

Evaluation of Hypersensitivity Reactions in Pediatric Patients Using Biological Drugs

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Keywords

Biological drugs · Hypersensitivity reactions · Children

Abstract

Introduction: Biological drugs are currently used for the treatment of chronic inflammatory, autoimmune, and neoplastic diseases. With their expanding indication spectrum and increasing use, hypersensitivity reactions to these drugs are also becoming more frequent. The present study aimed to report the incidence and the features of such reactions in pediatric patients using biologicals for the treatment of various diseases. **Methods:** The medical records of pediatric patients treated with biological agents between October 1, 2011 and August 31, 2019 were reviewed and adverse reactions were evaluated retrospectively. **Results:** During the study period, 211 patients (116 boys, 55%) used 21 different biological drugs for the treatment of various diseases. Their median age at the time of the first treatment was 139.9 (IQR: 92.2–187.8) months. Hematologic-oncologic diseases were the most common indication for biological therapy (97/211; 46.0%), followed by rheumatologic diseases (82/211; 38.9%). Of the 211 patients, 14 (6.64%) experienced reactions to bio-

logical drugs. The most common culprit agent was rituximab (57.1%). Most of the patients (85.7%) had a history of reactions either during the infusion or within 1 h after taking the drug. Five patients underwent desensitization to the culprit drug, while 7 other patients continued treatment with a reduced dose/infusion rate or premedication. Also 1 patient continued to take the drug without any additional treatment. **Conclusion:** It was reported that 6.64% of the patients who received biologic drug therapy for various reasons in our hospital had hypersensitivity. The most common culprit agent was rituximab, and most of the reactions were immediate reactions.

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Introduction

The World Health Organization (WHO) defines biological drugs as “biotherapeutic protein products prepared by recombinant DNA technology” [1]. Biological drugs are currently used for the treatment of chronic in-

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flammatory, autoimmune, and neoplastic diseases. With their expanding indication spectrum and increasing use, hypersensitivity reactions to these drugs are also becoming more frequent [2].

Hypersensitivity reactions to biological drugs can be type I (IgE/non-IgE-mediated), infusion-related, cytokine release, type III, and delayed reactions [3]. Infusion-related reactions are generally considered the most common adverse reactions to monoclonal antibodies. These reactions are usually mild, involving fever, flushing, nausea, vomiting, diarrhea, shortness of breath, back pain, and abdominal pain and are self-limiting reactions that respond to premedication [4, 5]. Type I reactions can vary from local injection site reactions to systemic reactions with urticaria, dyspnea, hypotension, and anaphylaxis [3, 4]. Some monoclonal antibodies cause the release of different cytokines (especially tumor necrosis factor alpha, interferon gamma, and IL-6) into the systemic circulation, resulting in cytokine release characterized by flushing, arthralgia, nausea, vomiting, diarrhea, and hypertension/hypotension [3, 6]. While infusion-related reactions and cytokine release syndromes can be seen at the first administration of the drug, IgE-mediated reactions occur with repeated doses of the drug. Type I reactions with cetuximab can be seen during the first exposure due to pre-existing IgE antibodies against galactose-alpha-1,3-galactose [3, 7].

The frequency and clinical features of adverse reactions vary depending on the biological drug therapy used. The rates of immediate hypersensitivity reactions to monoclonal antibodies were reported as 5–10% with rituximab, 2–3% with infliximab, and 0.6–5% with trastuzumab [8].

There has been limited research into hypersensitivity reactions to biological drugs in the pediatric population. Therefore, the present study aimed to report the incidence and the features of such reactions in pediatric patients using biologicals for the treatment of inflammatory, neoplastic, and rheumatologic diseases.

Methods

Patients

The medical records of pediatric patients treated with biological agents between October 1, 2011 and August 31, 2019 were reviewed, and adverse reactions were evaluated retrospectively. The patients' demographic characteristics, the disease for which they were receiving biological therapy, the onset and timing of the reaction, the culprit biological drug, signs and symptoms associated with the reaction, management of the reaction, and the protocol used to continue biological therapy after the reaction were record-

ed. Also liver and kidney function test results and total eosinophil count of the patients were recorded. Kidney and liver function tests results were interpreted as impaired if they were outside of the normal range accepted by the laboratory. Having a total eosinophil count $>500/\mu\text{L}$ was considered as eosinophilia.

