–8.90] per 100 patients-year, being similar between sex (IR: 7.46 [5.33–10.44] for females, IR: 7.24 [5.69–9.22] for males). Regarding age groups, older patients (between 15 and 18 years of age) had the highest IR of switching (8.75 [5.51–13.89]). In the stratified analysis across JIA groups, the systemic JIA group exhibited the highest incidence (IR:17.01 [11.20-25.84]), whereas for polyarticular group (IR: 6.58 [4.72–9.16]) and oligoarticular group (IR: 6.86 [4.82–9.75] the IR were similar. The JSpA group had the lowest incidence of the four categories (IR: 4.73 [2.69–8.34]).

Regarding switching due to inefficacy, global incidence was 4.53 [3.53–5.82], being similar between sexes (IR: 4.61 [3.40–6.24] for females, and IR: 4.39 [2.83–6.80] for males). In the stratified analysis between JIA groups, systemic JIA was the group with the highest incidence (IR: 9.28 [5.27–16.34]), followed by polyarticular group (IR: 4.89 [3.32–7.18]), oligoarticular group (IR: 3.54 [2.16–5.78] and the JSpA group (IR: 3.15 [1.57–6.31]). The survival data for the b/tsDMARDs in the different JIA groups are shown in Fig. 4.

The results of the univariate analysis for switching due to inefficacy are detailed in Table 2. Although variables included did not reach statistical significance, several achieve a trend towards. The multivariable analysis was adjusted for age, sex, and time period of b/tsDMARDs prescription. The model showed that patients with systemic JIA needed more switching due to inefficacy (2.43 [1.01–5.89], $p = 0.04$) compared to oligoarticular group. We found other interesting findings such as the effect of year of prescription, increasing risk from 2019 onwards compared to the previous decade (1.50 [1.01–2.25], $p = 0.04$) (Table 2).

Concerning other co-variables, patients older than six years old reported a lower risk of switching, while females were associated with higher risk than males, however the differences reported for both variables did not reach statistical significance.

Notably, other variables such as concomitant methotrexate use ($p = 0.83$) or time to first b/tsDMARDs ($p = 0.23$) did not reach significance and were dropped from the model. The proportionality of this regression model was tested with a p value = 0.11.

Discussion

This study provides a contemporary picture of therapeutic sequencing among JIA patients treated with b/tsDMARDs in real life conditions, suggesting that long-term control of JIA may require different therapeutic switching strategies. Despite other articles reporting the switching frequency in patients with JIA, our study goes one step

