The Turkish Journal of Pediatrics 2023; 65: 980-989
https://doi.org/10.24953/turkjped.2023.22

Original Article

Choice and switch of biologic drugs in juvenile idiopathic arthritis

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ABSTRACT

Background. In this study, we aimed to evaluate choices and changes of biologic drugs in juvenile idiopathic arthritis (JIA) patients according to disease subtypes.

Methods. We retrospectively analyzed JIA patients who received biologic treatment between January 2004 and July 2022.

Results. Of 294 JIA patients, 80 (27.2%) had systemic JIA, 68 (23.1%) had oligoarticular JIA, 61 (20.7%) had polyarticular JIA, 79 (26.9%) had enthesitis-associated arthritis (ERA), and six (2.1%) had psoriatic arthritis (PsA). Anakinra (n=66, 82.5%) was the most commonly preferred first line biologic in systemic JIA. Etanercept was the most frequently used biologic drug in patients with ERA (n=69, 87.3%), oligoarticular (n=37, 54.4%) and polyarticular JIA (n=43, 70.5%). Adalimumab was used as a first-line biologic drug in all PsA patients (n=6, 100%). One hundred-fourteen patients (38.8%) were switched to second-line and 29 (9.9%) to third-line biologic drugs. While the most common reason for switching to a second-line biologic was difficulty in usage of daily injections (n=37, 60.6%) in systemic JIA patients, it was an inadequate response to first biologics in non-systemic JIA patients (n=42, 79.2%). Side effects were detected in only seven patients (2.4%) during the follow-up.

Conclusion. In this study, we revealed the biologic drug usage and switch strategies in our JIA patients. Good responses were obtained in most of our patients with a reliable profile. However, studies on larger patient groups are needed to clarify these results.

Key words: adalimumab, anakinra, etanercept, juvenile idiopathic arthritis.

Juvenile idiopathic arthritis (JIA) is the most frequent chronic rheumatic disease of childhood and was classified into seven categories according to the International League of Associations of Rheumatology (ILAR).[1,2] These are systemic, oligoarticular (persistent or extended), polyarticular (rheumatoid factor [RF]-positive, RF-negative), enthesitis-related arthritis (ERA), psoriatic arthritis (PsA), and undifferentiated arthritis.

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Received 25th Jan 2023, revised 5th Sep 2023, 11th Nov 2023, accepted 11th Nov 2023.

Early and efficient treatment is crucial in JIA since the disease causes disability if inadequately treated.[3,4] The prognosis of JIA patients has changed dramatically after the introduction of biologic drugs in the treatment.[5,6] Biologic drugs are highly effective in patients who do not respond or are intolerant to treatment with disease-modifying anti-rheumatic drugs (DMARDs).[7]

In general, tumor necrosis factor-alpha (TNF-α) inhibitors are used in patients with polyarticular JIA and ERA, and biologic drugs targeting interleukin (IL)-1 and IL-6 activity are used in patients with systemic JIA.[8-13] TNF-α inhibitors are divided into two categories, the monoclonal anti-TNF-α antibodies, such

as infliximab (IFX), adalimumab (ADA), golimumab, and certolizumab pegol, and the soluble TNF receptor fusion protein, etanercept (ETN). They are recommended as second- or third-line drugs in polyarticular JIA treatment, often after at least three months of DMARD therapy, and their efficacy has been established in numerous trials.[14,15] Anakinra (IL-1 receptor antagonist), canakinumab (anti-IL-1 antibody), rilonacept (IL-1 receptor antagonist), and tocilizumab (TCZ, IL-6 receptor antibody) are among the biologic drugs frequently used in the treatment of systemic JIA patients.[10,11,16] TCZ is also used to treat patients with polyarticular JIA.[17] Secukinumab, a fully human monoclonal antibody that directly inhibits IL-17A, is also among the drugs of choice in some types of JIA.[18] In addition, tofacitinib, a Janus kinase (JAK) inhibitor, has recently been introduced to the treatment of refractory JIA patients.[19]

Physicians involved in JIA treatment have an increasing number of biologic treatment options, and choosing between them may be challenging. Unfortunately, there is no clear treatment guideline for JIA patients on which biologic to use as first-line neither with regards to biologic switch strategies. The subtype of JIA is the most important factor determining the choice of biologic drug. While the disease pathogenesis, which varies according to JIA subtypes, plays a major role in predicting the efficacy of a biologic drug, the side effect profile should also be taken into consideration. Therefore, it is necessary to carefully weigh the benefits and risks before initiating biological agents. In the present study, we aimed to evaluate biologic drug choices and switching strategies between biologics in our JIA patients.

