OMALIZUMAB MAY FACILITATE DRUG DESENSITIZATION IN PATIENTS FAILING STANDARD PROTOCOLS

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To the Editor,

Nephrotic syndrome (NS) is a common glomerular disorder in children, for which steroids are the first-line treatment. While most children with NS respond to steroid therapy, 20% of children are resistant to steroids. Some children with steroid-responsive NS develop a frequently relapsing or steroid-dependent course and experience significant side effects of steroid therapy. Alternative medications such as calcineurin inhibitors, mycophenolate mofetil, cyclophosphamide, and rituximab, an anti-CD20 monoclonal antibody, are being considered for such patients with difficult-to-treat NS (1,2).

Hypersensitivity reactions to monoclonal antibodies are quite limited in clinical practice, such as the release of cytokines that occur during intravenous infusion. However, IgE-mediated reactions may also occur. Life-threatening IgE-mediated reactions such as anaphylaxis lead to discontinuation of treatment or conversion to a less beneficial treatment. Rapid drug desensitization (RDD) is a therapeutic option that allows continuation of treatment with the causative drug (3). Omalizumab is a recombinant humanized anti-IgE monoclonal antibody. Treatment indications include severe asthma and idiopathic chronic urticaria. However, the efficacy of omalizumab has also been described in food allergy, as a bridge to oral immunotherapies, atopic dermatitis, idiopathic anaphylaxis, and mastocytosis (4). Previous studies have reported the use of omalizumab for rapid desensitization to chemotherapeutic agents (5). Here, we describe a patient with steroid-resistant NS who developed anaphylaxis on the first infusion of rituximab and subsequent type 1 hypersensitivity reactions during desensitization trials with rituximab using 12-, 16-, and 20-step protocols.

A 4-year-old boy diagnosed with steroid-resistant NS and unresponsive to calcineurin inhibitors, either cyclosporine A or tacrolimus, and in their combination with mycophenolate mofetil, received rituximab. After premedication with methylprednisolone at a dose of 2 mg/kg, rituximab 375 mg/m^2 was administered intravenously. During the infusion, he developed anaphylaxis (vomiting and dyspnea). The infusion was stopped and intramuscular epinephrine was administered, and a 12-step rapid desensitization protocol was planned for further infusions (Table 1). He was premedicated with H1 blockers and systemic steroids. However, the patient developed breakthrough reactions (urticaria) that required additional antihistamines at the 4th step. Infusion was resumed at a slower rate. Ten minutes after re-administration, generalized urticaria and angioedema developed. Montelukast was administered according to ENDA/EAACI recommendations for rapid desensitization in drug allergy (6). After 7 days, the protocol was modified to administer 375 mg/m^2 rituximab in 16 steps with premedication (Table 2). The patient developed generalized urticaria and angioedema again at the 4th step. The next week, the desensitization protocol was designed with 375

mg/m^2 rituximab in 20 steps (Table 3). Again, generalized urticaria and angioedema occurred in the 2nd step. A skin prick test was performed 3 weeks after the initial reaction. During the skin prick test, the patient developed generalized urticaria.

In the absence of alternative treatment options for NS, desensitization with omalizumab treatment was suggested to prevent hypersensitivity reactions to rituksimab. Omalizumab (patient weight: 17.5 kg; total IgE:71 UI /ml; dose: 150 mg/ every 2 weeks) was added to treatment. The last omalizumab dose was administered 1 day before the following desensitization. After premedication, 375 mg/m^{2}rituximab was administered in 20 steps. In the 5th step, the patient developed local urticaria requiring an antihistamine. The infusion was resumed and successfully completed. Under omalizumab treatment, the patient was administered 375 mg/m^2 rituximab for the second time in a 20-step protocol. After the 6th dose, the interval of omalizumab treatment was changed to every 4 weeks. The rituximab dose was then increased to 750 mg/m^2 at the third infusion. After premedication, the 20-step desensitization protocols were successfully applied in the following days.

Rituximab is a chimeric monoclonal antibody that targets the CD20 antigen on the surface of B cells and causes elimination of B lymphocytes by complement- and antibody-dependent cellular cytotoxicity for 6-12 months (2). Efficacy has also been demonstrated in the treatment of steroid-resistant NS (7). Rituximab is one of the most common biologic agents with infusion-related reactions. Rituximab-associated hypersensitivity reactions can be classified as infusion-related reactions, cytokine release, IgE-mediated/non-IgE-mediated hypersensitivity reactions, mixed reactions, type 3 and type 4 hypersensitivity reactions (8).

Omalizumab is a recombinant humanized IgG1 monoclonal antibody and prevents degranulation in effector cells by specifically binding to the FceRI receptor site of free IgE, causing a decrease in the level of free IgE in serum, and causing downregulation of FceRI receptors (9). Omalizumab has previously been used as a co-adjuvant in RDD along with insulin, the enzyme elosulfase alpha, chemotherapeutic agents, and aspirin (9). In a randomized, double-blind, placebo-controlled trial by Lang et al, desensitization was achieved after 16 weeks treatment with omalizumab. In other case reports, omalizumab treatment was generally started 7-14 days before RDD; only in one case report was the first omalizumab dose given 4 days before RDD (9). In previous studies, omalizumab dosing in allergic asthma was based on patient weight and total IgE. In our case, we administered 6 doses of omalizumab (150 mg/dose) every two weeks before desensitization and continued treatment once a month until completion of rituximab therapy. In patients with successful RDD on omalizumab, RDD steps can be reduced on subsequent infusions. Arroaberran et al. (10) presented a patient who tolerated elosulfase alpha enzyme without desensitization after omalizumab treatment.

