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Retrospective analyzes of adverse events during biologic agents in children with juvenile idiopathic arthritis from a single center in Turkey

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Abstract

Objectives: Juvenile idiopathic arthritis is the most common rheumatic disease in childhood. Biologic agents have changed the course of juvenile idiopathic arthritis. However, there are concerns regarding the occurrence of serious adverse events in patients receiving biologic agents. The aim of this study was to evaluate adverse events in children with juvenile idiopathic arthritis receiving biologic agents.

Material and methods: This retrospective study includes juvenile idiopathic arthritis patients receiving biologic agents. Demographic features and adverse events during biologic agents were collected from medical files. Adverse events that either resulted in death, were life-threatening, required inpatient hospitalization, or resulted in persistent or significant disability/incapacity were considered as serious adverse events.

Results: In total, 162 juvenile idiopathic arthritis patients (55.6% female) receiving biologic agents were enrolled: 101 (62.3%) patients treated with etanercept, 27 (16.7) with tocilizumab, 14 (8.6%) with adalimumab, 15 (9.2%) with anti-interleukin 1 agents (13 canakinumab, 2 anakinra), and 5 (3.1%) with infliximab. 75.9% of the patients received concomitantly disease-modifying anti-rheumatic drugs, and 20.4% received disease-modifying anti-rheumatic drugs plus corticosteroid. The mean age at initiation of the biologic agent was 10.5 ±4.3 years. The mean age at the study enrolment was 12.1 ±4.5 years. The mean follow-up duration was 19.7 ±2.1 months. The most frequent adverse event was upper respiratory tract infections (54.3%) followed by urinary tract infections (21%). Anaphylaxis occurred in 3 patients (1.9%): 2 with tocilizumab and one with infliximab. Macrophage activation syndrome occurred in 1 patient (0.6%) receiving tocilizumab. Lung tuberculosis developed in 2 patients (1.2%) receiving canakinumab. The frequency of serious adverse events in total was 6.7%.

Conclusions: While the most frequent adverse events during biologic agents was upper respiratory tract infections, the frequency of serious adverse events was 6.7%; therefore, juvenile idiopathic arthritis patients receiving biologic agents should be carefully evaluated for these adverse events in clinical practice.

Key words: juvenile idiopathic arthritis, biologic agents, infections, adverse events.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in childhood with a chronic course. Over the past decades, pharmacotherapy of JIA has improved dramatically with the utilization of biologic agents (BAs) that control the disease activity much more effectively, thus improving the quality of life of the patients [1–3].

Biologic agents are a new sort of drugs that differ from non-biologic disease-modifying antirheumatic drugs (DMARDs) in that they are manufactured with

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biologic processes and target specific molecules that are expressed on cells or secreted into the extracellular space, such as tumour necrosis factor α (TNF-α), interleukin (IL) 1β, and IL-6 [4].

Essentially, all biologics are immunogenic because they are non-self; therefore, they may lead to antibody responses that give rise to neutralization of biologic activity, anaphylactoid reactions, and loss of efficacy. These effects seem to be related with host-related factors, the dose, and the route of administration [5].

There are several studies investigating the efficacy and safety of BAs with various results [6–11]. The most frequent adverse event on BAs is upper respiratory tract infections (URTIs) [6–11].

There are also concerns about the association between occurrence of serious infections, malignancies, and autoimmune diseases with exposure to BAs [4]. However, due to the difficulty of a randomized placebo-controlled study design, clinical trials are disempowered to determine whether serious infections, malignancies, and autoimmune diseases are associated with BAs [4].

Therefore, the data on the long-term safety of BAs in children are still scarce. The objective of the current study is to retrospectively analyze the adverse events in JIA patients on BAs from a pediatric rheumatology center.

Material and methods

This is a retrospective study investigating adverse events during BA treatment in children with JIA. Juvenile idiopathic arthritis patients diagnosed between August 2008 and March 2019, who were still in follow-up in our pediatric rheumatology department, were included in the study.

Diagnosis of the patients and treatment choices were designated by pediatric rheumatologists accordingly. The patients were diagnosed according to the International League of Associations for Rheumatology (ILAR) classification criteria and sub-grouped as oligoarticular JIA, rheumatoid factor (RF)-positive polyarticular JIA, RF-negative polyarticular JIA, systemic-onset JIA (soJIA), and enthesitis-related arthritis (ERA) [12].

