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How Safe Are Biological Agents in Pediatric Rheumatology?

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What is already known on this topic?

- *Since the use of biological agents in children is limited, there is concern that side effects such as severe infection and malignancy may develop with their use.*

What this study adds on this topic?

- *Mild and temporary side effects are observed with the use of biological agents, but no life-threatening side effects are observed. However, close monitoring should be done for serious side effects.*

ABSTRACT

Objective: Biologic therapy has changed the prognosis of patients with rheumatologic disease. Despite all benefits of the biological agents, adverse events may occur due to their long-term use. The aim of this study is to analyze the adverse events observed in pediatric patients who received biological treatment.

Materials and Methods: This retrospective observational cohort study was conducted between January 2010 and January 2022. File records of 139 patients used biological agents for rheumatologic diseases in a pediatric rheumatology clinic were evaluated. Diagnosis, received treatment, the rationale for stopping treatment, requirement of tuberculosis prophylaxis, presence of an adverse event, and results were recorded.

Results: The most used biological therapy was etanercept (41.7%). Anakinra, adalimumab, canakinumab were used in 30.9%, 27.3%, 23.7% of patients, and the others in less than 10%. Totally 491 adverse events (97.9/100 patient-years) were encountered during the duration of biological treatment. The most often adverse event was recurrent upper respiratory tract infection in the patients (31.9/100 patient-years). Elevated aminotransferase levels (10.4/100 patient-years), abdominal pain (7/100 patient-years), and headache (5.2/100 patient-years) were among the other common side effects. Isoniazid (INH) prophylaxis was needed before biological treatment in 20.9% of the patients. Tuberculosis developed in none of the patients followed-up for latent tuberculosis, however, it developed in a patient while receiving etanercept due to noncompliance with his scheduled outpatient visits during etanercept treatment.

Conclusion: The most commonly used biological treatments were TNFi and IL-antagonists, and the majority of side effects were infections and laboratory abnormalities. Although the rate of serious adverse events is quite low, close follow-up of patients receiving biological therapy is very important.

Keywords: Adverse events, biological treatments, pediatric rheumatology

INTRODUCTION

Rheumatologic diseases generally have unknown etiology and an autoimmune or autoinflammatory characteristic in which immune system mediators play a role in the pathogenesis.[1] As the role of the immune system in inflammation has been understood, novel targeted biological drugs have been invented. The knowledge of the role of tumor necrosis factor α (TNF-α) in inflammation, and its overproduction in serum and synovial fluid in arthritis, has permitted the successful use of anti-TNF-α therapy.[2] Tumor necrosis factor α inhibitors (TNFi) currently in use or under study in children are etanercept, infliximab, adalimumab, golimumab, and certolizumab. Tumor necrosis factor α inhibitors have been proven to be effective in the treatment of different inflammatory conditions, including polyarticular course juvenile idiopathic arthritis (JIA), psoriatic arthritis, ankylosing spondylitis, and

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inflammatory bowel disease. With the increasing use of TNFi, several concerns have arisen, one of which is the increased risk of infection, particularly tuberculosis, fungal infections such as histoplasmosis, and opportunistic infections.[3,4] Interleukin 1 (IL-1) is a proinflammatory cytokine that plays a critical role in maintenance of chronic inflammation. Interleukin-1 receptor antagonist (IL-1Ra) is the most important physiological regulator of IL-1 induced activity involving IL1α and IL1β. Anakinra is a manufactured, human recombinant form of IL-1Ra. Dramatic responses to anakinra, selected patients with systemic juvenile idiopathic arthritis (sJIA), cryopyrin-associated periodic syndrome (CAPS), and the deficiency of the IL-1Ra (DIRA) provide the evidence for pediatric use. Generally adverse events have not been serious and were mostly injection site reactions. To date, despite reports of serious infections, no deaths from infections have been reported nor have there been opportunistic infections. There seems to be no increased incidence of tuberculosis.[5] Canakinumab is a fully human anti-IL-1 beta monoclonal antibody that selectively blocks. The use of canakinumab was not associated with life-threatening adverse effects other than an increased rate of infections.[6] In the United States and the European Union, canakinumab is approved for CAPS, tumor necrosis factor receptor-associated periodic syndrome (TRAPS), mevalonate kinase deficiency (MKD), familial Mediterranean fever (FMF) and sJIA in children, aged 2 and above.[7,8] Tosilizumab is a monoclonal antibody against IL-6 that has recently emerged as an alternative treatment modality for JIA. Common adverse events are mild gastrointestinal and upper respiratory tract infections. Infusion reactions, an increase in serum cholesterol, and transient neutropenia have also been reported.[9] Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen found on B cells and used in the treatment of various autoimmune and immune mediated disorders such as rheumatoid arthritis, systemic lupus erythematosus (SLE), dermatomyositis, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), and idiopathic thrombocytopenic purpura.[10] Some side effects may occur during or after rituximab infusion. The most common of these are infusion reactions, hypogammaglobulinemia, infections, hepatitis B reactivation, and neutropenia.[11]