The Local Ethics Committee approved the study design and protocols. Written informed consent was obtained from the patient's parents to perform desensitization.

Indication of Biological Drugs That Have Been Used

Rituximab was used for autoimmune/limbic encephalitis, nephrotic syndrome, systemic lupus erythematosus, thrombotic or immune thrombocytopenic purpura, autoimmune hemolytic anemia, chronic graft versus host disease, relaps CD 20 + Hodgkin and relaps of high-grade non-Hodgkin's lymphoma, and hematopoietic stem cell transplantation. Infliximab was used for ulcerative colitis, Crohn's disease, Takayasu's arteritis, juvenile idiopathic arthritis (JIA), and neuro-Behcet's disease. Omalizumab was used for severe asthma and chronic urticaria. Tocilizumab was used for Takayasu's arteritis, JIA, and autoinflammatory disease. Adalimumab was used for JIA and uveitis. Anakinra and canakinumab were used for JIA. Ruksolitinib, bortezomib, and blinatumomab were used for children with refractory acute lymphoblastic leukemia (ALL). Brentuximab and nivolumab were used for brain tumors with constitutional mismatch repair-deficiency syndrome and relaps of refractory Hodgkin's lymphoma. Imatinib, nilotinib, and dasatinib were used for Ph + ALL, acute myeloid leukemia, chronic myeloid leukemia (CML), and myelodysplastic syndrome. Bevacizumab was used for optic glioma and relaps of solid tumors. Nimotuzumab was used for pons glioma and relaps of brain tumors. Sorafenib was used for hepatocellular cancer, FLT + ITD + ALL, and refractory Ewing sarcoma. Crizotinib was used for children with ALK + inflammatory myofibroblastic tumor. Etanercept was used for adenosine deaminase deficiency 2, and eculizumab was used for nephrotic and nephritic syndrome.

Classification and Severity of the Reactions

The patients' reactions were classified into 4 categories such as type I IgE/non-IgE-mediated, cytokine release reactions, infusion-related and delayed immunoglobulin, and T-cell-mediated reactions [4, 5, 9]. Reaction severity was categorized as grades 1–3 (mild, moderate, and severe, respectively) according to the Brown classification [10].

Acute Treatment of Reactions

Acute treatment of immediate reactions was determined according to the severity and type of reaction. First, the infusion was interrupted. If the reaction was considered anaphylaxis based on physical examination and vital signs, intramuscular adrenaline, corticosteroid, and antihistamines were administered. Oxygen, intravenous fluid, and nebulized beta-2 agonist were given as supportive treatment. Mild to moderate, non-life-threatening reactions such as urticaria and angioedema were treated with antihistamines and/or corticosteroid. Paracetamol was given at the onset of fever, and nebulized beta-2 agonist and oxygen were given in the event of bronchospasm.

Management of Biological Therapy

If no alternative treatment was available, if the patient was already taking the most effective agent, or if there was a possibility

Table 1. Sex, age, results of the laboratory parameters, and type of the culprit biological drugs of the patients with and without hypersensitivity reactions

	Total patients (n = 211), n (%)	Hypersensitive patients (n = 14), n (%)	Tolerant patients (n = 197), n (%)	p value
Gender				
Male/female	116/95	9/5	107/90	0.447
Age, months (median/IQR)	139.9/92.2–187.8	96.97/80.7–160.38	145.35/94.6–187.9	0.137
Kidney function tests				
Normal	189	13	176	1.000
Impaired	22	1	21	
Liver function tests				
Normal	163	12	151	0.434
Impaired	48	2	46	
Total eosinophil count				
≤500/μL	200	13	187	0.539
>500/μL	11	1	10	
Biological drugs				
Monoclonal antibodies	170	12	158	0.547
Soluble fusion receptors	22	0	22	
Receptor antagonists	52	2	50	
Proteasome inhibitors	2	0	2	

of toxicity with other agents, treatment was continued by reducing the infusion rate and premedicating with corticosteroids and/or paracetamol in mild and nonrecurrent reactions with symptoms such as nausea, fever, headache, itching, and dizziness. Desensitization was preferred for moderate, recurrent, or severe reactions. Successful desensitization protocols in the literature were adapted to our cases [11]. All desensitization procedures were performed by trained clinicians (allergy specialists) in the hospital setting. A standard desensitization protocol to monoclonal antibodies with 3 intravenous dilution bags and 12 steps was applied, but the protocol could be adapted with additional dilutions and/or steps to make a total of 16 or 20 steps for patients predicted to be in a higher risk group [2, 11]. Premedication may be administered before desensitization depending on the severity of the initial reaction. Montelukast for bronchospasm and antihistamines, paracetamol, and corticosteroids for chills and fever were administered to some patients as premedication.