All patients' data were collected from the medical files of the patients. Demographic characteristics, treatment modalities, laboratory data of the patients, and the diagnosis of rheumatic disease in first-degree relatives were included in the data. Prior to study initiation, written informed consent was obtained from all the patients' parents. Ethical approval was obtained from the Institutional Review Board of the local medical school.

The biologic agents that were received by the participants consisted of TNF-α inhibitors (etanercept, adalimumab, and infliximab), fully human monoclonal antibody targeting IL-1β (canakinumab), IL-1 receptor antagonist (anakinra), and humanized monoclonal antibody targeting IL-6 receptor (tocilizumab). Pediatric rheumatologists selected the BAs in agreement with type and activity of the disease and switched or discontinued the BAs due to adverse events or remission. The patients receiving BAs were followed up regularly by pediatric rheumatologists according to JIA subgroup, disease activity, and the type of BAs, in at least three-month intervals.

Adverse events (AEs) and serious adverse events (SAEs) were recorded from the medical files of the patients, which included comprehensive information about adverse events that were based on interrogation of symptoms, physical examination, and laboratory parameters at least quarterly during routine follow-up. Adverse events that either resulted in death, were life-threatening, required inpatient hospitalization, or resulted in persistent or significant disability/incapacity were considered as SAEs [13].

Upper respiratory tract infections (URTIs) included rhinosinusitis, pharyngitis, laryngitis, laryngotracheitis, and otitis media, which were treated in outpatient clinics. Pneumonia referred to lower respiratory tract infection with symptoms included fever, chills, and cough with sputum production and confirmed by X-ray testing. Anaphylaxis was defined according to National Institutes of Health Food Allergy and Anaphylaxis Network criteria for anaphylaxis [14].

Local injection site reactions (ISRs) were defined as having redness, itching, pain, swelling, and burning at the injection site. However, injection site reactions more than 4 cm in diameter were defined as large local reactions, which were also considered as SAEs. Microscopic analyses of midstream urine samples were used to determine urinary tract infections (UTIs). The finding of > 5 white blood cells per high-power field in a centrifuged urine specimen in a symptomatic patient was reported as a UTI.

Statistical analysis

All statistical analyses were performed by using Statistical Package for the Social Sciences (SPSS) software version 20.0 (IBM SPSS Statistics). Demographic features and disease characteristics were summarized with the use of descriptive statistics.

Categorical variables were presented as numbers and percentages. Continuous variables were summarized as mean and standard deviation and as median and minimum-maximum where appropriate. χ^2 test was performed to compare frequencies of AEs among the administered BAs. The statistical level of significance for all tests was determined to be 0.05.

Results

Baseline characteristics

A total of 162 juvenile idiopathic arthritis patients were included in the present study, of whom 90 (55.6%) were female and 72 (44.4%) were male. While the mean age at the initiation of a biologic agent was 10.5 ±4.3 years, the mean age at the study enrolment was 12.1 ±4.5 years. The mean follow-up duration was 19.7 ±2.1 months. The total duration of exposure to BAs was 269.7 years. Demographic features of the disease are given in Table I.

The distribution of juvenile idiopathic arthritis patients in agreement with International League of Associations for Rheumatology (ILAR) criteria were as follows: oligoarticular JIA (n = 53, 32.7%), systemic onset JIA (soJIA, n = 51, 31.5%), RF-negative polyarticular JIA (n = 28, 17.3%), ERA (n = 24, 14.8%), and RF-positive polyarticular JIA (n = 6, 3.7%). The distribution of the disease subgroups is given in detail in Table I.

Biological agents and concomitantly administered immunosuppressive drugs

Etanercept was the most administered BA, with a frequency of 62.3% (n = 101). Moreover, TNF-α antagonists represented 70.9% (n = 115) of all BAs. The median administered dosage of all BAs was 31 (range; 1–520) doses. A total of 123 (75.9%) patients were given DMARDs concomitantly, particularly methotrexate. Moreover, 20.4% (n = 33) of the patients were prescribed both corticosteroid and DMARDs.

The distribution of BAs and concomitantly administered immunosuppressive drugs are given in Table I.