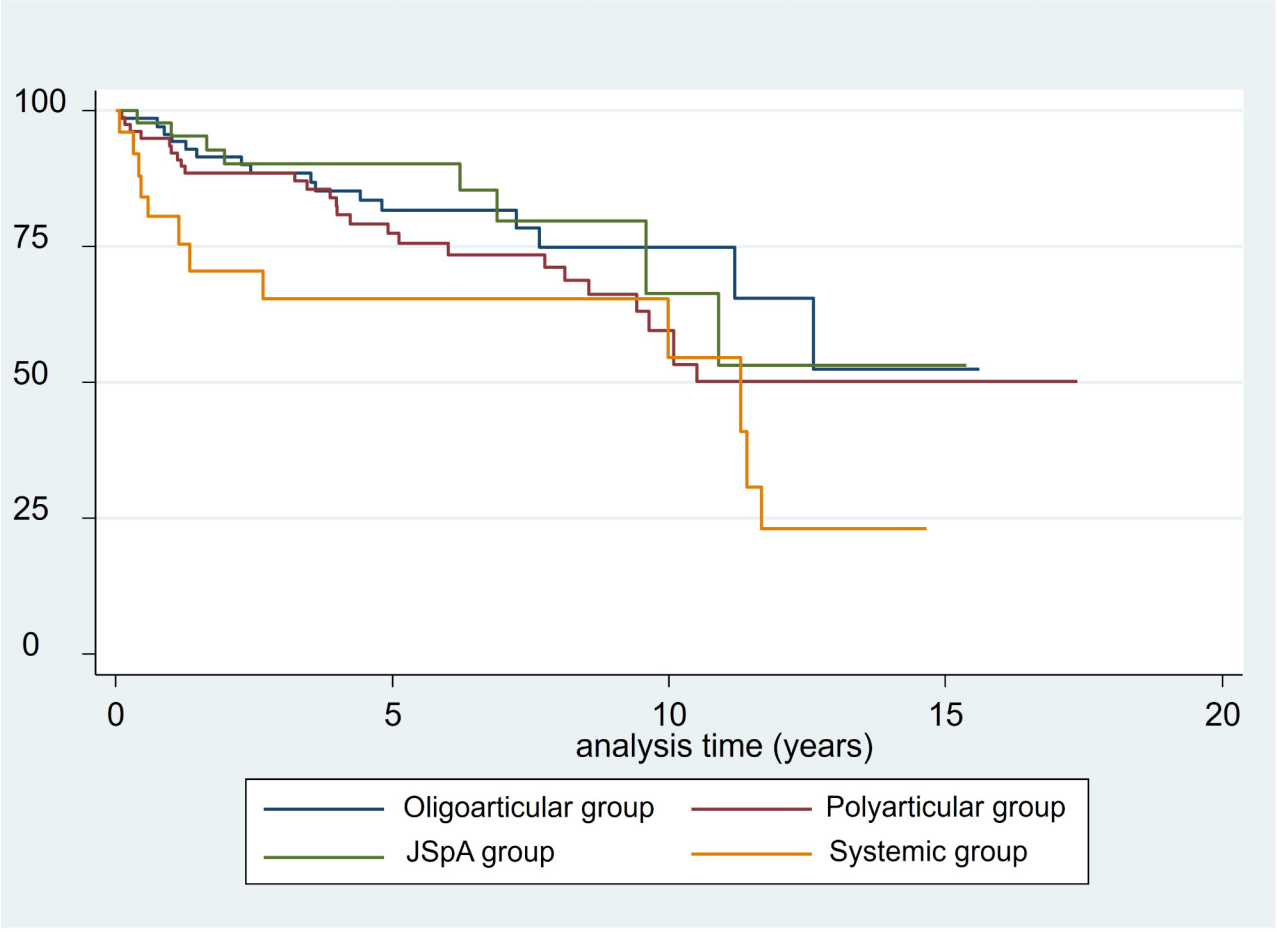

Fig. 4 Kaplan-Meier survival estimates curves for inefficacy by JIA groups

Table 2 Cox regression analysis assessing variables associated to risk of switch in patients who have experienced inefficacy

	Univariate analysis		Multivariate analysis	
	Hazard Ratio CI [95%]	***P value***	**Hazard Ratio CI [95%]**	***P value***
Female sex	1.05 [0.57–1.96]	0.85	1.07[0.59–1.95]	0.80
Age at ts/bDMARDs ≥ 6 years	0.73[0.49–1.09]	0.13	0.73[0.48–1.12]	0.15
JIA group:	1	-	1	-
o-JIA	1.34 [0.61–2.96]	0.46	1.46 [0.66–3.21]	0.34
poly-JIA	0.90 [0.30–2.60]	0.83	1.06 [0.34–3.32]	0.90
ERA/JPsA	2.43 [0.96–6.10]	0.05	2.43 [1.01–5.89]	0.04
sJIA				
Year of b/tsDMARDs prescription (≥ 2019)	1.47 [0.35–3.67]	0.12	1.50 [1.01–2.25]	0.04
Concomitant Methotrexate	1.13 [0.61–2.96]	0.83	-	-
Refractory disease	1.45[0.75–2.79]	0.26	-	-

b/tsDMARDs: Targeted synthetic and Biologic Disease Modifying anti-rheumatic drugs; CI: confidence interval. Refractory disease defined as resistance to ≤ 2 b/tsDMARDs with different mechanisms of action

further and compare the incidence, causes and strategies of switching for all JIA groups.

We found that 32% of patients undergoing biological or targeted synthetic drugs require b/tsDMARDs switching. Our data are in line with previous studies, where the data showed percentages around 22–40% [4, 13, 21, 22]. Based on our results and previous studies, the proportion of patients on biological treatments who require switching has been approaching 30%. This trend is driven by the increasing availability of therapies and the implementation of the T2T strategy, which aims to achieve clinical remission and, in turn, contributes to the rise in treatment switches.

Each JIA subtype requires different therapeutic approaches, so drug choices differed according to the groups. In our study, TNFi was the most commonly used first-line biologic drug in non-systemic JIA, while IL-1 was preferred in patients with systemic JIA. Among the patients who needed to switch, 20 patients met the definition of refractory disease, being mostly in the systemic JIA group, possibly reflecting a more difficult treatment approach. In fact, few patients need more than 4 b/tsDMARDs courses, and in our study only 13 of the courses were above fourth lines of treatment, with more than half belonging to the systemic patients. However, the study patient who needed more courses was an oligoarticular patient with refractory uveitis. Previous studies confirmed that presence of ANA positivity and uveitis was strongly associated with disease activity and need for systemic therapy in oligoarticular patients [9, 23].