Physical activity and exercise are effective in children with rheumatism at all stages of the disease.[12] However, biological treatments become prominent in pediatric rheumatology if disease activity cannot be controlled with physical activity and classical treatment. In the recent 20 years, the course of many diseases remarkably improved with the increasingly frequent use of biological agents and remission has become more achievable. Despite all these benefits of novel treatments, adverse events may occur due to their long-term use. Increased risk for infection, particularly the development of tuberculosis and malignancy is concerning.[1] In the present study, we aimed to analyze the adverse events observed in pediatric patients who received biological treatment due to rheumatologic disorder over 12 years in our pediatric rheumatology clinic.

MATERIALS AND METHODS

Study Participants

The file records of the 139 patients who received biological treatment because of rheumatologic disorders between January 2010 and January 2022 in the Division of Pediatric Rheumatology at Gazi University Faculty of Medicine, were retrospectively analyzed. All the patients were below 18 years of age at the time of diagnosis. The study included the patients who received treatment with a biological agent for at least 3 months with a diagnosis of a rheumatologic disease and regularly followed up with outpatient visits at intervals of 1-3 months.

Diagnostic Procedures and Study Design

Patients presenting with rheumatological symptoms and signs were examined. Appropriate clinical diagnoses were made for patients who underwent a detailed clinical evaluation by pediatric rheumatologists. The adverse events, such as infections, gastrointestinal system, cardiopulmonary, central nervous and other system events, and laboratory abnormalities observed in the patients were recorded. These adverse events were the reasons that were seen between 2 visits or that brought the patient to the hospital. Sex and date of birth of the patient, diagnosis, date of diagnosis, comorbidities, received treatment, treatment onset and ending date, the rationale for stopping treatment, concomitant medications with a biological agent, tuberculosis prophylaxis, presence of an adverse event, and results were recorded. Hepatitis markers, tuberculin skin test, and QuantiFERON test were applied in all patients who were planning to initiate biological treatment. The patients with tuberculin skin test ≥5 mm or positive QuantiFERON test result were given isoniazid (INH) prophylaxis for 9 months.

Ethics Committee Approval was obtained for the current study from Gazi University Faculty of Medicine (Decision number: E-77082166-604.01.02-356046 dated April 19, 2022). Since this was a retrospective study, written informed consent was not required.

Statistical Analysis

The study patients were defined using descriptive statistics indicating the type and distribution of the variables. The variables' fitness to normal distribution were examined using visual (histogram and probability graphics) and analytic methods (Shapiro–Wilk or Kolmogorov–Smirnov test). All quantitative data were non-normally distributed. Categorical variables were summarized as count and percentage, while continuous variables were given as median, minimum, and maximum. The incidence rate (IR) per 100 patient-years was defined. The correlation between the duration and number of biological treatments and the number of adverse effects was evaluated by spearman correlation analysis. The Rho value was interpreted as follows: <0.20; no or negligible relationship, 0.20-0.29; weak relationship, 0.30-0.39; moderate relationship, 0.40-0.69; strong relationship, ≥0.70; strong relationship. A *P* value <.05 was considered statistically significant. The confidence interval was calculated with MedCalc Software Ltd. Confidence interval for a rate calculator.[13] Data were analyzed with SPSS® version 21.0 software (IBM Corp., Armonk, NY, USA).