Adverse events

The most frequently encountered adverse events were upper respiratory tract infections, with a 54.3% (n = 88) frequency, which were treated in an outpatient clinic. Ten patients (6.2%) developed pneumonia, which required hospitalization in 3 patients. While urinary tract infections occurred in 34 (21%) patients, none of them developed pyelonephritis.

Twenty-four (17.8%) out of 135 patients developed injection-site reactions with BAs administered subcutaneously. Injection-site reactions were below 4 cm in diameter and were treated in an outpatient clinic, except for the two patients having etanercept.

Etanercept treatments were discontinued due to the large ISRs in those two patients. Throughout the follow-up, anaphylactic reactions occurred in two patients having tocilizumab and in one patient having infliximab (a total of 3 patients, 1.9%), which led to discontinuation of those BAs. An episode of macrophage activation syndrome (MAS) occurred in one JIA patient on tocilizumab treatment.

Moreover, two siblings with soJIA having canakinumab were diagnosed with lung tuberculosis. Serious adverse events were as follows: 1 MAS episode in a soJIA patient, 3 anaphylactic reactions in 1 oligoarticular JIA and in 2 soJIA patients, 2 lung tuberculosis in soJIA patients, and 3 pneumonia cases that required hospitalization in soJIA patients, and 2 large local injection site reactions occurred in two ERA patients on BAs.

In total, serious adverse events occurred with a frequency of 6.7% (n = 11) among JIA patients on BAs. None of the patients developed malignancy or died during BA treatment due to AEs. The frequency of all adverse events during BAs in JIA patients are given in Table II, in detail.

Table I. Demographic features and distribution of the disease subgroups and administered biologic agents of juvenile idiopathic arthritis patients

Parameters	Numerical values
Demographic features	162 (100)
Female/male, *n* (%)	90 (55.6)/72 (44.4)
The mean age of biologic treatment onset, years (SD)	10.5 (4.3)
The mean age at study time, years (SD)	12.1 (4.5)
Mean follow-up duration, months (SD)	19.7 (2.1)
Median administered dose of biologic agents; minimum-maximum	31 (1–520)
JIA subgroups	
Oligoarticular JIA, *n* (%)	53 (32.7)
Systemic-onset JIA, *n* (%)	51 (31.5)
RF-negative polyarticular JIA, *n* (%)	28 (17.3)
Enthesitis-related arthritis JIA, *n* (%)	24 (14.8)
RF-positive polyarticular JIA, *n* (%)	6 (3.7)
Biologic agents	
Etanercept, *n* (%)	101 (62.3)
Tocilizumab, *n* (%)	27 (16.7)
Adalimumab, *n* (%)	14 (8.6)
Canakinumab, *n* (%)	13 (8)
Infliximab, *n* (%)	5 (3.1)
Anakinra, *n* (%)	2 (1.2)
Co-prescriptions with biologic agents	
DMARDs, *n* (%)	123 (75.9)
DMARDs plus corticosteroid, *n* (%)	33 (20.4)

DMARDs – disease-modifying antirheumatic drugs, JIA – juvenile idiopathic arthritis, RF – rheumatoid factor, SD – standard deviation.

Table II. The frequency of adverse events during biological drug therapy in children with juvenile idiopathic arthritis

Parameters	Numerical values
Infections	
Upper respiratory tract infections, *n* (%)	88 (54.3)
Urinary tract infections, *n* (%)	34 (21)
Herpes labialis, *n* (%)	17 (10.5)
Pneumoniae, *n* (%)	10 (6.2)
Tuberculosis, *n* (%)	2 (1.2)
Abscess, *n* (%)	2 (1.2)
Impetigo, *n* (%)	1 (0.6)
Chickenpox, *n* (%)	1 (0.6)
Hematologic events	
Lymphopenia, *n* (%)	12 (7.4)
Neutropenia, *n* (%)	6 (3.7)
Thrombocytopenia, *n* (%)	2 (1.2)
Haemolytic anaemia, *n* (%)	1 (0.6)
Others	
Injection site reactions, *n* (%)	24 (17.8)
Erythematous skin rashes, *n* (%)	5 (3.1)
Elevated liver function tests, *n* (%)	5 (3.1)
Anaphylaxis, *n* (%)	3 (1.9)
Macrophage activation syndrome, *n* (%)	1 (0.6)

Table III. Tuberculin skin test results and the frequency of isoniazid preventive therapy of juvenile idiopathic arthritis patients on biologic agents

Parameters	Numerical values
Initial TST, median (min–max)	0 (0–20)
Last TST, median (min–max)	0 (0–20)
IPT, *n* (%)	23 (14.2)
Tuberculosis, *n* (%)	2 (1.2)

TST – tuberculin skin test, IPT – isoniazid preventive therapy.

