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Research

Biologic Therapies in Juvenile Idiopathic Arthritis

Jüvenil İdiyopatik Artritte Biyolojik Tedaviler

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ABSTRACT

Objective: To investigate the single-center experience of the efficacy and safety profile of biologic therapies in patients with juvenile idiopathic arthritis (JIA) and identify risk factors associated with adverse events (AEs).

Methods: The medical charts of children with JIA diagnosed between January 2010 and December 2021 were reviewed retrospectively, and patients treated with biological agents were included in the study. Demographic data, clinical features, laboratory results, treatments used, and AEs during the treatment period were collected.

Results: From the total JIA cohort (n=814), 237 patients who received biologic therapy for at least 3 months were enrolled in the study. The most frequent subtype was persistent oligoarticular JIA (45.1%) and the most frequently used biologic drug was etanercept (n=118), followed by adalimumab (n=64), tocilizumab (n=31), anti-interleukin-1 (anti-IL-1) agents (n=12; 7 anakinra and 5 canakinumab), infliximab (n=6), abatacept (n=3), secukinumab (n=2) and tofacitinib (n=1). One hundred sixty-four (69.2%) patients received disease-modifying antirheumatic drugs (DMARDs) concomitantly, 10.5% received DMARDs plus corticosteroids and 2.1% received only corticosteroids. The median [interquartile range (IQR)] age and median age at initiation of the biologics were 14.4 (10.7-18) years and 10.9 (6.6-14.5) years, respectively. The median (IQR) follow-up period was 3.9 (2-6.3) years. On biologic therapy, the median (IQR) JADAS-71 decreased from 13 (11-19) at baseline to 0 (0-2) after median 22 (10-40) months of treatment (p<0.001). The most frequent AE was local injection site reactions with biologics administered subcutaneously (n=8), followed by upper respiratory tract infections (n=4) and diffuse erythematous skin rashes (n=4). Serious AEs were observed in 11 (4.6%) patients. To compare the frequency of AEs, patients were divided into three groups according to the biologics administered, as follows: Group 1: Tumor necrosis factor inhibitors, group 2: anti-IL-1 agents, group 3: anti-IL-6 agent. The frequency of AEs was significantly higher in JIA patients on anti-IL-1 therapy than in the other two groups (58.3% vs. 29% and 8.5%, p<0.001).

Conclusion: Biological agents are used with increasing frequency in children with JIA, and their off-label use is quite common. Although these agents are considerably effective and quite safe, AEs should not be underestimated. While planning the management of patients with refractory JIA, careful interpretation of benefit-risk balance for every individual patient seems to be reasonable and required.

Keywords: Adverse events, biologic therapy, juvenile idiopathic arthritis

ÖZ

Amaç: Jüvenil idiyopatik artrit (JİA) hastalarında biyolojik tedavilerin etkinlik ve güvenlik profiline ilişkin tek merkez deneyimini araştırmak ve olumsuz olaylarla (AE'ler) ilişkili risk faktörlerini belirlemektir.

Gereç ve Yöntem: Ocak 2010-Aralık 2021 tarihlerinde JİA tanısı alan çocukların tıbbi dosyaları retrospektif olarak incelendi ve biyolojik ajanlarla tedavi edilen hastalar çalışmaya dahil edildi. Tedavi süresince demografik veriler, klinik özellikler, laboratuvar sonuçları, kullanılan tedaviler ve AE'ler toplandı.

Bulgular: Toplam JİA kohortundan (n=814) en az 3 ay biyolojik tedavi almış 237 hasta çalışmaya alındı. En sık görülen JİA alt tipi persistan oligoartiküler JİA'ydı (%45,1) ve en sık kullanılan biyolojik ilaç etanerseptti (n=118), bunu sırasıyla adalimumab (n=64), tosilizumab (n=31), anti-interlökin-1 (anti-IL-1) ajanlar (n=12; 7 anakinra ve 5 kanakinumab), infliksimab (n=6), abatasept (n=3), sekukinumab (n=2) ve tofasitinib (n=1) izledi. 164 (%69,2) hasta eş zamanlı olarak hastalık modifiye edici antiromatizmal ilaç (DMARD), %10,5'i DMARD ve kortikosteroid ve %2,1'i sadece kortikosteroid almıştır. Hastaların medyan [çeyrekler açıklığı (IQR)] yaşı 14,4 (10,7-18) yıl ve biyolojik ilaçların başlangıcındaki medyan yaşları 10,9 (6,6-14,5) yıldı. Medyan (IQR) takip süresi 3,9 (2-6,3) yıldı. Medyan 22 (10-40) aylık biyolojik tedavi ile başlangıçtaki medyan (IQR) JADAS-71 13'ten (11-19) tedaviden sonra 0'a (0-2) düştü (p<0,001). En sık görülen AE, subkütan uygulanan biyolojiklerle lokal enjeksiyon yeri reaksiyonlarıydı (n=8), bunu üst solunum yolu enfeksiyonları (n=4) ve yaygın eritematöz deri döküntüleri (n=4) izledi. On bir (%4,6) hastada ciddi

