Successful Desensitization to Isatuximab in a Patient With Refractory Multiple Myeloma and Indolent Systemic Mastocytosis
Reply to: Anaphylactic Shock due to Isatuximab and Successful Desensitization

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To the Editor:

We read with interest the manuscript by Torres Górriz et al [1] recently published in this journal, where the authors describe a successful rapid drug desensitization (RDD) procedure for isatuximab in a patient who received 4 cycles of isatuximab-carfilzomib-dexamethasone and an autologous hematopoietic stem cell transplant (aHSCT) for refractory multiple myeloma. In the first retreatment cycle, the patient developed a systemic allergic reaction to isatuximab, with mast cell degranulation (postreaction serum tryptase 22.3 µg/L [baseline, 3.1 µg/L]). These findings, together with a positive intradermal test result for isatuximab (20 mg/mL, undiluted), were highly suggestive of IgE-mediated allergy to isatuximab. The basophil activation test (BAT) result remained negative. A 4-dilution, 16-step desensitization protocol was developed and applied effectively. In the 3 consecutive cycles, the protocol was tapered to a 3-dilution, 12-step protocol and continued uneventfully. To our knowledge, this is the first report of isatuximab-mediated anaphylaxis and successful desensitization. We here report the second case and confirm that desensitization is feasible, even with a 12-step protocol, notably, in a patient with underlying systemic mastocytosis.

The patient was a 52-year-old woman with multiple myeloma (R-ISS stage III) and paravertebral plasmacytoma. Her medical history included the diagnosis of indolent systemic mastocytosis based on the criteria of the World Health Organization, with severe Hymenoptera venom allergy causing anaphylactic shock. She took H1- and H2-antihistamines daily to suppress mastocytosis-related flushing and palpitations. Pretransplant treatment included the anti-CD38 monoclonal antibody isatuximab. She was scheduled for four 28-day treatment cycles of Isa-KRd introduction therapy, which includes oral lenalidomide (days 1-21) and dexamethasone 40 mg (days 1, 8, 15, and 22) and intravenous carfilzomib (days 1, 8, and 15) and isatuximab (first cycle, days 1, 8, 15, 22; cycles 2 to 4, days 1 and 15). The first 10 doses of isatuximab were administered without incident, and aHSCT was performed after administration of high-dose melphalan. Six months after the last pretransplant dose of isatuximab, the monoclonal antibody was reintroduced for light post-aHSCT Isa-KRd consolidation. Within 15 minutes after initiating the infusion, the patient developed flushing, nausea, tachycardia, cough, and dyspnea. The isatuximab infusion was stopped, and the patient was treated with clemastine and prednisolone, after which her symptoms resolved. A postreaction tryptase level was not obtained; baseline levels were between 55 and 65 µg/L. Consolidation therapy was continued without isatuximab.

However, 1 year after the start of consolidation, recurrence of multiple myeloma was diagnosed and treated with new cycles of isatuximab-pomalidomide-dexamethasone. The allergology department was consulted to start RDD in this patient, who had indolent systemic mastocytosis. Intradermal testing (at concentrations of 0.1, 1, and 10 mg/mL) was attempted but could not be interpreted reliably owing to a poor positive control; antihistamines could not be fully paused without causing significant clinical discomfort. As specific IgE against isatuximab is not commercially available, a BAT was performed. The patient's peripheral blood was stimulated with different concentrations of isatuximab (range 1 µg/mL to 1 mg/mL), and expression of CD63 and CD203 on the basophils was measured (Supplementary Figure S1). Clear basophil activation was observed upon stimulation with isatuximab, as shown by expression of CD63 and upregulation of CD203c, suggesting sensitization to isatuximab.