Materials and Methods

The study was approved by the ethics committee of our center (GO 21/743). The study was performed following the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Patients

All JIA patients treated with biologics from January 2004 to July 2022 at the Department of Pediatric Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Türkiye, were retrospectively evaluated. All participants met the ILAR classification criteria for JIA.[2] In addition, they had attended at least two visits in our center after the initiation of biologic therapy and their general evaluations and examinations were made by a pediatric rheumatologist. JIA patients who did not use biologic drugs were excluded.

Data collection

The collected data included patients' demographic characteristics, JIA subtypes, laboratory findings, biologic drug used according to JIA subtypes, duration of biologic drug use, reasons for using and switching of biologic drugs, and outcomes. In addition, the Juvenile Arthritis Disease Activity Score-71 (JADAS-71) and Childhood Health Assessment Questionnaire (CHAQ) of the patients were calculated before treatment with first biologic drug and after treatment with last biologic drug.[20,21] Outcomes were determined according to the American College of Rheumatology (ACR) criteria.[22]

Statistical analysis

All data were analyzed using IBM Statistical Package for Social Sciences (SPSS) software v. 24. Descriptive statistics were presented as frequency (n) and percentage (%), median and 1st-3rd quartiles (Q1-Q3), or mean ± standard deviation (SD). The numeric variables were investigated using visual and analytic methods (Kolmogorov-Smirnov / Shapiro-Wilk's test) to determine whether they were normally distributed. Where appropriate, the chi-square test, or Fisher's exact test, was used to analyze relationships between categorical variables. The Mann-Whitney U test or Kruskal-Wallis test was used to test whether the medians between comparison groups were different. A p-value

of less than 0.05 was considered to show a statistically significant result.

Results

General characteristics of juvenile idiopathic arthritis patients treated with various biologic drugs

Among the total 812 JIA patients, 294 patients treated with biologic drugs were included in the study. The median age of 294 patients at diagnosis was 8.9 (3.8-11.4) years, and 153 (52%) were female. Eighty of them (27.2%) had systemic JIA, 68 (23.1%) had oligoarticular JIA, 61 (20.7%) had polyarticular JIA, 79 (26.9%) had ERA and 6 (2.1%) had PsA (Table I). Forty-one (13.9%) patients had uveitis (mostly oligoarticular JIA), 17 (5.8%) had inflammatory bowel disease (IBD) (mostly oligoarticular JIA), and 32 (10.9%) had macrophage activation syndrome (MAS) (all systemic JIA).

Except for patients with oligoarticular JIA, most patients (n=222, 75.5%) had elevated acute phase reactants before biologic therapy. The majority of the patients, especially those with polyarticular JIA, had high JADAS-71 and CHAQ scores before treatment with the first-line biologic drug. JADAS-71 and CHAQ scores significantly decreased in all patient groups after biologic treatment(s) ($p<0.001$ for both). Complete remission was achieved in 242 patients (82.3%) at the last visit.

First-line biologic drugs according to disease subtypes in patients with juvenile idiopathic arthritis

There were several differences between JIA subtypes regarding the selection of biologic

Table I. General characteristics, disease scores and outcome of juvenile idio pathic arthritis patients treated with biologic drugs.