RESULTS

Patient Characteristics

The total number of patients who received biological treatment was 139. Of the patients, 52.5% (73/139) were female. The median age at the initiation of biological treatment was 11 (minimum: 0.6; maximum: 20.3) years. Sixty-five (46.5%), 41

(29.5%), 10 (7.2%), 7 (5%), 4 (2.9%), and 12 (3.4%) patients were receiving biological treatment for JIA, FMF, uveitis, Behçet's syndrome, SLE, and other rheumatologic diseases, respectively. The median biological treatment duration was 45 (min: 1-max: 146) months. Before biological treatment, 75 (54%), 57 (41%), 64 (46%), 15 (10.8%), and 56 (40.3%), patients had received the treatments of the non-steroid anti-inflammatory drug (NSAID), glucocorticoid, methotrexate, sulfasalazine, and colchicine, respectively. Of the patients, 93 (66.9%) had used only one biological agent whereas 34 (24.5%), 5 (3.6%), 2 (1.4%), 2 (1.4%) and 3 (2.2%) patients had sequentially used 2, 3, 4, 5, and 6 biological treatment agents, respectively. The most used biological therapy is etanercept (41.7%). Anakinra was used in 30.9% of the patients, adalimumab in 27.3%, canakinumab in 23.7%, and the others in less than 10% (Table 1).

All Adverse Events During Biologic Treatment

Totally 491 adverse events were encountered during the whole duration of biological treatment (501.7 patient-years) and the incidence rate was found to be 97.9 per 100 patient-years (95% CI 89.3-106.9). The most observed adverse events were infection, gastrointestinal system events, laboratory abnormalities, dermatological events, and central nervous system findings. The most frequently seen adverse event was recurrent upper respiratory tract infection in the patients (31.9/100 patient-years 95% CI 27.1-37.2). Elevated aminotransferase level (10.4/100 patient-years, 95% CI (7.7-13.6)), abdominal pain (7/100 patient-years, 95% CI (4.8-9.7)) and headache (5.2/100 patient-years, 95% CI (3.4-7.6)) were among the other common side effects (Table 2). There was a positive correlation between the duration (rho = 0.431, $P < .001$) and number (rho = 0.470, $P < .001$) of biological therapy use and the number of adverse effects.

Injection site reactions were observed in 5 patients; however, no anaphylaxis was recorded. Tocilizumab and infliximab treatments were switched to other biological agents because of increased intracranial pressure in 2 patients. The treatment of 1 patient was changed due to the development of macrophage activation syndrome (MAS) during anakinra treatment. Other adverse events were elevated liver enzymes, neutropenia, headache, abdominal pain, and diarrhea without a need for changing treatment (Table 2). Malignancy developed in none of our patients during entire follow-up periods.

INH prophylaxis was needed before biological treatment in 20.9% of the patients. Tuberculin skin test or QuantiFERON test were applied in all patients before initiating biological agents. As the tests performed in the dispensary were not registered in the system, test results of only 84 patients could be reached. Tuberculin skin test ≥5 mm or positive QuantiFERON test results were accepted to be significant regarding latent tuberculosis and these patients, 20 (23.8%) and 4 (2.9%), respectively were initiated INH prophylaxis. Tuberculosis developed in none of the patients who followed up for latent tuberculosis, except 1 patient who was using etanercept and not attending his regular hospital visits during etanercept treatment.

Adverse Events by Biological Treatment Groups

The adverse events were separately evaluated based on drug groups. The adverse events that developed because of

Table 1. Demographic and Clinical Characteristics of Pediatric Rheumatology Patients Treated with Biologic Drugs