We developed a novel desensitization schedule for immediate isatuximab-related drug hypersensitivity reactions (Table). Three intravenous solutions were prepared. Isatuximab was incrementally administered in 12 steps over 1 day. Premedication consisted of the generally recommended premedication for isatuximab (dexamethasone 40 mg with oral

Table. Twelve-step Desensitization Schedule for Immediate Drug Hypersensitivity Reactions to Isatuximab

Step	Time per step, min	Cumulative time, min	Solution, mg/mL	Volume per step, mL	Rate, mL/h	Dose Administered with this step, mg	Cumulative dose, mg
1	15	0	0.02092	0.5	2	0.01	0.01
2	15	15	0.02092	1.25	5	0.026	0.037
3	15	30	0.02092	2.5	10	0.052	0.089
4	15	45	0.02092	5	20	0.105	0.194
5	15	60	0.2092	1.25	5	0.262	0.455
6	15	75	0.2092	2.5	10	0.523	0.978
7	15	90	0.2092	5	20	1.046	2.024
8	15	105	0.2092	10	40	2.092	4.116
9	15	120	2.092	5	20	10.5	14.576
10	15	135	2.092	10	40	20.9	35.496
11	15	150	2.092	20	80	41.8	77.336
12	128	278	2.092	213	100	445.7	523

Premedication (on days of desensitization)	
Time, min	
–60	10 mg levocetirizine
–60	80 mg famotidine
–30	2 mg clemastine
–30	40 mg dexamethasone
–30	10 mg montelukast

Other days (because of mastocytosis)	
Prescription	
2 doses/d	5 mg levocetirizine
2 doses/d	40 mg famotidine

or intravenous H1-antihistamines), the patient's maintenance antihistamines for indolent systemic mastocytosis, and the leukotriene antagonist montelukast. During the first desensitization procedure, at the 12th and last step, the patient developed nasal obstruction and nausea; the infusion was temporarily interrupted and additional clemastine was administered. When symptoms resolved, the remaining dose of isatuximab was infused without complications. The following 2 procedures were carried out uneventfully. In the fourth desensitization procedure, the patient reported dizziness, nausea, and facial erythema, which resolved after brief interruption of the isatuximab infusion and intravenous clemastine 2 mg. After a further 2 uncomplicated desensitization procedures, detection of disease progression necessitated a switch to telclistamab, a bispecific antibody directed against B-cell maturation antigen.

This is the second report of RDD to isatuximab. We describe a slightly different but equally successful procedure in a patient with underlying systemic mastocytosis and previous severe anaphylaxis as additional risk factors. The novelty of our findings is 2-fold. First, the successful use of BAT for isatuximab has not been described previously. The positive BAT outcome indicates the presence of specific IgE antibodies to isatuximab. Isatuximab targets the abundantly expressed CD38 on the surface of multiple myeloma cells. However, CD38 is a ubiquitous glycoprotein that is expressed on multiple tissues, including basophils [2]. Hence, we were uncertain whether a BAT would be feasible for an anti-CD38 monoclonal antibody or whether the drug would have deleterious effects on the basophils. Second, our RDD protocol had an initially more liberal approach, starting directly with a 3-dilution, 12-step schedule instead of a 4-dilution protocol. In contrast with Torres Górriz et al [1], we did not reduce the number of steps over time but were able to lower the antiallergic premedication. In conclusion, we confirm that even in a high-risk patient, RDD is possible and prevented (IgE-mediated) isatuximab-mediated anaphylaxis. Additionally, the BAT is a potential complementary or alternative diagnostic modality, particularly for patients in whom intradermal testing is not feasible.

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Conflicts of Interest

WR declares that he participated on data and safety monitoring boards or advisory boards for BMS and Janssen, for which his institution received payment. His institution also received honoraria for lectures and educational events from Janssen, Amgen, and Sanofi and support for attending meetings and/or travel from Takeda, Janssen, and AbbVie. The remaining authors declare that they have no conflicts of interest.

References

1. Torres Górriz MC, Borrás Cuartero J, Germán Sánchez A, Pesántez Méndez CG, Stein Coronado C, Fernández-Delgado M, et al. Anaphylactic shock due to isatuximab and

successful desensitization. J Investig Allergol Clin Immunol. 2024;34(3):200-2. doi: 10.18176/jiaci.0951.
2. Tissue expression of CD38 - Summary - The Human Protein Atlas. Available at: https://www.proteinatlas.org/ENSG00000004468-CD38/tissue (Accessed November 10, 2023).

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