Considering the diagnoses of the patients who required switching, systemic and poliarticular course were the groups with the most frequent b/tsDMARDs changes, in line with other recent study from Turkey and previous registries, like BiKeR, CARRA, or Dutch ABC [13, 21, 24, 25].

This suggests that achieving remission may be more challenging in systemic and polyarticular JIA, and that children with these disease courses may require additional strategies to improve long-term outcomes. The growing use of switching strategies aligns with the ongoing effort to achieve minimally active or inactive disease, as recommended by T2T guidelines. In patients with JIA, this has been accompanied by an increase in b/tsDMARD use and improved clinical outcomes [24, 26].

Another important topic to discuss is that due to the high percentage of relapses after clinical remission, it is probably advisable about treatment should be tapered cautiously, using lower doses to maintain clinical remission, including their transition to adulthood period [27].

Inefficacy was the main reason for switching and was recorded in 62% of all switches. This percentage is somewhat higher than those reported to date in adults [28].

Systemic JIA was the group with more switches due to inefficacy and it was also the group where the swapping strategy was used over cycling. While several studies on comparative effectiveness between cycling and swapping strategies in rheumatic disease in adulthood, in JIA this data is scarce. A study found that the response to a second biologic was similar between JIA patients who switched to a biologic of the same class and those who switched to a biologic of a different class [4]. The ACR 2019 guideline proposal about treatment of juvenile idiopathic arthritis for whom an initial TNFi was ineffective recommend switching to a non-TNFi (IL-6 or SI like abatacept) [10]. Differentiation of therapeutic approaches according to disease phenotype is in line with ACR recommendations for the treatment of JIA [10, 11].

In our study, we explored predictive factors of switches due to inefficacy. In addition to systemic disease as a risk factor for increased switching, patients with courses starting after 2019 were found to have a significantly higher risk of switches, probably due to the full implementation of T2T strategy in clinical practice. All this may be related, moreover, to the rapidly increasing number of new therapies on the market along with the publication of the ACR recommendations for the treatment of JIA.

Nevertheless, this research also has certain limitations to consider. The main limitations of this study are those that affect any retrospective observational studies, since we collected data of a broad non-selected real-world patient spectrum and a wide variety of treatment options. Moreover, all this data were available for analysis, allowing adjustment for confounders to elude possible bias. Given the extended follow-up, some of the data may reflect clinical practice that has changed over time. To alleviate this imbalance, we have included the calendar time variable in the analysis. Because of the nature of the available clinical documentation, we were not able to incorporate validated disease activity measures. To enhance the external validity of our results, we categorized our registry into four groups based on the relevant pathophysiological mechanisms. However, the polyarticular course group may still be heterogeneous, as it includes patients who are ANA positive. Finally, our study was performed in a single healthcare system, thus our results may not be generalizable to populations outside Spain, e.g. countries with restricted availability of financial coverage for b/tsDMARDs.

Our study has several strengths. First, we included a large EHR-based patients registry with a long follow-up, including detailed data on prescription history as well as laboratory data and clinical notes. We investigated the reasons for b/tsDMARD discontinuation using a detailed review of medical records. Furthermore, we used separate JIA patient groups to describe incidences and reasons for medication switching, in contrast to previous research that often grouped all JIA patients, only systemic or non-systemic JIA. In addition, this real-life study provides valuable data on different switches pattern in different subtypes of JIA regarding efficacy, and comparing cycling and swapping strategies. Furthermore, we explored the predictive factors of switches due to inefficacy, which has not been investigated so far.

In summary, this real-life study provides valuable data on the course of treatment in patients with JIA, as well as on the differences on switching patterns of b/tsDMARDs, focusing on inefficacy. This study also compares swapping vs. cycling of b/tsDMARDs strategies.

Contemporary therapeutic goals include early achievement of complete clinical remission, and achievement of a better quality of life. Because of that, nowadays, more switches are made due to inefficacy, looking for better patient outcomes. Defining differences in treatment response across JIA subtypes enables clinicians to make more relevant treatment decisions. The increasing number of available drugs and the treat-to-target paradigm make this issue even more relevant for clinical practice, so additional research on patients who require multiple treatments is needed to develop personalized treatment pathways.

Conclusions

In conclusion, results from our study suggest that the percentage of patients with JIA switching from one b/tsDMARDs to another one during follow-up varies between JIA groups and it increases substantially over time. The systemic JIA group was more likely to swapping, and also, in the stratified analysis across JIA groups, the systemic JIA group exhibited the highest incidence of switching. This underlines the important need to better understand the management of JIA patients to characterize trends in the use of b/tsDMARDs and develop personalized treatment pathways.