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AE gözlendi. AE'lerin sıklığını karşılaştırmak için, hastalar uygulanan biyolojiklere göre aşağıdaki gibi üç gruba ayrıldı: Grup 1: Tümör nekroz faktör inhibitörleri, grup 2: anti-IL-1 ajanlar, grup 3: anti-IL-6 ajan. AE sıklığı, anti-IL-1 tedavisi alan JİA hastalarında diğer iki gruba göre anlamlı olarak daha yüksekti (%58,3'e karşı %29 ve %8,5, p<0,001).

Sonuç: Biyolojik ajanlar JİA'lı çocuklarda artan sıklıkta kullanılmaktadır ve endikasyon dışı kullanımları da oldukça yaygındır. Bu ajanlar oldukça etkili ve güvenli olmalarına rağmen, yan etkileri hafife alınmamalıdır. Dirençli JİA hastalarının yönetimini planlarken, her bir hasta için fayda-risk dengesinin dikkatli bir şekilde yorumlanması makul ve gerekli görünmektedir.

Anahtar Kelimeler: Advers olaylar, biyolojik tedavi, jüvenil idiyopatik artrit

INTRODUCTION

The most prevalent pediatric rheumatic disease is juvenile idiopathic arthritis (JIA), which is classified into seven subtypes by the International League of Associations for Rheumatology: oligoarticular (oJIA), rheumatoid factor (RF) negative and positive polyarticular (pJIA), systemic (sJIA), psoriatic arthritis (PsA), enthesitis-related (ERA), and undifferentiated arthritis (1).

Non-steroidal anti-inflammatory drugs, corticosteroids, and disease-modifying antirheumatic drugs (DMARDs) are still the mainstay of JIA treatment. However, biologic drugs are increasingly used when remission cannot be achieved with these main treatments or as initial therapy in patients with aggressive diseases.

During the past 20 years of the biologic era, restoring synovitis and tissue damage, preventing extraarticular complications, and providing low disease activity became achievable goals in JIA. However, the increased risk of infections and the potential threat of malignancy are critical issues that should be considered while making a decision about the biologic therapy (2).

This study analyzed the efficacy and safety profile of biologic therapies in JIA patients followed by a tertiary reference hospital.

METHODS

Patients

The medical charts of 237 patients treated with biologic agents out of 814 JIA patients who were diagnosed with JIA and followed up regularly every 1-3-month intervals in the Pediatric Rheumatology Unit of İstanbul Faculty of Medicine, İstanbul University, Türkiye between January 2010 and December 2021 were reviewed retrospectively. The patients who received biologic therapy for at least 3 months and at least 6 months of follow-up were included in the study. Demographic characteristics, clinical features, laboratory tests and treatment modalities, and adverse events (AEs) during the treatment period were retrospectively collected.

The juvenile arthritis disease activity score-71 (JADAS-71) was calculated to assess disease activity and was calculated as follows: physician visual analog scale (VAS) + patient VAS + active joint count + erythrocyte sedimentation rate (ESR)-20/10 (3). Response to treatment was defined according to JADAS-71 (4). The criteria described by Wallace et al. (5) was used for the definition of inactive disease as no active arthritis or uveitis; a physician's global assessment indicating no disease activity; no fever, rash, serositis, splenomegaly, or lymphadenopathy; and no elevated ESR or C-reactive protein level attributable to JIA.

TNFi (etanercept, adalimumab, and infliximab), interleukin (IL)-1 antagonist (anakinra and canakinumab), anti-IL-6 agent (tocilizumab) and cytotoxic T-lymphocyte-associated protein 4 agonist (abatacept), IL-17A receptor antagonist (secukinumab) and janus-kinase inhibitor (tofacitinib) were the biologics used by the patients.