	SJIA (n=80)	OJIA (n=68)	PJIA (n=61)	ERA (n=79)	PsA (n=6)
Female, n (%)	39 (48.8)	54 (79.4)	32 (52.5)	24 (30.3)	4 (66.7)
Age at diagnosis, years, median (Q1-Q3)	5.1 (2.2-6.9)	4.5 (3.1-7.2)	6.4 (3.1-10.2)	9.7 (6.8-12.4)	9.3 (7.1-12.7)
Disease duration, years, median (Q1-Q3)	5.9 (2.3-6.8)	6.4 (3.2-8.6)	4.4 (2.7-6.5)	5.3 (3.9-7.2)	4.7 (3.1-6.4)
Laboratory findings, n (%)					
Elevated APR*	80 (100)	29 (42.6)	49 (80.3)	59 (79.7)	5 (83.3)
ANA	1 (1.3)	47 (69.1)	14 (22.9)	1 (1.3)	2 (33.3)
HLA-B27	0	0	0	54 (68.3)	1 (16.7)
RF	2 (2.5)	0	13 (21.3)	0	0
First JADAS-71*, median (Q1-Q3)	9.3 (4.7-11.9)	12.1 (9.1-16.5)	21.5 (17.1-25.2)	15.2 (9.9-21.3)	16.3 (11.2-21.8)
First CHAQ*, mean ± SD	1.1 ± 1.3	1.3 ± 1.8	1.9 ± 2.4	1.6 ± 2.3	1.5 ± 2.1
Last JADAS-71**, median (Q1-Q3)	0.45 (0.3-0.7)	0.3 (0.15-0.5)	0.7 (0.5-1.0)	0.6 (0.4-0.9)	0.3 (0.1-0.5)
Last CHAQ**, mean ± SD	0.2 ± 0.3	0.1 ± 0.3	0.3 ± 0.6	0.2 ± 0.5	0.1 ± 0.2
Outcome**, n (%)					
Complete remission	68 (85)	63 (92.6)	46 (75.4)	60 (75.9)	5 (83.3)
Partial remission	12 (15)	5 (7.3)	15 (24.6)	19 (24.1)	1 (16.7)

JADAS-71 and CHAQ scores significantly decreased in all patient groups after biologic treatment(s) ($p<0.001$ for both).
ANA: antinuclear antibodies, APR: acute phase reactants, CHAQ: Childhood Health Assessment Questionnaire, ERA: enthesitis-related arthritis, HLA: human lymphocyte antigen, JADAS-71: Juvenile Arthritis Disease Activity Score-71, JIA: juvenile idiopathic arthritis, OJIA: oligoarticular juvenile idiopathic arthritis, PJIA: polyarticular juvenile idiopathic arthritis, PsA: psoriatic arthritis, RF: rheumatoid factor, SD: standard deviation, SJIA: systemic juvenile idiopathic arthritis
*before treatment with first biologic drug
**after treatment with last biologic drug

drugs (Table II). Anakinra (n=66, 82.5%) was the most commonly used first line biologic drug in systemic JIA, especially with MAS. TCZ was used in systemic JIA patients with prominent joint involvement (n=9, 11.3%). ETN was the most frequently used biologic drug in ERA patients (n=69, 87.3%). ETN was also mostly preferred in oligoarticular (n=37, 54.4%) and polyarticular JIA patients (n=43, 70.5%). ADA was used as first-line biologic drug in all PsA patients (n=6, 100%). In addition, ADA was commonly preferred in oligoarticular (n=25, 36.8%) and polyarticular JIA (n=13, 21.3%) patients, especially those who had uveitis or IBD. Biologic drugs were mostly initiated due to the uncontrolled disease activity with NSAIDs/corticosteroids in systemic JIA, however were initiated due to the uncontrolled disease activity with DMARDs in non-systemic JIA subtypes. Concomitant corticosteroid use was frequent in patients who used anakinra or TCZ, and concomitant use of methotrexate (MTX) was prevalent in patients receiving ADA or IFX.

ACR100 responses were achieved by most patients (n=223, 75.9%) after the first-line biologic drug. However, ACR100 responses to the first-line biologics were more frequent among patients with oligoarticular JIA and PsA (p=0.025 and p=0.010) (Table II).

