

Successful Rapid Desensitization of a Pediatric Multiple Sclerosis Patient with Anaphylaxis to Ocrelizumab

Dear Editor,

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease of the central nervous system. As a result of chronic inflammation and neurodegeneration, disability occurs, especially in adolescents and young adults. Pediatric onset MS comprises 3%-5% of all cases.^[1] Recent studies have shown that B-cell-mediated autoantigen presentation can cause T-cell activation in the pathogenesis of MS.^[2] Monoclonal antibodies are increasingly used in the treatment of inflammatory diseases and malignancies. Biological agents, including their own proteins, which are perceived by the immune system as foreign antigens, can elicit an immune response. Originally, biological agents tended to be more immunogenic due to their higher content of nonhuman proteins (e.g., chimeric structures). However, over time, the content of proteins resembling human proteins increased and their immunogenicity decreased.^[3]

Ocrelizumab is a humanized monoclonal antibody that targets CD20-positive B-cells and was approved in 2017

for the treatment of relapsing-remitting and progressive MS.^[3] Mild infusion-related reactions occur in 1/3 of ocrelizumab-treated patients. Although treatment can be continued for mild reactions, more severe reactions lead to treatment discontinuation. In particular, life-threatening type 1 hypersensitivity reactions such as anaphylaxis lead to treatment discontinuation.^[4] However, continuation of treatment is critical for reducing morbidity in patients with MS. Rapid drug desensitization allows continuation of treatment in patients who develop a type 1 hypersensitivity reaction without an alternative drug option.^[5,6] Here, we present an adolescent patient who developed anaphylaxis during the first infusion of ocrelizumab and was subsequently treated successfully and safely with rapid drug desensitization.

A 14-year-old female patient with relapsing remitting MS, was admitted to our clinic to receive ocrelizumab. In her medical history, the patient's first clinical attack was observed at the age of 13 years as an optic neuritis of the left eye. She was diagnosed

as a pediatric onset relapsing remitting MS as per International Pediatric Multiple Sclerosis Study Group and McDonald 2017 diagnostic criteria.^[7] She had started disease modifying treatment with interferon beta-1b (INF beta-1b), an immunomodulatory agent that is considered a first-line agent. Despite treatment with INF beta-1b, she had three clinical MS attacks within nine months [Figure 1]. High-dose steroids and plasmapheresis also did not improve. Therefore, the treatment was escalated to monoclonal antibody therapy, which is the second-line disease modifying treatment. Because the patient's serum was positive for John Cunningham virus antibodies, ocrelizumab was considered appropriate given the risk of progressive multifocal leukoencephalopathy. Because ocrelizumab is not approved by Turkish Ministry of Health for pediatric MS patients, special approvals from Turkish Ministry of Health, patient, and her parents were granted before the onset of treatment.

After premedication with paracetamol, diphenhydramine, and 100 mg of intravenous methylprednisolone, 300 mg of ocrelizumab was administered. During the first hour of infusion, the patient developed a diffuse urticarial rash, severe dyspnea, and bronchospasm. Hypotension and tachycardia were not observed. The patient was classified as anaphylaxis and received appropriate treatment. The patient underwent risk stratification and was classified as Brown classification grade 3 immediate hypersensitivity reaction (IHR).^[8,9]

In the absence of alternative treatment, 300 mg ocrelizumab treatment was administered with a 12-step rapid desensitization protocol, as summarized in Table 1. Before rapid drug desensitization (RDD), she was premedicated with methylprednisolone and pheniramine maleate and the protocol was performed without reactions. After six months, the patient successfully received a new infusion with a 600-mg dose of ocrelizumab after dose adjustment as per the protocol shown in Table 2.

We present the first case of an adolescent who was successfully desensitized with ocrelizumab after anaphylaxis. Although life-threatening reactions such as anaphylaxis are a serious risk during treatment, discontinuation or modification of MS treatment may worsen the condition. Reactions occurring during or after treatment with monoclonal antibodies can be classified as infusion-related reactions, cytokine-release reactions, type 1 hypersensitivity reactions (IgE-mediated or non-IgE-mediated), mixed reactions, delayed hypersensitivity reactions (type 4), and rarely type 3 hypersensitivity reactions.^[8]

Infusion-related reactions occur within a short time after infusion and are usually dependent on the rate of infusion. They are milder than type 1 hypersensitivity reactions and cytokine release reactions, and the severity can be reduced by subsequent administrations.^[8]