	All patients (n = 139)
Age, year (median, minimum–maximum)	15.3 (3.7-27.3)
Age of onset of biological therapy, year (median, minimum–maximum)	11 (0.6-20.3)
Sex, female†	73 (52.5)
Biological therapy usage time, months, (median, minimum–maximum)	45 (1-146)
Diagnoses†	
JIA	65 (46.8)
FMF	41 (29.5)
Uveitis	10 (7.2)
Behcet syndrome	7 (5)
SLE	4 (2.9)
HIDS	2 (1.4)
JDM	2 (1.4)
CINCA	1 (0.7)
CRMO	1 (0.7)
FCAS	1 (0.7)
Enteropathic arthritis	1 (0.7)
PAN	1 (0.7)
Retroperitoneal fibrosis	1 (0.7)
Anca associated vasculitis	1 (0.7)
Majeed syndrome	1 (0.7)
Drugs used before biological treatment†	
NSAİİ	75 (54)
Glucocorticoid	57 (41)
Methotrexate	64 (46)
Sulfasalazine	15 (10.8)
Colchicine	56 (40.3)
Biological pretreatment tuberculosis prophylaxis†	
Tuberculin skin test ≥5 mm	20/84 (23.8)
QuantiFERON test positivity	4/84 (2.9)
Patient receiving isoniazid prophylaxis	29 (20.9)
Distribution of the number of biological agents used per patient†	
1 Biological therapy	93 (66.9)
2 Biological therapy in different times	34 (24.5)
3 Biological therapy in different times	5 (3.6)
4 Biological therapy in different times	2 (1.4)
5 Biological therapy in different times	2 (1.4)
6 Biological therapy in different times	3 (2.2)
Biological agents used†	
Etanercept	58 (41.7)
Anakinra	43 (30.9)
Canakinumab	33 (23.7)
Adalimumab	38 (27.3)
Tocilizumab	11 (8)
Infliximab	8 (5.8)
Rituximab	6 (4.3)
Tofacitinib	3 (2.2)
Abatacept	2 (1.4)
Secukinumab	1 (0.7)

CINCA, chronic infantile neurologic, cutaneous, and articular syndrome; CRMO, chronic recurrent multifocal osteomyelitis; FCAS; familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulin D syndrome; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis, NSAID; non-steroidal anti-inflammatory drug; PAN, polyarteritis nodosa; SLE, systemic lupus erythematosus.
†Data are given as numbers and percentages.

anti-TNF (adalimumab, etanercept, infliximab), IL-1 antagonists (anakinra and canakinumab) and other biological (rituximab, tofacitinib, tocilizumab, and abatacept) agents were presented in Tables 3, 4 and 5. Headache was prominent in infliximab treatment among anti-TNF agents (26 per 100 patient-years). Dermatological side effects such as urticaria, alopecia, rash and ecchymosis were common with rituximab treatment (Table 5). The rate of infection per 100 patient-years was more common with IL-1 antagonists and other biologic treatments than with anti-TNF agents.

Reasons for Switching or Discontinuing the Biologic Treatment

Biological treatments were stopped a total of 114 times during the treatment duration. The most common reason for discontinuation of therapy was drug ineffectiveness (43.8%). In 24.5% of the patients, treatment was stopped because the disease was in remission. Biological therapy was interrupted in less than 10% of the patients due to the side effects (allergic reaction in 6 patients, pseudotumor cerebri in 2 patients, uveitis, palpitation, and eruption in 1 patient for each) or infection (because of active tuberculosis in 1 patient and development of latent tuberculosis in 5 patients) (Table 6).

DISCUSSION

In our study, we aimed to analyze the adverse events observed in pediatric patients receiving biological treatment. The most used biological treatment was etanercept, followed by anakinra, adalimumab and canakinumab. The most common adverse events were upper respiratory tract infection and laboratory disorders. Although numerous adverse events were observed during biological treatment according to our results, most of those events were transient and non-serious. Biological drugs generally target to inhibit pro-inflammatory cytokines such as TNFα, IL-1, and IL-6, mechanisms employed in the synthesis of pro-inflammatory cytokines such as the Janus-kinase pathway or activation of B and T cells.[14]