Statistical Analyses

Statistical analyses were performed using IBM SPSS Statistics for Windows version 22.0 statistical software package (IBM Corp., Armonk, NY). Numbers and percentages were reported for discrete variables; continuous variables were expressed as mean and standard deviation for data with normal distribution and as median and interquartile range (IQR) for non-normally distributed data. Chi-square (χ^2) test was performed to compare the categorical variables and Mann-Whitney U test was used in comparisons of non-normally distributed continuous variables. A p value of <0.05 was considered statistically significant.

Results

During the study period, 211 patients (116 boys, 55%) used 21 different biological drugs for the treatment for various diseases. Their median age at time of the first treatment was 139.9 (IQR: 92.2–187.8) months.

Of the 211 patients, 14 (6.64%) experienced reactions to biological drugs. One patient had a reaction with rituximab and 1 patient with infliximab during both the first and the second infusion. The characteristics of the patients who developed reactions and of those who tolerated treatment are presented in Table 1.

Twelve patients (85.7%) had a history of reactions either during the infusion or within 1 h after taking the drug, and 2 other patients had a history of reactions >1 h after taking the drug. Seven patients (50%) had a reaction to the first dose of the drug. The most common culprit agent was rituximab (57.1%), followed by infliximab (21.4%).

Eleven of 108 (10.2%) drugs administered intravenously, 1 of 86 (1.2%) drugs administered subcutaneously, and 2 of 52 (3.85%) drugs administered orally were the suspected agents. Most of the patients (11/14; 78.57%) had a reaction history with BD administered by intravenous infusion (p: 0.007).

Hematologic-oncologic diseases were the most common indication for biological therapy (97/211; 46.0%),

Table 2. Characteristics of the patients who had hypersensitivity to rituximab

Patient	Age, months/ sex	Underlying primary disease	Reaction dose	Characterization of the reaction	Acute treatment	Management
1	84/F	CD27 deficiency, Hodgkin lymphoma	Second	Angioedema of eyelids and lips, vomiting, cyanotic lips, shortness of breath, bronchospasm, hypotension Grade 3	Infusion was interrupted Intramuscular adrenaline 0.01 mg/kg, hydroxyzine 1 mg/kg, and methylprednisolone 1 mg/ kg	Desensitization (13-step), premedicated with hydroxyzine, methylprednisolone and montelukast. The patient received 4 more infusions
2	78/M	Nephrotic syndrome	Second	Urticaria on his face Grade 1	Infusion was interrupted Hydroxyzine 1 mg/kg and methylprednisolone 1 mg/kg	Desensitization (12-step), premedicated with hydroxyzine. The patient received 2 more infusions
3	82/M	Burkitt ALL	First and second	Fever and shaking on first infusion; vomiting and abdominal pain on second infusion Grade 2	For first infusion: infusion was interrupted Paracetamol For second infusion: infusion was interrupted Hydroxyzine 1 mg/kg and methylprednisolone 1 mg/kg	Desensitization (12-step), premedicated with hydroxyzine
4	214/M	Nephrotic syndrome	First	Hypertension, dyspnea, and nausea Grade 2	Infusion was interrupted Oxygen	The patient received 3 more infusions with premedication (hydroxyzine) and slow infusion rate
5	13/M	Wiskott-Aldrich and bone marrow transplantation	First	High fever Grade 1	Infusion was interrupted Paracetamol	The patient received 2 more infusions with premedication (paracetamol) and slow infusion rate
6	122/M	Chronic ITP	First	Hypotension and cough Grade 3	Infusion was interrupted Intramuscular adrenaline 0.01 mg/kg, hydroxyzine 1 mg/kg, and methylprednisolone 1 mg/ kg	Desensitization (12-step). The patient received 3 more infusions
7	97/M	Nephrotic syndrome	First	Headache and hypertension Grade 2	Infusion was interrupted	The patient received 3 more infusions with slow infusion rate
8	203/M	Hodgkin lymphoma	First	Itching and headache Grade 2	Infusion was interrupted Hydroxyzine 1 mg/kg	The patient received 4 more infusions with premedication (hydroxyzine and paracetamol) and slow infusion rate
ALL, acute lymphoblastic leukemia.						