The median initial tuberculin skin test result was 0 (range; 0–20). After administration of BAs, isoniazid preventive therapy (IPT) was given to 23 (14.2%) JIA patients due to increased tuberculin skin test (TST).

Moreover, two siblings with soJIA developed lung tuberculosis during canakinumab treatment and were treated accordingly, which resulted in restarting BAs. Those two soJIA patients were treated with etanercept, abatacept, and tocilizumab before canakinumab treatment.

Tuberculin skin test results and the frequency of isoniazid preventive therapy of JIA patients on BAs are given in Table III.

For comparison of the frequency of adverse events, the patients were grouped according to the administered BAs as follows:

- group 1: anti-TNF-α agents (etanercept, adalimumab and infliximab),
- group 2: anti-IL-1 agents (canakinumab and anakinra),
- group 3: tocilizumab.

The frequency of adverse events did not differ between the groups except for lung tuberculosis and neutropenia. The frequency of neutropenia was significantly higher in JIA patients on tocilizumab and the frequency of lung tuberculosis in patients on canakinumab.

Moreover, the frequency of co-treatment with corticosteroid and disease-modifying anti-rheumatic drugs was significantly higher in the groups using anti-IL-1 agents and tocilizumab. Comparison of the frequency of adverse events between juvenile idiopathic arthritis patients according to the administered BAs are given in Table IV.

In the present study, we could not compare the frequency of AEs in patients according to the JIA subgroups due to the small number of some subgroups.

Discussion

In the present study, adverse events during BAs were retrospectively investigated in JIA patients. The most utilized biologic agents were anti-TNF-α agents, and the most encountered adverse event was URTIs in JIA patients on BAs in this study. The second most encountered adverse event was UTIs in which none of them developed pyelonephritis and required hospitalization.

In total, serious adverse events occurred with a frequency of 6.7% (n = 11) among JIA patients on BAs – in detail: 1 MAS episode in a soJIA patient on tocilizumab, 3 anaphylactic reactions in 1 oligoarticular JIA on infliximab and in 2 soJIA patients on tocilizumab, 2 lung tuberculosis in soJIA patients on canakinumab, and 3 pneumonia that required hospitalization in soJIA patients on tocilizumab, and 2 large local injection site reactions in 2 ERA patients on etanercept occurred. Although none of the patients developed malignancy or died during BAs treatment due to AEs, the short length of the study period makes the interruption difficult in this regard.

Up to now, there have been two observational retrospective studies investigated all BAs, 1 in JIA patients and the other in all pediatric rheumatic diseases [11, 15].

Cabrera et al. [11] reported a multicenter, observational, retrospective study investigating the incidence of side effects of biological agents in 813 pediatric patients with inflammatory diseases. The main diagnosis

Table IV. Comparison of the frequency of adverse events between juvenile idiopathic arthritis patients according to the administered biologic agents

Parameter	Anti-TNF-α agents 120 (74.1)	Anti-IL-1 agents 15 (9.3)	Tocilizumab 27 (16.7)	*p*-value
Co-prescriptions				
Co-prescription of DMARDs, *n* (%)	87 (72.5)	11 (73.3)	25 (92.5)	0.066
Co-prescription of DMARDs + CS, *n* (%)	13 (10.8)	6 (40.4)	14 (51.8)	0.001
Adverse events				
URTI, *n* (%)	67 (55.8)	6 (40)	15 (55.6)	0.505
UTIs, *n* (%)	21 (17.5)	6 (40)	7 (25.9)	0.103
Herpes labialis, *n* (%)	13 (10.8)	1 (6.7)	3 (11.1)	0.878
Pneumoniae, *n* (%)	5 (4.2)	2 (13.3)	3 (11.1)	0.192
Tuberculosis, *n* (%)	0 (0)	2 (13.3)	0 (0)	0.001
Abscess, *n* (%)	1 (0.8)	0 (0)	1 (3.7)	0.428
Impetigo, *n* (%)	1 (0.8)	0 (0)	0 (0)	0.839
Chickenpox, *n* (%)	0 (0)	0 (0)	1 (3.7)	0.081
ISRs, *n* (%)	20 (16.7)	3 (20)	0 (0)	0.193
Erythematous skin rashes, *n* (%)	3 (2.5)	0 (0)	2 (7.4)	0.316
Elevated LFTs, *n* (%)	4 (3.3)	0 (0)	1 (3.7)	0.765
Anaphylaxis, *n* (%)	1 (0.8)	0 (0)	2 (7.4)	0.062
MAS, *n* (%)	0 (0)	0 (0)	1 (3.7)	0.081
Neutropaenia, *n* (%)	0 (0)	1 (6.7)	5 (18.5)	0.001
Lymphopaenia, *n* (%)	8 (6.7)	2 (13.3)	2 (7.4)	0.649
Thrombocytopaenia, *n* (%)	1 (0.8)	0 (0)	1 (3.7)	0.428