Changes from the first- to second- or third-line biologic drugs

One hundred-fourteen patients (38.8%) were switched to the second-line and 29 (9.9%) to the third-line biologic drugs in the follow-up (Fig. 1 and Fig. 2). In systemic JIA patients, the reasons for switching to a second-line biologic

Table II. First-line of biologic drugs, reasons and treatment responses according to subtypes of juvenile idiopathic arthritis.

	SJIA (n=80)	OJIA (n=68)	PJIA (n=61)	ERA (n=79)	PsA (n=6)
Biologic drugs, n (%)					
Anakinra	66 (82.5)	0	0	0	0
Canakinumab	5 (6.3)	0	0	0	0
Etanercept	0	37 (54.4)	43 (70.5)	69 (87.3)	0
Adalimumab	0	25 (36.8)	13 (21.3)	7 (8.9)	6 (100)
Infliximab	0	6 (8.8)	2 (3.3)	2 (2.5)	0
Tocilizumab	9 (11.3)	0	3 (4.9)	0	0
Reasons to start biologics, n (%)					
Disease not controlled with NSAIDs/corticosteroids	72 (90)	7 (10.3)	6 (9.8)	9 (11.4)	1 (16.7)
Disease not controlled with DMARDs	8 (10)	61 (89.7)	55 (90.1)	70 (88.6)	5 (83.3)
Duration of biologic use, months, median (Q1-Q3)	16 (6-24)	12 (12-18)	18 (12-24)	18 (12-26)	24 (12-30)
Treatment response, n (%)					
ACR30	71 (88.8)	64 (94.1)	55 (90.1)	75 (83.3)	6 (100)
ACR50	65 (81.3)	61 (89.7)	53 (86.9)	72 (91.1)	6 (100)
ACR70	61 (76.3)	58 (85.3)	49 (80.3)	66 (83.6)	6 (100)
ACR90	59 (73.8)	56 (82.4)	45 (73.8)	63 (79.7)	5 (83.3)
ACR100	58 (72.5)	55 (80.9)	43 (70.5)	62 (78.5)	5 (83.3)

ACR100 responses to the first-line biologics were higher among patients with oligoarticular JIA and PsA (p=0.025 and p=0.010), compared to other groups.
ACR: American College of Rheumatology, DMARDs: disease-modifying anti-rheumatic drugs, ERA: enthesitis-related arthritis, NSAIDs:non-steroidal anti-inflammatory drugs, OJIA: oligoarticular juvenile idiopathic arthritis, PJIA: polyarticular juvenile idiopathic arthritis, PsA: psoriatic arthritis, SJIA:systemic juvenile idiopathic arthritis.