AEs and serious adverse events (SAEs) were recorded from the patients' medical charts. SAEs were considered AEs that resulted in death, life-threatening, hospitalization, malignancy, or permanent or significant disability/incapacity (6).

This study was approved by the Institutional Review Board of İstanbul University, İstanbul Faculty of Medicine (decision no: 07, date: 08.04.2022), and informed consent was obtained from all patients/parents.

Statistical Analysis

Statistical analysis was carried out using SPSS software version 28.0. Descriptive statistics are presented as proportions for categorical variables. Chi-square test or Fisher's Exact test was used to compare categorical variables, whichever was appropriate. The normality of continuous data was assessed using the Shapiro-Wilk tests. Continuous data were expressed as median and interquartile ranges (IQR) when not normally distributed and mean ± standard deviation when normally distributed. Independent samples t-test or Mann-Whitney U test were used to compare the continuous variables. All statistical analyzes were carried out at a 5% significance level and an overall p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

Of 237 patients, 122 (51.5%) were male. The most common subtype was persistent oJIA (45.1%). With a median 46.4 (IQR 24-76) months follow-up, the duration of biologic drug usage was median 22 months (IQR 10-40). Demographic features, the distribution of the JIA subgroups, and the biologic therapies used for the patients are shown in Table 1.

A total of 22 (9.3%) patients had uveitis, and 8 of them were diagnosed with uveitis at baseline, while 14 patients had uveitis during follow-up. Six of the 14 patients were on etanercept therapy, and the remaining 8 patients were on methotrexate therapy at the time of diagnosis of uveitis. Of the 22 patients with uveitis, 18 patients had persistent oJIA, 3 patients had RF (-) pJIA, one patient had PsA.

Antinuclear antibody (ANA) test positivity for the whole cohort was 32.5% (n=77) and 17 (70.8%) of them experienced uveitis (p<0.001).

The most frequently used biologic drug was etanercept 49.8% (n=118), followed by adalimumab 27% (n=64), and tocilizumab 13% (n=31); respectively. One hundred sixty-four (69.2%) patients received DMARDs, 10.5% received DMARDs plus corticosteroids, and 2.1% received corticosteroids concomitantly.

Biologic agents were switched one time in 41 (80.4%) patients, 2 times in 3 (5.9%) patients, and 3 times in 7 (13.7%) patients, in 51 (21.5%) patients.

On biologic therapy, the median (IQR) JADAS-71 decreased from 13 (11-19) at baseline to 0 (0-2) after median 22 (10-40) months of treatment (p<0.001). At the last visit, 118 (49.8%) patients were still receiving biologic therapy. Biologics were discontinued in 36 (15.2%) patients due to inactive disease during follow-up. Nine patients (25%) experienced disease flare after 10 (2-46) months of biologic (b)DMARDs cessation. The remaining 27 patients maintained remission to the last visit. The median follow-up period after biologic cessation was 1.2 (0.5-1.8) years.

When the patients were evaluated for AEs; it was seen that 27 (11.4%) patients experienced at least one AE. The most common AE was local injection site reactions (n=8) with biologics administered subcutaneously, followed by upper respiratory tract infections (n=4) and diffuse erythematous skin rashes (n=4) (Table 2).

SAEs were observed in 11 (4.6%) patients (Table 2). Three of these patients had sJIA using anakinra. Anakinra was discontinued in one patient because of the development of diffuse hypersensitivity reaction and angioedema after the first dose. Concomitant cytomegalovirus (CMV)

Table 1. The demographic characteristics, the distribution of disease subgroups, and biologic therapies used for juvenile idiopathic arthritis patients