and 7 of the patients (7.2%) had reactions. Most of the reactions (5/7 patients; 71.4%) were with rituximab. Biologic drug therapy was initiated in 82 patients (82/211; 38.9%) due to rheumatologic diseases, and 2 patients (2.4%) had reactions. Twelve patients were under biological therapy due to nephrologic disease, all of them undergoing rituximab treatment, and 3 of them had reaction history (25%). Other diseases that caused the initiation of biological drugs were gastroenterological diseases in 11 patients, allergic diseases in 7 patients, and

neurological diseases in 2 patients. There was no statistically significant relationship among the development of reaction and gender, age, abnormal kidney and liver function tests, and eosinophilia type of the BD used (Table 1).

Reactions with Rituximab

The most common culprit drug was rituximab, with reactions reported in 15.7% (8/51) of patients treated with rituximab. All the reactions occurred either during

Table 3. Characteristics of the patients who had hypersensitivity to infliximab

Patient	Age, years/sex	Underlying primary disease	Reaction dose	Characterization of the reaction	Acute treatment	Management
1	12/M	Crohn's disease	Third	Dizziness and tachycardia Grade 2	Infusion was interrupted	The patient received 23 more infusions with premedication (hydroxyzine) and slow infusion rate
2	1/F	JIA	Fifteenth	Flushing and dyspnea Grade 3	Infusion was interrupted Intramuscular adrenaline 0.01 mg/kg, hydroxyzine 1 mg/kg, and methylprednisolone 1 mg/kg	The patient did not receive biological drug therapy again
3	2.5/M	Crohn's disease	First and second dose	Urticaria Grade 1	Infusion was interrupted Hydroxyzine 1 mg/kg	Desensitization, premedicated with hydroxyzine. The patient received 3 more infusions

JIA, juvenile idiopathic arthritis.

the infusion or within the first hour after treatment. Four patients were desensitized successfully. Twelve- or 13-step desensitization protocols were implemented. The protocols applied and the number of desensitization procedures performed with the same protocol for each patient are shown in Table 2. Four other patients continued treatment with a reduced infusion rate, with or without premedication. The characteristics, reaction features, and treatment management of the patients who developed reactions to rituximab are also presented in Table 2.

Of 9 reactions to rituximab reported in these 8 patients, 5 reactions were evaluated as type 1 IgE/non-IgE-mediated or cytokine release reactions and 4 as infusion-related reactions. Reaction severity was evaluated as grade 2 for 5 reactions (55.5%), grade 1 for 2 reactions (22.2%), and grade 3 for 2 reactions (22.2%).

Reactions with Infliximab

Three of 23 patients treated with infliximab had reactions (13%). A 12-year-old boy was undergoing treatment for Crohn's disease, and his reaction was classified as infusion-related. A 1-year-old girl was undergoing treatment for JIA and exhibited signs of anaphylaxis during infusion. The third patient experienced urticaria on the first and second infliximab infusions and underwent desensitization for recurrent urticaria with infliximab. The latter 2 patients' reactions were classified as type 1 IgE/non-IgE-mediated or cytokine release reaction. The clinical features and management of reactions to infliximab are given in Table 3.

Reactions to Adalimumab

One patient exhibited a large local cutaneous reaction at the subcutaneous injection site after the 12th dose (1/23; 4.3%). The patient presented to our clinic with a reaction history and was administered one-tenth of the required dose, followed by the remaining nine-tenths of the dose 30 min later. After 20 min, a local induration was observed at the injection site. The patient was immediately given 1 mg/kg hydroxyzine as acute antihistaminic treatment. For the next treatment, the patient was premedicated with 1 mg/kg hydroxyzine 30 min before subcutaneous injection, and this time, no reaction was observed. The patient is continuing to receive treatment with 1 mg/kg hydroxyzine premedication. The reaction was classified as type 1 IgE/non-IgE-mediated local injection site reaction.

Reactions with Nilotinib

A 7.5-year-old girl diagnosed with CML in the pediatric hematology-oncology department complained of a rash on the days she took the drug. The reaction was classified as a delayed reaction. At her outpatient clinic visit, the dose of the drug was reduced by half and no rash was observed. This allowed her to continue treatment at the halved dose.