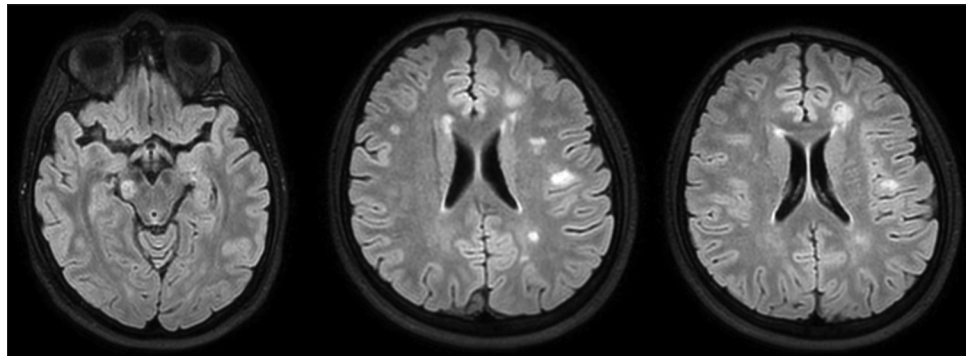


Figure 1: MS plaques in FLAIR

Table 1: Desensitization protocol for ocrelizumab 300 mg

Step	Solution	Rate	Time per step	Volume per step	Dose/Step	Cumulative Dose
1	A	2 mL/hr	15 min	0.5 mL	0.006 mg	0.006 mg
2	A	5 mL/hr	15 min	1.25 mL	0.015 mg	0.021 mg
3	A	10 mL/hr	15 min	2.5 mL	0.03 mg	0.051 mg
4	A	20 mL/hr	15 min	5 mL	0.06 mg	0.111 mg
5	B	5 mL/hr	15 min	1.25 mL	0.15 mg	0.261 mg
6	B	10 mL/hr	15 min	2.5 mL	0.3 mg	0.561 mg
7	B	20 mL/hr	15 min	5 mL	0.6 mg	1.161 mg
8	B	40 mL/hr	15 min	10 mL	1.2 mg	2.361 mg
9	C	10 mL/hr	15 min	2.5 mL	3 mg	5.361 mg
10	C	20 mL/hr	15 min	5 mL	6 mg	11.361 mg
11	C	40 mL/hr	15 min	10 mL	12 mg	23.361 mg
12	C	80 mL/hr	173 min	230 mL	276.639 mg	300 mg

Solution A: 250 mL, 5% dextrose, (0.012 mg/mL, 1:100 of total dose). Solution B: 250 mL, 5% dextrose, (0.12 mg/mL, 1:10 of total dose). Solution C: 250 mL, 5% dextrose, (1.2 mg/mL, 1:1 of total dose)

Table 2: Desensitization protocol to ocrelizumab 600 mg

Step	Solution	Rate	Time per step	Volume per step	Dose/Step	Cumulative Dose
1	A	2 mL/hr	15 min	0.5 mL	0.012 mg	0.012 mg
2	A	5 mL/hr	15 min	1.25 mL	0.003 mg	0.042 mg
3	A	10 mL/hr	15 min	2.5 mL	0.06 mg	0.102 mg
4	A	20 mL/hr	15 min	5 mL	0.12 mg	0.222 mg
5	B	5 mL/hr	15 min	1.25 mL	0.3 mg	0.522 mg
6	B	10 mL/hr	15 min	2.5 mL	0.6 mg	1.122 mg
7	B	20 mL/hr	15 min	5 mL	1.2 mg	2.322 mg
8	B	40 mL/hr	15 min	10 mL	2.4 mg	4.722 mg
9	C	10 mL/hr	15 min	2.5 mL	6 mg	10.722 mg
10	C	20 mL/hr	15 min	5 mL	12 mg	22.722 mg
11	C	40 mL/hr	15 min	10 mL	24 mg	46.722 mg
12	C	80 mL/hr	173 min	230 mL	553.278 mg	600 mg

Solution A: 250 mL, 5% dextrose, (0.024 mg/mL, 1:100 of total dose). Solution B: 250 mL, 5% dextrose, (0.24 mg/mL, 1:10 of total dose). Solution C: 250 mL, 5% dextrose, (2.4 mg/mL, 1:1 of total dose)

Reactions due to cytokine release are usually self-limiting and can be prevented by premedication. They present a broad symptom profile with fever, tachycardia, flushing, chills, dyspnea, nausea, and vomiting and often occur during infusion and especially during the first infusion.^[10]

Type 1 hypersensitivity reactions include the findings of early hypersensitivity reactions as per the Brown classification. Findings such as urticaria, angioedema, pruritus, hypotension, shortness of breath, and cardiac or respiratory arrest are observed as a result of mast cell activation occurring through IgE-mediated or non-IgE-mediated mechanisms.^[10]

In rare cases, delayed-type (type 4) hypersensitivity reactions are also observed. Type 4 hypersensitivity reactions account for < 5% of reactions triggered by monoclonal antibodies and usually occur 12-24 hours after infusion. Type 3 reactions are the Arthus reaction or serum sickness and are very rare.^[10]

Our patient was classified as a type 1 reaction because she had severe bronchospasm and urticaria. In ORATORIA trial, where patients treated with ocrelizumab were evaluated by Mayer *et al.*,^[4] severe infusion-related reactions were observed in two patients but were not defined as type 1 reactions. Clements *et al.*^[5] had previously presented two cases at a scientific meeting. One patient, who suffered from hypoxia, chest pain, and itching in the throat and ears, and the other, who developed urticaria, were subsequently successfully desensitized with ocrelizumab. The case report by Aun *et al.*^[6] describes a patient with urticaria and angioedema after the first infusion and successful desensitization. To our knowledge, this is the first case of an adolescent in whom successful and safe desensitization was performed after anaphylaxis.

We could not perform skin prick tests because our patient needed urgent treatment. Therefore, we could not prove whether the reaction was IgE-mediated. However, in all type 1 hypersensitivity reactions, whether IgE-mediated or not, treatment can be continued with rapid desensitization.^[10]

In conclusion, for the continuation of ocrelizumab treatment in a pediatric MS patient with type 1 hypersensitivity reactions during ocrelizumab infusion, it is possible to successfully and safely perform rapid desensitization. In this way, treatment can be continued and exacerbation of the disease prevented. For this reason, the presentation of a successful rapid desensitization treatment is important for the exchange of experiences.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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