Parameters	Numerical values
Demographic characteristics	
Gender (female/male), n (%)	115/122 (48.5/51.5)
Age, years (median, IQR)	14.4 (10.7-18)
Age at disease onset, years (median, IQR)	8.5 (3.2-11.9)
Age at diagnosis, years (median, IQR)	9 (4.3-12.6)
The disease duration, years (median, IQR)	4.6 (2.5-7)
The delay in diagnosis, months (median, IQR)	2.4 (1-8.6)
Follow-up period, years (median, IQR)	3.9 (2-6.3)
Age at biologic onset, years (median, IQR)	10.9 (6.6-14.5)
The disease duration at initiation of biologic therapy, months (median, IQR)	21.2 (8-37)
The duration of biologic therapy usage, months (median, IQR)	22 (10-40)
Biologic switch, n (%)	51 (21.5)
One time switch, n (%)	41 (80.4)
Two times switch, n (%)	3 (5.9)
≥ 3 times switch, n (%)	7 (13.7)
JIA subtypes	
Oligoarticular JIA, n (%)	115 (48.5)
Persistent, n (%)	107 (45.1)
Extended, n (%)	8 (3.4)
RF-negative polyarticular JIA, n (%)	35 (14.8)
Enthesitis-related arthritis JIA, n (%)	35 (14.8)
Systemic-onset JIA, n (%)	28 (11.8)
Psoriatic arthritis, n (%)	12 (5.1)
RF-positive polyarticular JIA, n (%)	10 (4.2)
Undifferentiated, n (%)	2 (0.8)
Biologic treatments	
Etanercept, n (%)	118 (49.8)
Adalimumab, n (%)	64 (27)
Tocilizumab, n (%)	31 (13)
Anakinra, n (%)	7 (3)
Infliximab, n (%)	6 (2.6)
Canakinumab, n (%)	5 (2.1)
Abatacept, n (%)	3 (1.3)
Secukinumab, n (%)	2 (0.8)
Tofacitinib, n (%)	1 (0.4)

Table 1. Continued

Concomitant therapy with biologic treatments	
DMARDs, n (%)	164 (69.2)
Methotrexate, n (%)	146 (61.6)
Sulphasalazine, n (%)	19 (8)
Leflunamide, n (%)	16 (6.8)
Ciclosporin, n (%)	8 (3.4)
DMARDs and corticosteroids, n (%)	25 (10.5)
Corticosteroids, n (%)	5 (2.1)

DMARDs: Disease-modifying antirheumatic drugs, JIA: Juvenile idiopathic arthritis, RF: Rheumatoid factor, IQR: Interquartile range

infection was detected in another patient who developed a diffuse hypersensitivity reaction at the second dose. The third patient presented with moderate to severe hepatic failure after the 12th dose of anakinra and recovered spontaneously after discontinuation of treatment. A patient using tocilizumab presented with convulsions after the 50th dose and neurological evaluation was consistent with posterior reversible encephalopathy syndrome (PRES) and the treatment was discontinued. No other pathology was found in the etiology. Pneumonia (one patient under etanercept and one patient under tocilizumab treatment) and presptal cellulitis (under etanercept treatment) requiring hospitalization developed in 3 patients. Two patients developed pulmonary tuberculosis under adalimumab treatment, and they both had Bacillus Calmette-Guérin vaccine before treatment.

For comparison of the frequency of AEs, patients were classified into three groups according to the administered biologics as follows (Table 2) (four patients using secukinumab, abatacept and tofacitinib were excluded due to the small number of patients):

- Group 1: TNFi (etanercept, adalimumab, and infliximab),
- Group 2: anti-IL-1 agents (anakinra and canakinumab),
- Group 3: anti-IL-6 agent (tocilizumab).

The frequency of AEs was significantly higher in JIA patients on anti-IL-1 therapy than in the other two groups (58.3% vs. 29% and 8.5%, p<0.001). However, most of them [3 of 7 AEs (42.9%)] were injection site reactions.

Although not statistically significant, children with sJIA (35.7%) had the highest risk of AEs, followed by PsA (16.7%), extended oJIA (12.5%), RF (+) pJIA (10%), ERA, RF (-) pJIA (8.6%), and persistent oJIA (5.6%).

Table 2. Comparison of the frequency of adverse events and serious adverse events between children with juvenile idiopathic arthritis according to the associated biologic drug

Adverse events	Anti-TNF-α agents (n=188)	Anti-IL-1 agents (n=12)	Tocilizumab (n=31)
Upper respiratory tract infections, n (%)	2 (1.1)	0 (0)	1 (3.2)
Chickenpox, n (%)	2 (1.1)	0 (0)	0 (0)
Cytomegalovirus, n (%)	0 (0)	1 (8.3)	0 (0)
COVID-19 infection (mild), n (%)	1 (0.5)	0 (0)	0 (0)
Scabies, n (%)	1 (0.5)	0 (0)	0 (0)
Verruca vulgaris, n (%)	2 (1.1)	0 (0)	0 (0)
Parotitis, n (%)	0 (0)	0 (0)	1 (3.2)
Leukopenia, n (%)	0 (0)	0 (0)	1 (3.2)
Low complement levels, n (%)	0 (0)	0 (0)	1 (3.2)
Injection site reactions, n (%)	3 (1.6)	3 (25)	2 (6.4)
Serious adverse events			
Pneumoniae, n (%)	1 (0.5)	0 (0)	1 (3.2)
Preseptal cellulitis, n (%)	1 (0.5)	0 (0)	0 (0)
Lung tuberculosis, n (%)	2 (1.1)	0 (0)	0 (0)
Convulsion and PRES, n (%)	0 (0)	0 (0)	1 (3.2)
Hepatic failure, n (%)	0 (0)	1 (8.3)	0 (0)
Erythematous skin rashes, n (%)	1 (0.5)	2 (16.7)	1 (3.2)
Total, n (%)	16 (8.5)	7 (58.3)	9 (29)