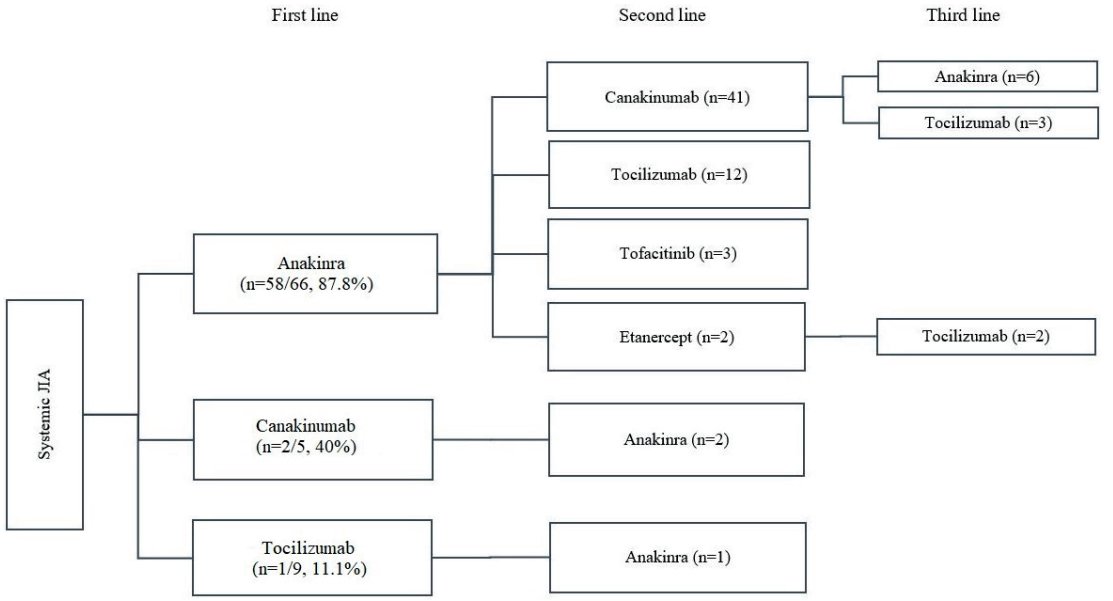

Fig. 1. Biologic drugs used as first-, second-, and third-line in patients with systemic juvenile idiopathic arthritis.

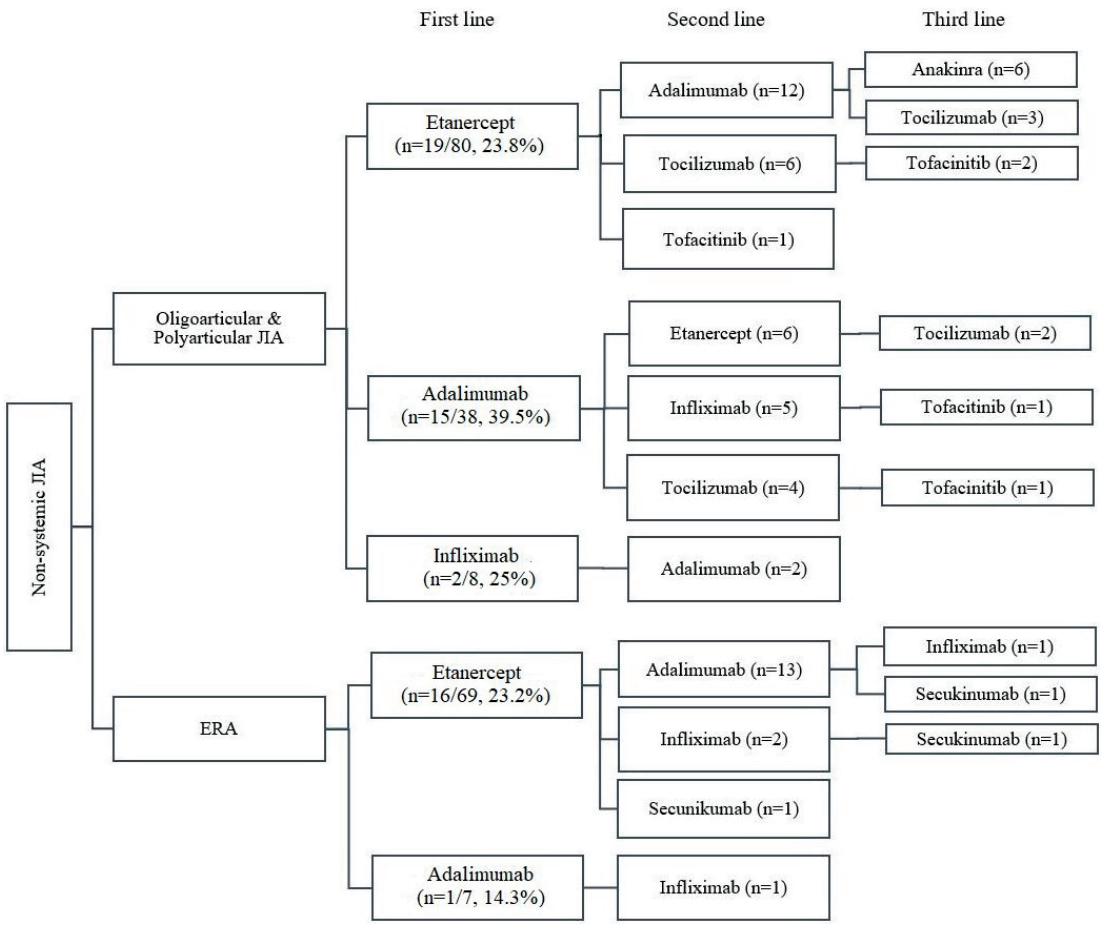

Fig. 2. Biologic drugs used as first-, second-, and third-line in patients with non-systemic juvenile idiopathic arthritis.