TNFi are the first biologics in pediatric rheumatology used in the treatment of JIA. The most used TNFi in children are etanercept and adalimumab which are followed by infliximab.[15-17] Unfortunately, TNFi, similar to other biological agents, may reduce immune response and create a predisposition to infections.[14] The risk for latent tuberculosis reactivation, hepatitis B infections, and fungal infections increases with TNFi usage.[1,18] Based on available data from Europe, the risk of tuberculosis is not high in children on TNFi as long as attending regular clinic visits. According to the German Pediatric Rheumatology Registry comprising 3350 JIA patients, 1720 patients were using etanercept and 177 patients were using adalimumab, while no patient developed tuberculosis.[19] In 2725 JIA patients using etanercept in the BiKeR registry from Germany, latent tuberculosis was detected in only 1 patient while using methotrexate before etanercept.[20] In a study conducted in Turkey by Barut et al[21] with 234 JIA patients, 28 patients were given prophylactic INH due to latent tuberculosis, and active tuberculosis developed in only 1 patient. In another Turkish study, among 144 patients with JIA receiving TNFi, INH prophylaxis was started in 7 patients and antituberculosis treatment was started in 1 patient.[22] In our study, before biological treatment latent tuberculosis was detected in 20.9% of the patients. Isoniazid

Table 2. All Adverse Events during Biologic Treatment in Pediatric Rheumatology Patients

	All Patients	
	Event (Number)	Incidence Rate (Event/100 Patient-Years), 95% CI
Infection	**218**	**43.4 [38.8-49.6]**
Upper respiratory tract infection, event	160	31.9 [27.1-37.2]
Urinary tract infection	15	2.9 [1.7-4.9]
COVID-19	10	1.9 [0.9-3.7]
Pneumonia	6	1.2 [0.4-2.6]
Gingivitis	4	0.8 [0.2-2]
Acute gastroenteritis	4	0.8 [0.2-2]
Varicella	4	0.8 [0.2-2]
Paronychia	3	0.6 [0.1-1.7]
Tuberculosis infection	1	0.2 [0- 1.1]
Other infections	11	2.2 [1.1-3.9]
GIS events	**79**	**15.7 [12.5-19.6]**
Abdominal pain	35	7 [4.8-9.7]
Diarrhea	21	4.2 [2.6-6.4]
Vomiting	9	1.8 [0.8-3.4]
Nausea	9	1.8 [0.8-3.4]
Constipation	4	0.8 [0.2-2]
Other GIS events	1	0.2 [0- 1.1]
CNS events	**35**	7 [4.8-9.7]
Headache	26	5.2 [3.4-7.6]
Dizziness	7	1.4 [0.6-2.9]
Increased intracranial pressure	2	0.4 [0-1.4]
Laboratory abnormalities	**81**	**16.1 [12.8-20]**
Elevated liver function tests	52	10.4 [7.7-13.6]
Neutropenia	17	3.4 [2-5.4]
Thrombocytopenia	5	1 [0.3-2.3]
Other laboratory abnormalities	7	1.4 [0.6-2.9]
Cardiopulmonary events	**6**	1.2 [0.4-2.6]
Chest pain	1	0.2 [0- 1.1]
Dyspnea	3	0.6 [0,1-1.7]
Palpitation	1	0.2 [0- 1.1]
Presyncope	1	0.2 [0- 1.1]
Dermatological events	**41**	**8.2 [5.9-11.1]**
Eruption	13	2.6 [1.4-4.4]
Hair loss	7	1.4 [0.6-2.9]
Urticaria	6	1.2 [0.4-2.6]
Injection site reaction	5	1 [0.3-2.3]
Other dermatological events	10	2 [0.9-3.7]
Ear, nose, and eye events	**19**	**3.8 [2.3-5.9]**
Cataract	7	1.4 [0.6-2.9]
Decreased visual acuity	4	0.8 [0.2-2]
Uveitis	2	0.4 [0-1.4]
Epistaxis	1	0.2 [0-1.41
Other ear, nose, and eye events	5	1 [0.3-2.3]
Other adverse events	**12**	2.4 [1.2-4.1]

CI, confidence interval; CNS, central nervous system; COVID-19, coronavirus disease 2019; GIS, gastrointestinal system.