Abbreviations

DMARD	Disease-modifying anti-rheumatic drug
csDMARDs	Classic DMARDs
EHR	Electronic health record
b/tsDMARDs	Biologic and targeted synthetic DMARDs
JAK	Janus-Kinase
JIA	Juvenile idiopathic arthritis
JSpA	Juvenile spondyloarthritis
IQR	Interquartile range
RMD	Rheumatic and musculoskeletal diseases
TNF	Tumor necrosis factor
T2T	Treat to target
STROBE	Strengthening the reporting of observational studies in epidemiology
ANA	Autoantibody positivity such as antinuclear antibody
RF	Rheumatoid factor
ACCP	Anticitrullinated cyclic peptide
HLA	Human leukocyte antigen
MoA	Mechanism of action
IR	Incidence rates
CI	Confidence interval
HR	Hazard ratio
anti-IL	Anti-interleukin
ACR	American college of rheumatology

Author contributions

Daniel Clemente: Conceptualization, Writing–review & editing; Leticia Leon: Conceptualization, Writing–review & editing; Juan Carlos Nieto: Conceptualization, and review & editing; Alina Lucica Boteanu: Conceptualization, and review & editing; Laura Trives Folguera: Conceptualization, and review & editing; Antía Asunción García Fernández: Conceptualization, and review & editing; Helena Amar Muñoz: Conceptualization, and review & editing; Aliuska Palomeque: Conceptualization, and review & editing; Juan Carlos López Robledillo: Conceptualization, and review & editing; Lydia Abasolo: Conceptualization, Writing– review & editing.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Parents or legal guardians gave their consent to the data collection. Ethics Review Board approval was granted by the ethic committee of the Hospital Gregorio Marañon (Reuma-01-2021).

Consent for publication

The final manuscript has been read and approved by all authors.

Competing interests

DC declare payment or honoraria for lectures, presentations, speakers bureaus (Pfizer and GSK), support for attending meetings and/or travel (Pfizer and Rubio) and participation on a Data Safety Monitoring Board or Advisory Board (Sanofi and Lilly). JCN declare payment or honoraria for lectures, presentations, speaker bureaus (Astra Zeneca, Pfizer, Abbvie, Lilly, Biogen, Galápagos/Alfa Sigma and Johnson and Johnson) and participation on advisory board (Astra Zeneca, Abbvie, Galápagos/Alfa Sigma and Johnson and Johnson). AB declare payment or honoraria for lectures, presentations, speakers bureaus (Novartis and GSK), support for attending meetings and/or travel (Pfizer, Roche, Nordic) Other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author details

[1]Pediatric Rheumatology Unit, Hospital Universitario Niño Jesús, Madrid, Spain
[2]Faculty of Health Sciences-HM Hospitals, Universidad Camilo José Cela, Madrid, Spain
[3]Musculoskeletal Pathology Group, Rheumatology Department, Health Research Institute (IdISSC), Hospital Clínico San Carlos, Madrid, Spain
[4]Rheumatology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[5]Rheumatology Department, Hospital General Universitario Ramon y Cajal, Madrid, Spain
[6]Rheumatology Department, Hospital Universitario Infanta Sofía, San Sebastián de los Reyes, Spain

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References

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. 2007;369. Available from: www.thelancet.com.
2. Nguyen K, Barsalou J, Basodan D, Batthish M, Benseler SM, Berard RA 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.
3. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P. International league of associations for rheumatology. International league of associations for rheumatology.classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;2(31):390–2.
4. Kearsley-Fleet L, Heaf E, Davies R, Baildam E, Beresford MW, Foster HE, et al. Frequency of biologic switching and the outcomes of switching in children and young people with juvenile idiopathic arthritis: a National cohort study. Lancet Rheumatol. 2020;2(4):e217–26.
5. Grazziotin LR, Currie G, Twilt M, Ijzerman MJ, Kip MMA, Koffijberg H et al. Real-world data reveals the complexity of disease modifying anti-rheumatic drug