were difficulty in usage of daily injections in 37 patients (60.6%), conversion to polyarticular course in 14 patients (22.9%), an inadequate response to the first-line biologic treatment in six patients (9.8%), and side effects in four patients (6.6%). Three of these side effects developed due to anakinra use (local redness and/or urticaria at the injection site) and the other was associated with TCZ (anaphylaxis). In non-systemic JIA patients, the reasons for switching to a second-line biologic were an inadequate response to the first-line biologic treatment in 42 patients (79.2%), development of uveitis in three patients (5.7%), development of IBD in two patients (3.8%), compliance problems in two patients (3.8%), and side effects in two patients (3.8%). One of the side effects was associated with ETN (viral upper respiratory tract infection-like symptoms) and the other was associated with IFX (anaphylaxis). The reason for the transition to the third-line biologic drugs was an inadequate response to the second-line biologic treatment in all patients except one. One patient with polyarticular JIA using TCZ was switched to tofacitinib due to the development of anaphylaxis associated with TCZ.

ACR100 response was achieved in 72% (44/61) of systemic JIA patients who switched to the second-line biologic drug, and 64.2% (34/53) of non-systemic JIA patients.

Discussion

In recent years, biologic drugs have changed the prognosis and treatment of many rheumatic diseases, including JIA.[23] Biologic drug preferences differ according to the JIA subtypes. In our study, anakinra was the most commonly used first-line biologic drug in systemic JIA, while TCZ was preferred in patients with significant joint involvement. While ETN was the most frequently used biologic drug in patients with ERA, oligoarticular and polyarticular JIA, the first-line biologic was ADA in all PsA patients. Biologic drugs were initiated in systemic JIA in cases of uncontrolled disease activity with NSAIDs/corticosteroids, and uncontrolled disease activity with DMARDs in non-systemic JIA subtypes.

Since IL-6 and IL-1β are known to play central roles in the pathogenesis of systemic JIA, biologics targeting these cytokines have also been frequently used in systemic JIA in the literature.[24,25] Likewise, in our study, the most commonly used drug in systemic JIA was anakinra, followed by TCZ. Most of our patients with systemic JIA who received anakinra also had a history of MAS. Successful treatment of patients with MAS associated with systemic JIA with anakinra has been demonstrated in many studies, and anakinra has taken its place in treatment guidelines.[26,27]

Of the TNF-α inhibitors, ETN was most commonly used in our ERA patients (86.1%). Many studies have shown that ETN improves the signs and symptoms of ERA, and remission is achieved with long-term treatment.[28-30] Horneff et al.[28] reported that 24 weeks of ETN treatment reduced the signs and symptoms of ERA, with marked improvement and a high number of patients achieving remission.

Etanercept was also used most frequently in our patients with oligoarticular and polyarticular JIA. TNF-α inhibitors are commonly preferred in patients with oligoarticular (especially in the extended subtype) and polyarticular JIA in the literature.[31,32] In our study, some of the resistant polyarticular JIA patients who did not respond to TNF-α inhibitors were switched to TCZ. Brunner et al.[17] expressed that polyarticular JIA patients treated with TCZ showed a high level of disease control for up to two years. Patients using TCZ also had higher post-treatment JADAS-71 and CHAQ scores than others, possibly due to its use in patients with resistant polyarticular JIA.

Adalimumab was frequently used in JIA patients with a history of uveitis or IBD. There are many studies in the literature reporting that ADA is effective in treating JIA patients with uveitis or IBD.[33,34] In a survey study by

Kotaniemi et al.[34], which evaluated the long-term effects of ADA, successful uveitis control was achieved in two-thirds of 54 JIA uveitis cases who were resistant or intolerant to other immunosuppressive drugs, and corticosteroid treatment was discontinued in 22%.