Table 3. All Adverse Events during Tumor Necrosis Factor Alpha Inhibitor Therapy in Pediatric Rheumatology Patients

	Adalimumab		Etanercept		Infliximab	
	Event (Number)	Incidence Rate (Event/100 Patient-Years) 95% CI	Event (number)	Incidence Rate (Event/100 Patient-Years 95% CI)	Event (Number)	Incidence Rate (Event/100 Patient-Year) 95% CI
Infection	26	24.5 [16-35.9]	48	27.8 [20.5-36.8]	7	16.7 [6.7-34.3]
GIS events	17	16 [9.3-25.7]	16	9.2 [5.3-15]	0	-
CNS events	3	2.8 [0,6-8.3]	9	5.2 [2.4-9.9]	14	33.3 [18.2-55.9]
Laboratory abnormalities	13	12.3 [6.5-21]	23	13.3 [8.4-19.9]	3	7.1 [1.5-20.9]
Cardiopulmonary events	2	1.9 [0.2-6.8]	4	2.3 [0.6-5.9]	0	-
Dermatological events	8	7.5 [3.3-14.9]	8	4.6 [2-9.1]	3	7.1 [1.5-20.9]
Ear, nose, and eye events	5	4.7 [1.5-11]	6	3.5 [1.3-7.5]	2	4.8 [0.6-17.2]
Other adverse events	1	0.9 [0-5.2]	4	2.3 [0.6-5.9]	2	4.8 [0.6-17.2]

CI, confidence interval; CNS, central nervous system; GIS, gastrointestinal system.
*The total duration of TNF inhibitor use is 320.25 patient-years.

Table 4. All Adverse Events during Interleukin-1 Antagonist Therapy in Pediatric Rheumatology Patients

	Anakinra		Canakinumab	
	Event (Number)	Incidence Rate (Event/100 Patient-Years), 95% CI	Event (number)	Incidence Rate (Event/100 Patient-Years), 95% CI
Infection	26	60.5 [39.5-88.6]	89	77.4 [62.1-95.2]
GIS events	6	14 [5.1-30.4]	18	15.7 [9.3-24.7]
CNS events	1	2.3 [0-13]	2	1.7 [0.2-6.3]
Laboratory abnormalities	12	28 [14.4-48.7]	23	20 [12.7-30]
Cardiopulmonary events	0	-	0	-
Dermatological events	5	11.6 [3.8-27.1]	9	7.8 [3.6-14.9]
Ear, nose, and eye events	1	2.3 [0-13]	0	-
Other adverse events	3	7 [1.4-20.4]	1	0.9 [0-4.8]

CI, confidence interval; CNS, central nervous system; GIS, gastrointestinal system.
*Total duration of IL-1 antagonist use is 157.8 patient-years.

prophylaxis was initiated in these patients and biological treatment was started after it is determined that there is no active tuberculosis. Drug cessation necessary for 1 patient due to the development of tuberculosis and in 5 due to the detection of evidence for latent tuberculosis during follow-up whereas baseline tuberculin skin test <5 mm or QuantiFERON test was negative. The administration of biological drugs was continued after the application of INH prophylaxis in these patients if the need for biological treatment still continued. In patient with active tuberculosis, antituberculosis treatment was started.

Table 5. All Adverse Events during the Use of other Biological Agents in Pediatric Rheumatology Patients

	Rituximab		Tofacitinib		Tocilizumab		Abatacept	
	Even (Number)	Incidence Rate (Event/100 patient year), 95% CI	Event (number)	Incidence Rate (Event/100 Patient-Years), 95% CI	Event (Number)	Incidence Rate (Event/100 Patient-Years), 95% CI	Event (Number)	Incidence Rate (Event/100 Patient-Years), 95% CI
Infection	2	126.6 [15.3-457.6]	3	52.6 [10.3-146]	15	98.4 [56-165]	2	240 [29.1-867.3]
GIS events	0	-	1	17.5 [0.4-92.9]	21	137.7 [86.7-214]	0	-
CNS events	0	-	2	35.1 [4-120.4]	4	26.2 [7.3-68.3]	0	-
Laboratory abnormalities	0	-	0	-	7	46 [18.8-96.1]	0	-
Cardiopulmonary events	0	-	0	-	0	-	0	-
Dermatological events	5	316.6 [102.8-739]	0	-	3	19.7 [4.1-58.4]	0	-
Ear, nose, and eye events	2	126.6 [15.3-457.6]	0	-	3	19.7 [4.1-58.4]	0	-
Other adverse events	0	-	0	-	1	6.6 [0.2-37.1]	0	-

CI, confidence interval; CNS, central nervous system; GIS, gastrointestinal system.
*The total duration of use of other biological therapies is 23.3 patient-years.