COVID-19: Coronavirus disease-2019, PRES: Posterior reversible encephalopathy syndrome

More AEs were encountered in patients with shorter disease duration at the start of bDMARDs [18.4 (2.2-20.7) vs. 31.3 (8.7-40) months; p=0.002]. There was no significant relationship between AEs and JADAS-71 score at initiation of biologic therapy, additional treatment with a biologic (DMARDs and steroids), total duration of biologic drug usage, age at biologic onset, and the number of previously used biologic therapy.

There was no malignancy or mortality in this cohort.

DISCUSSION

This study showed that although biologic agents increasingly used in children with JIA are highly effective and safe treatments, their side effects should not be underestimated. Rare side effects are reported daily. When planning the treatment management of JIA patients, it seems reasonable and necessary to carefully interpret the benefit-risk balance for each patient.

Anti-TNF drugs are the most effective and first choice bDMARDs for JIA treatment with their effects on pain, stiffness, growth and quality of life (7-10). Currently, etanercept is the most ordered biologic drug for the treatment of JIA. Children and adolescents with JIA are frequently treated with etanercept and an acceptable safety profile over long periods, sometimes even into adulthood (10-12). Prince et al. (11) reported that the most significant improvement occurred in the first 3 months of etanercept treatment and was sustained for a long time in most patients (up to 75 months). In a comprehensive study reporting combined data from nearly 15,000 patients from Pharmachild and national registries [German (BİKeR) and the Swedish registries], methotrexate (61-84%) and etanercept (24-61.8%) were the most used csDMARDs and bDMARDs, respectively (13). Similar to the literature, in our study, the most commonly used biologic drug was TNFi, and the most commonly used biologic drug was etanercept. Also, it was observed that the median (IQR) JADAS-71 was 13 (11-19) at baseline and decreased to 0 (0-2) after a median of 22 (10-40) months of biological treatment.

Placebo-controlled randomized trials of etanercept and adalimumab have not been reported to increase the number of infections during treatment with non-sJIA (14,15), although current evidence from observational studies indicates that infections are the most common AEs (13,16). Also, a large registry-based study (13) demonstrated that infections were the most common AEs (29.4-30.1%), followed by gastrointestinal complaints (11.5-19.6%). In our study, when the patients were evaluated for AEs; it was seen that 27 (11.4%) patients experienced at least one AE. The most common AE was local injection site reactions (n=8) with biologics administered subcutaneously, followed by upper respiratory tract infections (n=4) and diffuse erythematous skin rashes (n=4). The occurrence of AEs was not significantly different between JIA subtypes, similar to the literature (11). However, children with sJIA (35.7%) had the highest risk of AEs due to the injection site reactions commonly seen with anakinra.

Treatments with csDMARDs and bDMARDs in JIA are anticipated to increase the frequency of common infections as well as increase the risk of serious and opportunistic infections such as herpes virus and tuberculosis (16-20). Serious AEs occurred in 6.9% of patients in Pharmachild and in 7.4% of patients in the BiKeR registry (13). SAEs were observed in 11 (4.6%) patients in our cohort. Three of these patients had sJIA using anakinra. Anakinra was discontinued in one patient because of the development of diffuse hypersensitivity reaction and angioedema after the first dose. The clinical course of varicella and herpes zoster in children under immunosuppression is variable. Concomitant CMV infection was detected in a patient under anakinra who developed a diffuse hypersensitivity reaction at the second dose. Two of our patients developed chickenpox not requiring hospitalization after the second dose of TNFi treatment (one patient under etanercept and other under adalimumab). Pneumonia (one patient under etanercept and one patient under tocilizumab) and preseptal cellulitis (under etanercept) requiring hospitalization developed in 3 patients. Two patients developed pulmonary tuberculosis under adalimumab treatment. These patients diagnosed with asymptomatic tuberculosis by repeat screening emphasize the importance of vigilance in tuberculosis screening for all patients under TNFi biologics, particularly in tuberculosis-endemic areas (21).