treatment patterns in juvenile idiopathic arthritis: an observational study. Pediatr Rheumatol. 2022;20(1).
6. Davies R, Gaynor D, Hyrich KL, Pain CE. Efficacy of biologic therapy across individual juvenile idiopathic arthritis subtypes: A systematic review. Seminars in Arthritis and Rheumatism. Volume 46. W.B. Saunders; 2017. pp. 584–93.
7. MacCora I, Lombardi N, Crescioli G, Bettiol A, Bonaiuti R, Pagnini I, et al. OBSID-IAN - real-world evidence of originator to biosimilar drug switch in juvenile idiopathic arthritis. Rheumatol (United Kingdom). 2022;61(4):1518–28.
8. Hinze CH, Holzinger D, Lainka E, Haas JP, Speth F, Kallinich T et al. Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. Pediatr Rheumatol. 2018;16(1).
9. Zajc Avramovič M, Toplak N, Markelj G, Emeršič N, Avčin T. Long-term follow-up of 109 children with juvenile idiopathic oligoarthritis after first intra-articular corticosteroid injection. Arthritis Res Ther. 2024;26(1).
10. 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 Care Res (Hoboken). 2019;71(6):717–34.
11. Onel KB, Horton DB, Lovell DJ, Shenoi S, Cuello CA, Angeles-Han ST, et al. 2021 American college of rheumatology guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2022;74(4):521–37.
12. 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(6):819–28.
13. Mannion ML, Xie F, Horton DB, Ringold S, Correll CK, Dennos A, et al. Biologic switching among nonsystemic juvenile idiopathic arthritis patients: A cohort study in the childhood arthritis and rheumatology research alliance registry. J Rheumatol. 2021;48(8):1322–9.
14. Karadağ ŞG, Demirkan FG, Koç R, Çakmak F, Sönmez HE, Aktay Ayaz N. Approach to switching biologics in juvenile idiopathic arthritis: a real-life experience. Rheumatol Int. 2022;42(1):141–7.
15. Pedersen ML, Neve-Græsbøll A, Herlin T, Glerup M. Biologic switching patterns among children with non-systemic juvenile idiopathic arthritis. Pediatr Rheumatol. 2023;21(1).
16. Ma X, Xin L, Sun J, Liu Z. Antinuclear antibody-positive cohort constitutes homogeneous entity in juvenile idiopathic arthritis. Mod Rheumatol. 2016;26(1):75–9.
17. Ravelli A, Felici E, Magni-Manzoni S, Pistorio A, Novarini C, Bozzola E, et al. Patients with antinuclear antibody-positive juvenile idiopathic arthritis constitute a homogeneous subgroup irrespective of the course of joint disease. Arthritis Rheum. 2005;52(3):826–32.
18. Freeman DH. Applied Categorical Data Analysis (Statistics: Textbooks and Monographs series). 1987.
19. Concato J, Peduzzi P, Holford TR, Feinstein AR. Importance of events per independent variable in proportional hazards analysis. I. Background, goals, and general strategy. J Clin Epidemiol. 1995;48(12):1495–501.
20. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. J Clin Epidemiol. 1995;48(12):1503–10.
21. Schmeling H, Minden K, Foeldvari I, Ganser G, Hospach T, Horneff G. Efficacy and safety of adalimumab as the first and second biologic agent in juvenile idiopathic arthritis: the German biologics JIA registry. Arthritis Rheumatol. 2014;66(9):2580–9.
22. Romano M, Pontikaki I, Gattinara M, Ardoino I, Donati C, Boracchi P et al. Drug survival and reasons for discontinuation of the first course of biological therapy in 301 juvenile idiopathic arthritis patients. Vol. 65, Reumatismo. 2013.
23. Bertilsson L, Andersson-Gäre B, Fasth A, Petersson IF, Forsblad-D'elia H. Disease course, outcome, and predictors of outcome in a population-based juvenile chronic arthritis cohort followed for 17 years. J Rheumatol. 2013;40(5):715–24.
24. Otten MH, Prince FHM, Anink J, Ten Cate R, Hoppenreijs EPAH, 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(5):721–7.
25. Güngörer V, Çelikel E, Ekici Tekin Z, Polat MC, Öner N, Kurt T, et al. Biological agent switching in patients with juvenile idiopathic arthritis: A tertiary center experience. J Clin Rheumatol. 2023;29(6):255–61.
26. Minden K, Horneff G, Niewerth M, Seipelt E, Aringer M, Aries P, et al. Time of disease-modifying antirheumatic drug start in juvenile idiopathic arthritis and the likelihood of a drug-free remission in young adulthood. Arthritis Care Res (Hoboken). 2019;71(4):471–81.
27. Scagnellato L, Cozzi G, Prosepe I, Lorenzin M, Doria A, Martini G et al. Relapses of juvenile idiopathic arthritis in adulthood: A monocentric experience. PLoS ONE. 2024;19.
28. Taylor PC, Matucci Cerinic M, Alten R, Avouac J, Westhovens R. Managing inadequate response to initial anti-TNF therapy in rheumatoid arthritis: optimising treatment outcomes. Therapeutic Advances in Musculoskeletal Disease. Volume 14. SAGE Publications Ltd; 2022.

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