Table 6. Reasons for Switching or Discontinuing the Biologic Treatment in Pediatric Rheumatology Patients

	1. Biologic Therapy	2. Biologic Therapy	3. Biologic Therapy	4. Biologic Therapy	5. Biologic Therapy	6. Biologic Therapy	Total
Remission	24	4	0	0	0	0	28
Side effect	7	1	2	0	1	0	11
Ineffectiveness	23	12	6	5	3	1	50
Infection	5	1	0	0	0	0	6
Patient non-compliance	19	0	1	0	0	0	20
Total	78	18	8	5	4	1	114

Despite the well-organized worldwide vaccination program, tuberculosis remains one of the commonest general infections, particularly in endemic countries. Since our country is an endemic region in terms of tuberculosis infection, the rate of latent tuberculosis was higher than in the West.[23] However, we conclude that performing regular screening for latent tuberculosis and paying attention to the use of prophylactic INH is of particular importance and hence decreased the rate of cases with active tuberculosis in our study.

According to our data, the most frequently encountered adverse events were infections. Upper respiratory tract infections were the most prominent ones. There are also some studies reporting that infection risk induced with the treatment of TNFi is similar to the non-biological disease-modifying antirheumatic drugs (DMARDs) as well as studies showing that risk for serious infections increases with the treatment of TNFi.[19,24-26] The occurrence of infections in our immunocompromised patients was an expected condition. However, these infections, other than tuberculosis, were mild and transient infections that did not require a change in treatment and did not require hospitalization.

Another frightening adverse event due to the treatment of TNFi is malignancy. Fortunately, no malignancy was encountered during the follow-up period in our patients who used TNFi or other biological treatments. The risk for malignancy in the children with JIA increased compared to children without JIA in 2 cohorts carried out by Beukalman et al. However, TNFi was not found to be associated with the development of malignancy.[27,28] Although, it has been demonstrated that TNFi increases the risk for malignancy in young males with inflammatory bowel disease, increased risk in JIA could not be exhibited.[29] According to a recent meta-analysis in adults, no higher incidence of malignancy was found with (Janus kinase) JAK inhibitor uses than with placebo or methotrexate in inflammatory joint, skin, and bowel diseases. However, JAK inhibitors were associated with a higher incidence of malignancy compared with TNFi. Cancer events were rare across all treatments, the overall incidence rate was 1 event per 100 person years of exposure.[30]

Interleukin 1 is a proinflammatory cytokine released from monocytes and macrophages.[31,32] It has a key role in chronic inflammation. Anakinra is a recombinant human interleukin-1 beta receptor antagonist (IL-1RA). Canakinumab is a humanized monoclonal antibody against IL-1β. Interleukin-1β inhibitors are effective in the conditions such as JIA, autoinflammatory diseases, and MAS.[33,34] Although neutropenia, nausea, diarrhea, influenza-like symptoms, serious infections and cardiopulmonary arrest have been reported during the treatment of anakinra, the most common adverse side effects are injection site reactions and infections.[2,35] Increased risk for infection was detected in a multicenter study conducted on 45 patients with CAPS who were given canakinumab, however, it was reported that no other life-threatening side effect was identified. Injection site reaction was determined at a lower rate compared with other IL-1 blockers.[6] No opportunist infection, tuberculosis, or malignancy was reported in 2 randomized, controlled trials conducted in the systemic JIA patients, however, increased frequencies of infection risk, disease attacks, and development of MAS were reported.[34,36] In our patients who received IL-1 antagonist treatment; the most often adverse events were infections, elevated liver enzymes, and complaints of the gastrointestinal system. The patients who used IL-1 antagonist were most commonly colchicine-resistant FMF patients, and these patients also continued to receive colchicine treatment together with IL-1 antagonist treatment. Its concurrent use with colchicine may be the reason for both elevated liver enzymes and gastrointestinal system complaints. Even though we did not statistically compare the frequency of infection between patients using IL-1 antagonist and TNFi, we determined that the incidence rate of infection was higher in patients using IL-1 antagonist than in patients using TNFi. The most important factor for this outcome can be predicted as that the total treatment duration of the patients who used TNFi was approximately 2-fold higher than those who used IL-1 antagonists. As treatment durations become shorter, the development of even a single adverse event may significantly influence the incidence rate.