Although relatively mild liver enzyme elevations are common in the early phase of uncontrolled sJIA, they can also be seen in macrophage activation syndrome. However, when a patient's liver enzymes are initially normal and then increase rapidly and significantly, or in the presence of normal inflammatory markers, other causes should be considered. Liver diseases such as viral or autoimmune hepatitis, Wilson's disease, and drug-induced liver injury are possible etiologies. Severe hepatotoxicity has been reported as a rare side effect of anakinra therapy in patients with sJIA (22,23). One of our patients developed moderate to severe hepatic failure after the 12th dose of anakinra, the patient recovered spontaneously after discontinuation of treatment.

Acute phase reactants are reported to be rapidly reduced with tocilizumab. Although complement proteins are a

component of the acute phase, there are only two case series in the literature that provide information on the potential impact of tocilizumab on complement proteins (24,25). One of our patients in this cohort had low complement, which we noticed in the laboratory examinations we performed after the complaint of hair loss. Nasal ulcers and Raynaud's phenomenon developed during follow-up. Despite the maintenance of reduced complement components, no autoantibody positivity or other clinical signs of immunocomplex disease were seen throughout the 36-month median follow-up. The drop in C3 and C4 serum levels appears to be among the anti-inflammatory effects provided by tocilizumab and can therefore be considered a predicted impact of this medication mechanism of action.

Tocilizumab-associated neurological complications have been reported previously (26-28). In a patient with rheumatoid arthritis developed leukoencephalopathy, a patient with JIA presented with PRES, more recently a patient experienced PRES under tocilizumab as a treatment of giant cell arteritis, and finally, one patient with JIA in our cohort developed PRES after the 50th dose of tocilizumab and could not be explained for any other reason. Therefore, a link between IL-6 and the integrity of the vasculature may be considered. As a result, it seems beneficial to have strict blood pressure monitoring in an outpatient setting in patients receiving tocilizumab.

Uveitis is the most common extra-articular manifestation of JIA. The 2019 American College of Rheumatology recommendations classify patients by JIA subtype, age at diagnosis, duration of disease, and ANA status (29). Although studies have shown that some DMARDs affect uveitis incidence rates, drugs are not currently included in risk stratification guidelines. In our study, 22 (9.3%) patients had uveitis and 8 of them were diagnosed with uveitis at baseline, while 14 patients developed uveitis during follow-up. Six of the 14 patients were on etanercept therapy. The any new cases of uveitis under biologic were by etanercept in our study. We know that etanercept does not cause uveitis, it cannot prevent uveitis's development. This finding agrees with previous studies suggesting that the efficacy of etanercept in the prevention of uveitis is less than that of adalimumab (30-33).

Whether JIA patients have an increased risk of malignancy due to their rheumatic disease or treatment is still controversial. In the literature, an increased risk of malignancy has been reported in children with JIA compared with the general population, regardless of drug use. Conversely, other studies have not confirmed these findings (34-37), and more work is needed to estimate this risk more accurately. There was no malignancy or mortality in our cohort.

One of the important results of our study was that early biologic therapy was initiated in patients with poor prognosis, and AEs were more frequent. Patients with these characteristics should therefore be monitored more closely.

This study is a large cohort that presents a tertiary center experience evaluating the efficacy and safety profile of bDMARDs in patients with JIA. However, it is certain that it has some limitations, such as being a retrospective study, which may lead to inaccurate collection of AEs. Moreover, the relatively small number of some biologic therapy groups and JIA subgroups makes it difficult to interpret statistical analyses between groups. Therefore, multicenter prospective studies are needed to determine real-life data on adverse effects of bDMARDs in JIA.

CONCLUSION

This study supports the view that biological agents are effective in achieving remission by suppressing ongoing inflammation. However, AEs should not be underestimated, and when starting biologic treatment, patients and families should be clearly informed about the possible AEs.

ETHICS

Ethics Committee Approval: This study was approved by the Institutional Review Board of İstanbul University, İstanbul Faculty of Medicine (decision no: 07, date: 08.04.2022).

Informed Consent: Informed consent was obtained from all patients/parents.

Authorship Contributions

Concept: A.T., N.A.A., Design: A.T., N.A.A., Data Collection or Processing: A.T., Analysis or Interpretation: A.T., Literature Search: A.T., N.A.A., Writing: A.T., N.A.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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