Adalimumab was also used in all of our PsA patients. Poddubnyy et al.[35] reported that ADA was an effective and generally well-tolerated drug for treating the signs and symptoms of PsA.

In our study cohort, 38.8% were switched to second-line biologics, and 9.9% to third-line biologics. While the most common reason for switching to the second-line biologic therapy in systemic JIA patients were the difficulty in using daily injections and transition to a polyarticular course, an inadequate response to the first-line biologic was the most common cause in non-systemic JIA patients. The main reason for switching to the third biologic drugs was an inadequate response to the second biologics in both groups. There are previous studies on biologic drug switches in patients with JIA.[36,37] In a study evaluating a large cohort including JIA patients, 1152 of 2361 patients were initiated with at least one biologic drug and most of them were treated with TNF-α inhibitors as a first-line biologic (n=1050, 91%).[36] Two hundred seventy (23%) of 1152 patients received a second-line biologic drug, 61 (5%) a third-line biologic, and 11 (1%) a fourth-line biologic. Of 240 patients with polyarticular JIA, 194 (81%) used a second TNF-α inhibitor, and in 46 patients (19%) who did not respond to TNF-α inhibitors, these were switched to a non-TNF-α inhibitor biologic drug. In a study by Mannion et al.[37] which included 1361 patients with JIA using biologic drugs (94% TNF-α inhibitors), biologic drugs were switched in 349 (26%) patients. Among biologic switchers, ineffectiveness/disease flare was the most common reason for switching (n=202, 58%).

In our study, adverse effects related to biologic drugs were detected in seven patients (2.4%). Most of the adverse events were allergic reactions, and one patient had recurrent upper respiratory tract infections. Because of these side effects, the biologic drugs were changed in these patients. Allergic reactions and an increase in the frequency of infections (mostly upper respiratory tract infections) after biologic treatments have been reported in the literature.[38,39] In general, discontinuation and/or switch of the current treatment is recommended in these cases.

The retrospective nature was the main limitation of this study. The study relied heavily on clinical assessments and physical examinations, which can be subjective. Therefore, incomplete or incorrect medical records can lead to erroneous assumptions. In addition, it has a relatively small sample size (especially PsA patients), so it might not capture the full spectrum of JIA presentations. Some rare or atypical forms of JIA may not be adequately represented, limiting the generalizability of the study findings. Finally, only ACR responses could be evaluated after first-line biologic use, as it may have been confusing to assess ACR responses in the end, in patients who had used more than one biologic.

Conclusion

In this study, we demonstrated our preferences of biologic use and biologic switch in JIA patients. Anakinra was more commonly prescribed to systemic JIA patients, while ETN was most frequently used in ERA, oligoarticular and polyarticular JIA patients. A good response with a reliable safety profile was obtained with biologic drugs in most of our patients who had uncontrolled disease activity with NSAIDs/corticosteroids or DMARDs. In general, unresponsiveness to the prescribed biologic treatment was the main reason for switching to a second or third biologic drug, whereas the switch from anakinra to another biologic was frequently due to the challenges associated with daily injections. We believe that understanding the reasons for the use and transition of biologic drugs can help us gain insights into using personalized medicine strategies and

can improve the management of JIA patients. However, studies in larger cohorts are required to assess the efficacy and side-effect profiles of biologic drugs more clearly.

Ethical approval

This study has been approved by the Hacettepe University Ethics Commission (Approval Number: GO 21/743) and was performed following the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: SŞ, ÖB, EDB, YB and SÖ data collection: SŞ, MKC, ZB, EA, YB analysis and interpretation of results: SŞ, ÖB, EDB, MKC, ZB, EA, YB, YB and SÖ draft manuscript preparation: SŞ, ÖB, EDB, YB and SÖ. All authors reviewed and approved the final version of the manuscript.

Source of funding

The authors declare the study received no funding.

Conflict of interest

Ezgi Deniz Batu and Özge Başaran received payment for speakers' bureaus from Novartis. Seza Ozen received consultancy fees and payment for speakers bureaus from Novartis and Sobi. Other authors declare that is there is no conflicts of interest.

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