Interleukin 6 is a proinflammatory cytokine and high levels of IL-6 were detected in the serum and synovial fluid of the children with systemic JIA and polyarticular JIA.[37] Tocilizumab, developed in light of this information, is a recombinant humanized monoclonal antibody and shows its effect by blockading the release of IL-6.[38] It has been shown in the TENDER trial that tocilizumab was more effective than the placebo group in the sJIA patients. Although, more side effects were encountered in the group that received the treatment of tocilizumab compared with the placebo group, however, non-serious infections, transient neutropenia, and high level of transaminase were the most common ones.[39] The long-term efficacy, tolerability, and safety of tocilizumab are currently being researched. In line with our study results indicating transient gastrointestinal complaints and mild infectious events, in an international study addressing the use of tocilizumab in polyarticular JIA, mild gastrointestinal findings and upper respiratory tract infections were commonly seen as side effects.[40] In our cohort, in only 1

patient, changing treatment was needed due to the detection of increased intracranial pressure syndrome with intravenous administration of tocilizumab.

Abatacept is a fully human soluble fusion protein consisting of the extracellular domain of the CTL+ antigen and a fragment of the Fc domain of IgG.[41,42] It is the first biological agent that blockades the cellular activation signal to T-cell from the antigen-presenting cell. It causes the consumption of T-cells, inhibition of their functions, and activation of naive T and memory T cells.[42,43] Abatacept was approved by Food and Drug Administration for serious polyarticular JIA in 2008 in patients aged 6 years old or over who were refractory to other DMARDs or TNF inhibitors or those in whom an inadequate response was obtained.[44] Infusion reactions with abatacept have been usually reported as headache, dizziness, hypotension, or mild hypersensitivity.[2] Several serious unexpected effects such as varicella, encephalitis, and hematoma were observed in the studies on JIA. All of those were reported to be recovered without any sequelae.[45] In our study, abatacept was used in only 2 of our patients with JIA and no adverse event was monitored except non-serious infections, however, treatment could not be continued because of drug inefficacy.

Rituximab is useful in the treatment of AAV, SLE, JIA, and inflammatory central nervous system diseases. Infusion reaction, increased infection risk possibly due to prolonged low levels of immunoglobulins and activation of hepatitis B virus, and increased risk for progressive multifocal leukoencephalopathy when rarely used together with other agents have been denoted as the unexpected effects.[1] No serious adverse event was encountered in our patients under the treatment of rituximab. Even though it can be concluded as an outcome that infection and adverse gastrointestinal events were observed more frequently due to the treatments of rituximab, tofacitinib, tocilizumab, and abatacept classified as the other biological agents in our article compared with the treatments of TNF inhibitors and IL-1 antagonists, we should take into consideration that a short total treatment duration of these patients such as approximately 24 patient-years may have a misleading effect.

In pediatric rheumatology practice conventional DMARDs and colchicine are commonly used in addition to several biological agents. In the context of concurrent treatment, discerning whether side effects arise from biological treatment or other concurrent therapies is not feasible. The main limitations of our study were the effects of concomitant treatments and having a single-center retrospective design. However, our study has also strengths such as demonstrating the fact based on real-life data that how can the biological and targeted treatments used in pediatric rheumatology with increasing frequency can induce adverse effects and reporting this fact comprehensively. As the pathogenesis of rheumatological diseases has been understood, new treatment modalities are developed, and these treatments are introduced to our practice with increasing frequency. Although adverse events with the use of biological agents are mostly mild and transient, they should be paid attention to regarding serious side effects and the patient should be closely followed up.

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