CS – corticosteroid, DMARDs – disease-modifying antirheumatic drugs, ISRs – injection-site reactions, LFTs – liver function tests, MAS – macrophage activation syndrome, URTI – upper respiratory tract infection, UTIs – urinary tract infections. χ^2 *test was utilised to compare the frequency of adverse events among the three groups, significant p-values (< 0.05) are presented in bold.*

in that study was JIA with 84% frequency. The mean follow-up duration was 4.7 ±3.1 years. There was a total of 1179 BA prescriptions for 813 patients. The anti-TNF-α agents, particularly etanercept, represented 75% of all utilized BAs. A total of 419 adverse events reported in 222 patients. Adverse events were most frequently mild (46%). The frequency of severe and very severe adverse events was 15% in all patients. The incidence of adverse events was higher in JIA patients. There were two MAS episodes during tocilizumab treatment. Moreover, two serious events during etanercept treatment – one Hodgkin's lymphoma in a RF-positive JIA patient and one death due to JIA associated pulmonary fibrosis – occurred. Furthermore, one severe sepsis requiring intensive care unit hospitalization in the non-JIA group occurred during infliximab treatment, and one demyelinating lesion appeared with canakinumab. It was concluded that the study found an overall favorable outcome for children with pediatric inflammatory rheumatic diseases treated with all BAs [11].

The other study was from Finland by Tarkiainen et al. [15]. The study included 348 consecutive patients with JIA from three centers. Oligoarticular juvenile idiopathic arthritis was the most frequent disease subgroup, and etanercept was the most utilized biologic agent. Upper respiratory tract infections were the most encountered adverse event (71.8%). A total of 121 patients (35%) experienced SAEs and 12.6% of them were serious infections. Moreover, two systemic-onset juvenile idiopathic arthritis patients on etanercept died due to serious infections. None of the patients developed lung tuberculosis and malignancy [15]. Similarly to both studies, in our study, URTIs were the most encountered adverse events during BAs. The rate of serious adverse events in the current study was 6.7%, with no sequelae or death after discontinuation of BAs, similar to the report of Cabrera et al. [11]; however, the result was lower than the Finnish study in which SAEs were reported in 35% of the patients [15].

The difference between the rates of SAEs among studies might be due to the methodology of the studies.

In the Finnish study [15], at least three sources of information were used for collecting data, which may have led to more accurate data on AEs as compared to our study, in which data collection were based on medical records held by pediatric rheumatologists, similar to the report of Cabrera et al. [11]. Moreover, another explanation for the differences might be the diversity of definition of SAEs. In the Finnish study [15], adverse events, classified as serious according to the Common Terminology Criteria for Adverse Events (CTCAE) [16], which contain various organ infections and symptoms, psychiatric disorders, even elevated liver transaminase levels, neutropenia which may also lead to increased frequency of SAEs compare to our study, in which AEs either resulted in death, were life-threatening, required inpatient hospitalization, resulted in persistent or significant disability/incapacity were considered as SAEs.

Serious adverse events in the present study included anaphylaxis in 3 patients, large ISRs in 2 patients, tuberculosis in 2 patients, MAS in 1 patient, and pneumonia that required hospitalization in 3 patients.