Reactions with Sorafenib

A 10.5-year-old girl with hepatocellular carcinoma complained of a rash on her face that appeared on the days she took sorafenib and disappeared after 1 or 2 h. The reaction was classified as a delayed reaction. Because the reaction was limited to a mild cutaneous symptom that regressed spontaneously in a short time, she continued to take the drug without any additional treatment.

Discussion

In our study, 211 patients were treated with 21 different biological drugs, and 14 (6.64%) of those patients developed reactions. Five patients underwent desensitization to the culprit drug, while 7 other patients continued treatment with a reduced dose/infusion rate or premedication.

Biological drugs are used in anti-inflammatory and cancer therapies. Although these agents are very effective in certain diseases, they can also cause various adverse effects. These agents have good outcomes and extended treatment courses, and as patients use these treatments more frequently and for longer periods of time, the risk of sensitization increases [11]. The frequency and clinical features of the reactions vary depending on the biological drug therapy used [8]. Soyer et al. [12] observed only immediate reactions in a pediatric group with rheumatologic diseases, reporting that 6 of 128 (4.7%) pediatric patients had immediate hypersensitivity reactions to biological drugs. Kamei et al. [13] evaluated rituximab-induced immediate and nonimmediate infusion reactions in a pediatric population with nephrotic syndrome and determined that 165 reactions with 225 events were reported in 309 rituximab infusions (53.4%). The median time of onset of all 225 events was 1 h, and 214 events (95%) were observed within 3 h after the initiation of rituximab treatment [13]. Our study included patients with a history of both immediate and nonimmediate reactions. Fourteen (6.64%) of 211 patients treated with biologicals developed reactions, and 12 (85.7%) of them had a history of reaction during the infusion or within the first hour after infusion. Soyer et al. [12] reported that renal involvement was a risk factor for development of immediate BD hypersensitivity as it was an indicator of more severe disease. In our study, most of the ratio of the hypersensitive patients in the group of those who were under biological therapy was due to nephrologic disease. This was probably due to the fact that all patients were initiated with rituximab and also the most common culprit agent was rituximab.

Hypersensitivity reactions to biological drugs are classified as type I IgE/non-IgE-mediated reactions, infusion-related reactions, cytokine release syndromes, and delayed type reactions [4]. The most common reactions to monoclonal antibodies are infusion-related reactions [5]. Skin tests and elevated tryptase levels are hallmarks used to distinguish cytokine release syndrome from IgE-mediated hypersensitivity reactions [9]. However, standardized protocols have not been defined for most biological drugs [14]. Soyer et al. [12] reported that they were able to

perform skin tests on 4 of 6 patients who had a history of immediate hypersensitivity reactions, and 3 of them had positive results. In our study, most of the patients needed acute treatment and were often given antihistamine after the reaction, and due to the short interval between the reaction and subsequent treatment for their primary disease, treatment options were determined without skin testing. The lack of skin tests or tryptase levels to differentiate early cytokine release reactions from IgE-mediated reactions is a limitation of our study. We attempted to perform classification based on the patients' histories and reaction characteristics. Accordingly, we retrospectively evaluated 6 of our patients as having type I IgE/non-IgE-mediated or cytokine release reactions, 5 as infusion-related reactions, 2 as delayed reactions, and 1 as a type I IgE/non-IgE-mediated local injection site reaction.

For biological drugs, the mild and moderate reactions in cytokine release syndrome can be managed with prolonged infusion time and/or premedication with corticosteroids and paracetamol [7]. In our study, 5 patients (35.7%) were able to receive subsequent doses of the culprit drug with prolonged infusion time. As it can be difficult to differentiate between IgE-mediated reactions and cytokine release syndrome cases in patients with serious reactions, the same treatment approach is used for these 2 types of reactions [7]. Brennan et al. [8] evaluated the results of 105 desensitization procedures in 23 patients hypersensitive to monoclonal antibodies, and they concluded that desensitization is a promising method to continue monoclonal antibody treatment in hypersensitive patients. In our study, 5 patients received the culprit drug after desensitization and 4 of them received premedication with antihistamines and/or corticosteroids before the desensitization protocol. Only one of them took montelukast in addition to other premedications due to bronchospasm.

