

Eculizumab hypersensitivity and desensitization in a toddler with atypical hemolytic uremic syndrome

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Clinical Implications

- Eculizumab is the first-line treatment for preventing life-threatening relapses of atypical hemolytic uremic syndrome. We describe an anaphylactic reaction to eculizumab and successful subsequent desensitization in a toddler.

TO THE EDITOR:

Atypical hemolytic uremic syndrome (aHUS) is a life-threatening genetic disorder that clinically presents with the triad of acute kidney injury, thrombocytopenia, and anemia. Complement-mediated aHUS results from either gain-of-function mutations in effector genes of the alternative pathway of complement or loss-of-function mutations of regulatory genes; these defects allow excessive complement activation and cell damage.¹

Eculizumab is a humanized monoclonal antibody that is first-line therapy in aHUS. It targets complement protein C5, preventing cleavage into C5a and C5b, thus interfering with the subsequent formation of the membrane attack complex (C5b-9).² Without eculizumab, aHUS is associated with significant morbidity and mortality, and relapses are common.¹ Long-term

eculizumab treatment is effective in patients with aHUS.² The relapse rate is high with discontinuation.³ Although hypersensitivity reactions and rapid desensitization for other monoclonal antibodies have been described,^{4,5} to our knowledge, eculizumab has not been part of that literature. We describe here a case of eculizumab anaphylaxis and subsequent successful administration by rapid desensitization.

A 2.5-year-old girl with aHUS requiring eculizumab infusions every 2 weeks presented with a hypersensitivity reaction to eculizumab. Shiga toxin-negative aHUS had been diagnosed at 4 months of age, during admission for anuric renal failure, thrombocytopenia, microangiopathic hemolytic anemia, jaundice, and hypertension. Genetic studies ultimately showed a heterozygous, missense variant in the gene encoding the complement regulatory protein CD46 (c.565T>G, p.Tyr189Asp), a variant previously reported in association with clinically significant aHUS. Multiple polymorphisms in *CFH* and *MCP/CD46* were also found. She was started on eculizumab and then maintained with infusions every 3 weeks. At 10 kg, she was transitioned to infusions every 2 weeks.

She had been on eculizumab maintenance for over 2 years when she developed accelerating reactions during 3 successive infusions. During the first episode, she developed a single hive during an infusion, but was otherwise asymptomatic. During the next infusion and second episode, she developed multiple urticaria within 5 to 10 minutes of starting the infusion. Intravenous diphenhydramine was given and the infusion was aborted. She received diphenhydramine premedication for the subsequent infusion and third episode, but within 15 minutes of starting the infusion, she developed diffuse urticaria, coughing, duskiness, and hypoxemia (O₂ saturation 91%). After IV diphenhydramine and hydrocortisone, her urticaria resolved and vital signs normalized. With additional steroids and antihistamines, she

TABLE I. Eculizumab desensitization using a 12-step, 3-dilution protocol

Syringe	Volume per syringes (mL)	Concentration (mg/mL)	Total dose per syringe (mg)	Amount of syringe infused (mL)
1	20*	0.05	1	4.63
2	20*	0.5	10	9.38
3	60	4.918	295.081	60

Step	Syringe	Rate (mL/h)	Time (min)	Volume infused per step (mL) [†]	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	1	15	0.25	0.0125	0.0125
2	1	2.5	15	0.63	0.0313	0.0438
3	1	5	15	1.25	0.0625	0.1063
4	1	10	15	2.5	0.125	0.2313
5	2	2.5	15	0.63	0.3125	0.5438
6	2	5	15	1.25	0.625	1.1688
7	2	10	15	2.5	1.25	2.4188
8	2	20	15	5	2.5	4.9188
9	3	5	15	1.25	6.1475	11.0663
10	3	10	15	2.5	12.2951	23.3613
11	3	20	15	5	24.5901	47.9514
12	3	40	76.875	51.25	252.0486	300.0000

Target dose of 300 mg. Target concentration of 5 mg/mL.

*The total volume and dose dispensed are more than the final dose given to the patient because the solutions in syringe 1 and syringe 2 are not completely infused.

[†]Total time infused: 241.9 min = 4.03 h.

tolerated the rest of the eculizumab at a slowed rate. The allergy service was consulted. Serum tryptase drawn 2 hours from reaction and at baseline were normal (5.7 and 3.5 ng/mL, respectively). Given the anaphylactic episode and progressive reaction severity, we diagnosed her clinically with eculizumab hypersensitivity. Completion of the infusion immediately after the anaphylactic episode was not reassuring as her mast cells could have been in a refractory state after degranulation. We also considered the limited negative predictive value of tryptase for anaphylaxis.⁶ Because there was no reasonable therapeutic alternative, we recommended rapid desensitization to eculizumab.

She was premedicated with cetirizine and famotidine for desensitization. The protocol (Table 1) employed a 12-step protocol used at Brigham and Women's Hospital that has been used successfully for other monoclonal antibodies.⁴ The full dose was delivered in the course of the desensitization procedure, the first of which she tolerated well. Skin prick testing to 0.05, 0.5, and 5 mg/mL was negative. For logistical reasons, intradermal testing was done 2 weeks later and was positive with a dilution of 0.5 mg/mL. Four unrelated adult controls were negative to intradermal injections of 0.05, 0.5, and 5 mg/mL concentrations, so we considered them to be nonirritating. Nonirritating concentrations are published for some monoclonal antibodies,⁷ but not for eculizumab. Positive skin prick or intradermal testing with a nonirritating concentration suggests specific IgE antibodies to the drug being tested.⁸ In the setting of this patient's clinical presentation, the positive intradermal testing corroborated the diagnosis of eculizumab hypersensitivity. At the time of manuscript preparation, she had undergone 10 desensitizations, exhibiting only mild urticaria responsive to antihistamines during step 12 of 3 desensitizations. She now receives additional cetirizine before step 10.

Most monoclonal antibody infusion reactions are rate-related reactions, presenting on early exposures, often with features that can mimic hypersensitivity reactions including flushing and dyspnea.⁹ However, type I hypersensitivity reactions might be distinguished by urticaria and angioedema, can develop after any number of infusions, and may worsen with subsequent exposures. Within the classification scheme proposed by Pichler¹⁰ for adverse reactions to biologics, our patient likely experienced a type β reaction (type I). As with other causes of anaphylaxis, epinephrine and IV fluids should be considered early and used according to treatment guidelines.

As it inhibits C5 cleavage into C5a and C5b, eculizumab might theoretically dampen anaphylaxis as C5a is an anaphylatoxin thought to be involved in anaphylaxis. That our patient still manifested anaphylaxis to eculizumab could corroborate redundant pathways to anaphylaxis.

Although eculizumab desensitization has not previously been described, rapid desensitization has been shown to be safe and effective for patients with type I hypersensitivity reactions to other monoclonal antibodies.^{4,5} The literature on monoclonal antibody desensitization is primarily based on adult patients, with only a few case reports and series of pediatric patients.

In a large cohort of patients desensitized to monoclonal antibodies, 23% had breakthrough reactions during desensitization, with the majority having only mild reactions, most of which occurred in the last step.⁵ Our patient's course has been consistent with this observation. As desensitization is a temporary state of tolerance, not a cure of hypersensitivity, our patient will need to continue to receive eculizumab by desensitization. This case illustrates how rapid drug desensitization can help a young child continue first-line treatment despite the development of drug-induced anaphylaxis. To our knowledge, this is the first report of eculizumab hypersensitivity reaction and successful eculizumab desensitization.

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