

Successful isatuximab desensitization 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.* recently published in this journal [1], where they describe the successful rapid drug desensitization procedure (RDD) for isatuximab in a patient who received four cycles of isatuximab-carfilzomib-dexamethason and an autologous hematopoietic stem cell transplantation (aHSCT) for refractory multiple myeloma. In the first retreatment cycle, he developed a systemic allergic reaction to isatuximab with mast cell degranulation (serum tryptase 22.3 µg/l post-reaction, baseline 3.1 µg/l). These findings, together with a positive intradermal test for isatuximab (20 mg/mL, undiluted) were highly suggestive of an IgE-mediated allergy for isatuximab. The basophil activation test (BAT) remained negative. A four dilutions, 16-step desensitization protocol was developed and applied effectively. In the consecutive three cycles, the protocol was tapered to a three dilutions, 12 step protocol and continued uneventfully. To our knowledge, this is the first patient reported with isatuximab-mediated anaphylaxis and a successful desensitization. We here report the second patient and confirm that desensitization is feasible, even with a 12-step protocol notably in a patient with underlying systemic mastocytosis.

A 52-year-old female suffered from multiple myeloma R-ISS stage III with a paravertebral plasmacytoma. Her medical history included the diagnosis indolent systemic mastocytosis based on WHO criteria, with severe Hymenoptera venom allergy, causing anaphylactic shock. She used H1- and H2-antihistamines on a daily basis to suppress mastocytosis-related flushing and palpitations. Pre-transplant 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 (day 1-21) and

dexamethasone 40mg (day 1, 8, 15, 22), and intravenously administered carfilzomib (day 1, 8, 15) and isatuximab (first cycle day; 1, 8, 15, 22, cycle 2 to 4; day 1 and 15). The first ten doses of isatuximab were administered without incident and an autologous stem cell transplantation (aHSCT) could be performed after high-dose Melphalan. Six months after the last pre-transplant dose of isatuximab, the monoclonal antibody was reintroduced for Isa-KRd light post aHSCT consolidation. Within 15 minutes after initiating the infusion, the patient developed flushing, nausea, tachycardia, cough and dyspnea. The isatuximab infusion was aborted and the patient was treated with clemastine and prednisolone, after which her symptoms resolved. A tryptase level post-reaction was not obtained; baseline levels were between 55 and 65 µg/l. Consolidation therapy was continued without isatuximab.

However, one year after the start of consolidation, recurrence of multiple myeloma was diagnosed for which new cycles of isatuximab-pomalidomide-dexamethason were indicated. The Allergology department was consulted for developing RDD in this patient with indolent systemic mastocytosis. Intradermal testing (at concentrations of 0.1, 1 and 10mg/mL) was attempted but could not be interpreted reliably due 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. Peripheral blood of the patient was stimulated with different concentrations of isatuximab (range 1 µg/ml to 1 mg/ml), and CD63 and CD203 expression on the basophils was measured (Supplementary Figure S1). Upon stimulation with isatuximab, there was a clear basophil activation 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 (Figure 1). Three intravenous solutions were prepared. Isatuximab was incrementally administered in 12 steps over one day. Premedication consisted of the generally recommended premedication for isatuximab (dexamethasone 40mg with oral or intravenous H1-antihistamines), as well as her maintenance antihistamines for indolent systemic mastocytosis and the leukotriene antagonist

montelukast. During the first desensitization procedure, at the 12th and ultimate step, the patient developed nasal obstruction and nausea for which the infusion was temporarily interrupted and additional clemastine was given. When symptoms resolved, the remaining dose of isatuximab could be infused without complications. The following two procedures were carried out uneventfully. In the fourth desensitization procedure, the patient reported dizziness, nausea and facial erythema, which resolved after a brief interruption of isatuximab infusion and 2 mg clemastine intravenously. After another two uncomplicated desensitization procedures, detection of disease progression led to a therapy switch to telclistamab, a bispecific antibody directed against B-cell maturation antigen (BCMA).

This is the second patient in which isatuximab RDD is reported. We describe a slightly different, but equally successful procedure, in a patient with underlying systemic mastocytosis including previous severe anaphylaxis as an additional risk factor. The novelty of our findings is two-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 directed against isatuximab. Isatuximab targets the abundantly expressed CD38 on the surface of multiple myeloma cells, but CD38 is an 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 mAb or that the drug would have deleterious effects on the basophils. Second, our RDD protocol had an initial more liberal approach starting directly with a three dilutions, 12-step schedule instead of using a four dilutions protocol. Contrary to Torres Górriz *et al.*, we did not reduce the number of steps over time, but were able to lower the anti-allergic 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 which intradermal testing is not feasible.

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Conflict of interest

WR declares that he participated on a DSMB or Advisory Board of 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 received support for attending meetings and/or travel from Takeda, Janssen and AbbVie. The other authors declare that they have no relevant conflicts of interest related to this manuscript.

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Figure legend

Figure 1. Desensitization protocol in isatuximab-mediated anaphylaxis.

A, Results of the basophil activation test. Basophils of the patient and a healthy control were stimulated with 250 µg/ml isatuximab. Basophils are CD203c-positive (y-axis) and shown in the upper left quadrant; activated basophils upregulate CD203c, express CD63 (x-axis) and move to the upper right quadrant.

B, twelve-step desensitization schedule for immediate drug hypersensitivity reactions to isatuximab

DESENSITIZATION ISATUXIMAB								PREMEDICATION (on days of desensitization)	
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)	Time (min)	
1	15	0	0,02092	0,5	2	0,01	0,01	-60	10mg levocetirizine
2	15	15	0,02092	1,25	5	0,026	0,037	-60	80mg famotidine
3	15	30	0,02092	2,5	10	0,052	0,089	-30	2mg clemastine
4	15	45	0,02092	5	20	0,105	0,194	-30	40mg dexamethasone
5	15	60	0,2092	1,25	5	0,262	0,455	-30	10 mg montelukast
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		

OTHER DAYS (because of mastocytosis)	
Prescription	
2dd	5mg levocetirizine
2dd	40mg famotidine