Reactions to rituximab can be immediate and can occur upon first administration and even with premedication. IgE-mediated hypersensitivity reactions with rituximab account for approximately 5–10% of infusion reactions [2, 8, 15]. Of 225 infusion reactions in their study, Kamei et al. [13] did not report any anaphylaxis or reactions that were prolonged and unresponsive to symptomatic medication. In our study, the most common suspect agent was rituximab, with reactions reported in 15.7% (8/51) of patients after treatment. Although the number of reactions in our study was significantly less than that in the study by Kamei et al. [13], grade 3 reactions (2/9 reactions; 22.2%) were also seen with rituximab, and these patients continued to take the culprit drug with the

desensitization protocol. One of them had chronic immune thrombocytopenic purpura and the other patient had Hodgkin lymphoma. The difference in our results may be that these patients had hematologic-oncological diseases in our study.

Infliximab and adalimumab are both monoclonal antibodies against tumor necrosis factor alpha, but infliximab is used intravenously, while adalimumab is administered subcutaneously [2]. Vultaggio et al. [16] reported infliximab-induced immediate infusion reactions. Respiratory and cutaneous symptoms were the most common clinical findings, and most of the severe reactions occurred within 15 min of infusion [16]. In an adult study, 13.8% (31/225) of patients treated with infliximab had reactions, 91.3% of which were anaphylaxis [17]. In the present study, 3 reactions (3/23 patients; 13%) were reported with infliximab, and all were immediate reactions. One reaction was severe, and the patient was not given infliximab again. In the literature, it was reported that injection site reactions with adalimumab are mostly mild, T-lymphocyte-mediated delayed hypersensitivity reactions [2, 18]. Puxeddu et al. [17] observed no anaphylaxis with adalimumab, but 3.5% (7/201) of the patients treated with adalimumab had reactions (mainly local and mild). In our study, only one patient had a history of reaction to adalimumab, which was also a mild, local injection site reaction. The patient was able to continue treatment with premedication and exhibited no further reaction.

Sorafenib is a kinase inhibitor, and the most frequently observed adverse events are nausea, abdominal pain, and diarrhea [19–21]. Branco et al. [21] evaluated the adverse effects of sorafenib in an adult population and observed that the most common adverse events in the first 60 days of treatment were diarrhea (62.2%) and dermatological reactions (42%) (hand-foot syndrome in 35.4%, rash in 5.2%, and mucositis in 1.4%). They also reported that patients who experienced dermatologic adverse events in the first 60 days of treatment had a nearly 3-fold higher likelihood of survival than those who did not and concluded that adverse events did not necessarily indicate that sorafenib should be discontinued. Instead, they suggested immediate dose reduction or temporary interruption and recommended that the decision could be managed to optimize patient comfort and safety when possible [21]. Only one patient in our study was hypersensitive to sorafenib, and she continued treatment with no additional treatment because she had a mild, self-limiting cutaneous reaction.

Nilotinib is a second-generation tyrosine kinase inhibitor used as the first-line treatment for CML. It is gener-

ally well tolerated, although a meta-analysis indicated that rash is a frequent complaint with nilotinib [22]. In the same meta-analysis, the characteristics of patients on nilotinib or dasatinib were evaluated by dermatology consultation. Cutaneous reactions presented as morbiliform eruption, erythema and scaling, keratosis pilaris-like lesions, and multiple milia-like lesions. One patient discontinued nilotinib treatment due to adverse effects [22]. In our study, 1 patient complained of skin rash after treatment, and the reaction was eliminated by reducing the dose by half.

Limitations of our study include the lack of skin tests for immediate reactions. Therefore, we were able to provide limited data on the classification of patients' reactions with precise limits. This is mainly due to the fact that our study was retrospective.

In conclusion, we found that over a period of 8 years, 6.64% of pediatric patients who received biologic agent therapy for various reasons in our hospital exhibited a reaction to these agents. Such reactions are expected to be observed more frequently in treatment regimens where the use of biological drugs is increasingly common, and prospective studies on this subject will provide more data in the future.

Statement of Ethics

The study was approved by the Ethics Committee of the University of Health Sciences, Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital (No: 2019-192). Written informed consent was obtained from the parents or legal guardians of patients.

Conflict of Interest Statement

The authors indicate no such interest.

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Author Contributions

O.Y.T. wrote the article. O.Y.T., V.K., B.A., and G.H.: acquisition of data, or analysis and interpretation of data, and reviewed the article. B.A., U.S.B., D.O., B.K., N.Y.O., H.N.Y., M.T., and E.D.M. made substantial contributions to design, reviewed the article, and gave final approval of the version to be published.

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