In conclusion, omalizumab may facilitate desensitization protocols and allow continuation of the preferred treatment.

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Step	**Solution**	**Rate** (mL/hr)	**Time per step**	**Volume per step (mL)**	**Dose/Step** (mg)	**Cumulative Dose (mg)**
1	A	2	15 min	0.5	0.006	0.006
2	A	5	15 min	1.25	0.015	0.021
3	A	10	15 min	2.5	0.03	0.051
4	A	20	15 min	5	0.06	0.111
5	B	5	15 min	1.25	0.125	0.236
6	B	10	15 min	2.5	0.25	0.486
7	B	20	15 min	5	0.5	0.986
8	B	40	15 min	10	1	1.986
9	C	10	15 min	2.5	2.65	4.636
10	C	20	15 min	5	5.3	9.936
11	C	40	15 min	10	10.6	20.536
12	C	80	173 min	230	244.464	265

Table 1. Rituximab desensitization protocol for 12 steps (375 mg/m^2)

Solution A: 250 mL, 5% dextrose, (0.012 mg/mL).

Solution B: 250 mL, 5% dextrose, (0.106 mg/mL).

Solution C: 250 mL, 5% dextrose, (1.06 mg/mL).

Step	**Solution**	**Rate** (mL/hour)	**Time per step**	**Volume per step (mL)**	**Dose/Step (mg)**	**Cumulative Dose (mg)**
1	A	0.5	15 min	0.125	0.00015	0.00015
2	A	1	15 min	0.25	0.0003	0.00045
3	A	2	15 min	0.5	0.0006	0.00105
4	A	4	15 min	1	0.0012	0.00225
5	B	1	15 min	0.25	0.003	0.00525
6	B	2	15 min	0.5	0.006	0.01125
7	B	4	15 min	1	0.012	0.02325
8	B	8	15 min	2	0.024	0.04725
9	C	2	15 min	0.5	0.053	0.10025
10	C	4	15 min	1	0.106	0.20625
11	C	8	15 min	2	0.212	0.41825
12	C	16	15 min	4	0.424	0.84225
13	D	4	15 min	1	1.06	1.90225
14	D	10	15 min	2.5	2.65	4.55225
15	D	20	15 min	5	5.3	9.85225
16	D	40	361 min	240.7	255.14	265

Table 2. Rituximab desensitization protocol for 16 steps (375mg/m^2)

Solution A: 250 mL, 5% dextrose, (0.0012 mg/mL).

Solution B: 250 mL, 5% dextrose, (0.012 mg/mL).

Solution C: 250 mL, 5% dextrose, (0.106 mg/mL).

Solution D: 250 mL, 5% dextrose, (1.06 mg/mL).

Step	**Solution**	**Rate** (mL/hour)	**Time per step**	**Volume per step (mL)**	**Dose/Step (mg)**	**Cumulative Dose (mg)**
1	A	0.1	15 min	0.025	0.000003	0.000003
2	A	0.2	15 min	0.05	0.000006	0.000009
3	A	0.5	15 min	0.125	0.000015	0.000024
4	A	1	15 min	0.25	0.00003	0.000054
5	B	0.5	15 min	0.125	0.00015	0.000204
6	B	1	15 min	0.25	0.0003	0.000504
7	B	2	15 min	0.5	0.0006	0.001104
8	B	4	15 min	1	0.0012	0.002304
9	C	1	15 min	0.25	0.003	0.005304
10	C	2	15 min	0.5	0.006	0.011304
11	C	4	15 min	1	0.012	0.023304
12	C	8	15 min	2	0.024	0.047304
13	D	2	15 min	0.5	0.053	0.100304
14	D	4	15 min	1	0.106	0.206304
15	D	8	15 min	2	0.212	0.418304
16	D	16	15 min	4	0.424	0.842304
17	E	4	15 min	1	1.06	1.902304
18	E	10	15 min	2.5	2.65	4.5523049

Step	**Solution**	**Rate** (mL/hour)	**Time per step**	**Volume per step (mL)**	**Dose/Step (mg)**	**Cumulative Dose (mg)**
19	E	20	15 min	5	5.3	15.152
20	E	40	312 min	208	249.8	265

Table 3. Rituximab desensitization protocol for 20 steps (375mg/m^2)

Solution A: 250 mL, 5% dextrose, (0.00012 mg/mL).

Solution B: 250 mL, 5% dextrose, (0.0012 mg/mL).

Solution C: 250 mL, 5% dextrose, (0.012 mg/mL).

Solution D: 250 mL, 5% dextrose, (0.106 mg/mL).

Solution E: 250 mL, 5% dextrose, (1.06 mg/mL).