While biologic agents have revolutionized the therapies for chronic inflammatory, neoplastic, and autoinflammatory disease, like other pharmaceutical agents, they can cause anaphylactic reactions. Anaphylaxis has been reported with various BAs, including rituximab, infliximab, and tocilizumab in pediatric rheumatic diseases [17–21]. Anaphylactic reactions to BAs can occur on the first dose or after multiple exposures [22].

In the present study we encountered anaphylaxis in 3 patients – 2 during tocilizumab and 1 during infliximab treatment. Anaphylaxis was reported in 4 (1.1%) patients during infliximab treatment in the study of Tarkiainen et al. [15]. To our knowledge, there is only one study evaluating severe hypersensitivity reactions to biological agents in children with all rheumatic diseases from Turkey [23].

In that study, 128 patients using eight different BAs with all rheumatic diseases were evaluated. The frequency of anaphylaxis was reported to be 3.9% in children with all rheumatic diseases and 4% in JIA patients [23]. In the present study, the frequency of anaphylaxis was lower (1.9%) than the previous report among JIA patients. Unlike our study, the previous study enrolled patients with all rheumatic diseases, which might explain the higher frequency of anaphylaxis among patients receiving BAs in the previous study.

The most important complication of the soJIA is MAS, and it can be deadly. Macrophage activation syndrome occurs in almost 10% of soJIA patients and may occur even under BAs [24–26]. In the present study we encountered one MAS episode at the sixth dose of tocilizumab treatment in a soJIA patient. In regard to macrophage activation syndrome, Cabrera et al. [11] also reported two MAS episodes during tocilizumab treatment in JIA patients. However, in the other previous study, they did not report any MAS episode during follow-up, rather than soJIA activation [15].

The risk of tuberculosis development or activation is an area of concern in BA-administered patients [27]. In regard to tuberculosis, in this study 2 siblings with soJIA under canakinumab treatment were diagnosed with lung tuberculosis. However, they were also given methotrexate, methylprednisolone concomitantly, and had a long-lasting disease that led to being given various BAs before canakinumab treatment. Therefore, it is difficult to conclude that these side effects are solely related to canakinumab administration.

There are diverse clinical studies investigating the safety of BAs as well as the effectiveness of BAs in the treatment of pediatric rheumatic diseases, particularly JIA [6–11]. In those studies, BAs were found to be well tolerated and the most encountered infections were the URTIs which were treated at outpatient clinics. In the present study, the most frequent AEs were also URTIs with a frequency of 54.3%, which were also treated at outpatient clinics, similarly to the literature.

However, there is only one prospective study investigating the occurrence of infections in JIA patients on all BAs from Turkey [6]. A total of 307 juvenile idiopathic arthritis patients, mainly oligoarticular JIA, were included the study. Juvenile idiopathic arthritis patients on BAs were examined by a pediatric infectious disease specialist every 2 months during 1 year. The most frequently administered BA was etanercept. During the study period, 57% of the patients developed infection. Upper respiratory tract infections were the most frequently encountered infections, in which none of the patients required hospitalization. The rate of urinary tract infections was similar to our findings, with 18.8% frequency. Chickenpox was diagnosed in 7 patients (2.2%), none of whom were hospitalized or developed any complications. During one-year follow-up, pneumoniae was diagnosed in 12 patients (3.9%), in whom two required hospitalization. Lung tuberculosis occurred in 2 patients (0.6%) during etanercept and adalimumab treatments. The findings of our study and the previous study are comparable in terms of encountered infections, and most of the encountered AEs were easily treated at outpatient clinics.

The main limitation of the present study is the retrospective design, which might lead to miss-collection of some adverse events. Moreover, the relatively small number of each BA group and juvenile idiopathic arthritis subgroups make the interpretation of statistical analyses difficult between groups. Therefore, further, multicenter, prospective studies are needed for the iden-

tification of the real-life incidence of side effects of BAs in pediatric rheumatic diseases. However, we still think that the data on SAEs give us important knowledge about JIA patients on BAs.

Conclusions

In the current study, upper respiratory tract infections were the most frequently encountered adverse event in JIA patients using BAs. In total, the frequency of SAEs was 1.9%. Although serious adverse events are rare in clinical practice and can be managed easily either with discontinuation of therapy or with treatment of AEs, we suggest that patients on BAs should be monitored and interrogated for the possibility of various adverse events.

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