Anaphylactic shock due to isatuximab and successful desensitization

Torres Górriz MC[1,2], Borrás Cuartero J[3], Germán Sánchez A[1], Pesántez Méndez CG[1], Stein Coronado CI[1], Fernández-Delgado M[4], Beltrán Agost S[5], Enrique E[1,2]

[1]Allergy Department, Castellon University General Hospital, Castellón, Spain.

[2]Jaume I University Castellón, Spain.

[3]Allergy Department, Castellon Provincial Hospital Consortium, Castellón, Spain.

[4]Hematology Departament, Castellon University General Hospital, Castellón, Spain.

[5]Hematology Departament, Castellon Provincial Hospital Consortium, Castellón, Spain.

Corresponding author
Maria Cruz Torres Gorriz
Avda/ Benicassim, number 128
12004 Castelló de la Plana (Castelló) – Spain.
E-mail: mtorresgorriz@gmail.com

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Isatuximab is an IgG1 monoclonal antibody (mAb) against CD38. It`s indicated in combination with carfilzomib-dexamethasone for the treatment of adults with refractory multiple myeloma previously treated with another therapy line. It`s administered intravenously at a dose of 10 mg/kg weekly for 4 weeks and every 2 weeks thereafter [1].

The most frequent mAbs reaction phenotype is Type I and typically occurs after consecutive mAb exposures, while infusional and cytokine release reactions can occur during both the first mAb exposure and during desensitization procedures. MAbs most frequently implicated in hypersensitivity reactions are: rituximab, infliximab, cetuximab and trastuzumab [2-4]. In terms of allergological diagnosis, mAbs skin tests are not validated, so false positive and false negative results are possible [2].

An important factor to consider in hypersensitivity reactions to isatuximab is polysorbate (PS-20 and PS-80), an FDA-approved excipient used in multiple mAbs. Systemic administration of high doses of polysorbate can cause hypotension and tachycardia. Several studies have demonstrated in vitro generation of anaphylatoxins C3a and C5a, suggesting that the immunogenicity of polysorbate is complement-driven [5].

Immediate hypersensitivity reactions to mAbs, whether IgE-mediated or not, have been treated with rapid drug desensitization (RDD), which has been shown to be a safe and highly effective procedure [2,6].

We present a 64-year-old male diagnosed with multiple myeloma in January 2022. Personal history includes iron deficiency anemia and dyslipaemia. Initially, he received 3 cycles of lenalidomide and bortezomib ending in April 2022. Due to lack of response the treatment was changed, the patient received four cycles of isatuximab-carfilzomib-dexamethasone (June to October 2022) and autologous hematopoietic stem cell transplant (aHSCT) was performed. After aHSCT, it was decided to carry out a consolidation treatment with the same scheme. In

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April 2023, the patient received the first cycle of re-treatment (with a previous infusion of dexamethasone). Under normal conditions, the total dose of isatuximab for this patient, was 620 mg in 250 ml of normal saline for a total volume of 281 ml. After 9.3 ml (20.51 mg isatuximab) the patient suddenly developed facial flushing, palmar pruritus, exanthema, wheals on forearms and blurred vision. After stopping the infusion and aspirating the perfusion line, the patient's vital signs were taken: BP 74/33 mmHg, HR 109 bpm, temperature 36ºC. Immediately, the patient presented clinical deterioration with shivering (without fever) and syncope. He was treated with hydrocortisone 100 mg, dexclorpheniramine 5 mg, intensive fluid therapy, oxygen, paracetamol 1 g and pethidine 25 mg (by Oncology Day Unit personnel) showing complete resolution in a few minutes. The patient was not treated with adrenaline because of the rapid response. Ninety minutes later a blood test was drawn with tryptase and interleukin 6. Carfilzomib was not administered. He was admitted at the Hematology ward and upon dispatch was referred to the Allergy Department.

Due to lack of information on isatuximab testing we used dilutions based on publications of other mAbs [7]. Three weeks after the reaction, intraepidermal (20 mg/ml) and intradermal (concentrations 1/1000, 1/100, 1/10 and 1/1) and polysorbate 80 tests were performed, resulting in positive intradermal test for isatuximab at concentration 1/1. Polysorbate skin tests were negative. A control patient receiving the same isatuximab treatment regimen was obtained, showing no positive or irritative test results.

Post-reaction serum tryptase determination was 22.3 µg/l and post-reaction interleukin 6 was 33.5 pg/ml. Baseline levels of tryptase and interleukin 6 where 3.1 µg/l and 2.0 pg/ml. Flow CAST® Basophil Activation Test was performed with negative results.

After risk stratification, hematologist confirmed the need for isatuximab, so a RDD was proposed. A 16-step desensitization protocol was performed, based on that described previously [8]. This protocol was modified using four dilutions (table 1) and home premedication was indicated 48 hours prior (ebastine, acetylsalicylic acid and famotidine).

The RDD was performed at the Oncology Day Unit, after hospitalary premedication with dexchlorpheniramine 5 mg iv, paracetamol 1 gr iv and montelukast 10 mg vo (hematologists routinely prescribe montelukast alongside all anti-CD 38 drugs), with a final infusion rate of 140 ml/h, in a total time of 5.25 hours.

Isatuximab is a recently approved mAb for the treatment of refractory multiple myeloma. Isabwe et al. have found positive skin testing results and/or positive specific IgE in infusional

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reactions with biologicals, as well as increased levels of tryptase, IL- 1, IL- 6, and TNF- α [3]. Taking all of this into account, the probable mechanism of this reaction is a type I IgE mediated hypersensitivity reaction. A concomitant cytokine release reaction cannot be ruled out, even though it is improbable due to the lack of fever and the slight increase in IL-6. In our experience, cytokine release reactions present IL 6 values around 1,000 pg/ml. Therefore, we don't consider the IL6 value relevant in this patient.

Basophil activation test (BAT) has been described to diagnose hypersensitivity reactions to biologicals, particularly in rituximab reactions [3]. However, studies in larger series of patients are needed to confirm the findings and establish BAT as a diagnostic tool.

Desensitization protocols have proven to be safe and effective procedures for patients with a hypersensitivity reaction to mAbs. This procedure allows patients to maintain their most effective treatment [2] and has proven to be cost-effective compared to standard administration [6,8].

Isabwe et al recorded a 23% rate of disruptive reactions during RDD with mAb. These disruptive reactions were mainly Brown's grade I and occur commonly during the final step of the RDD protocol [3]. Other groups have observed a shift from a Type I to a cytokine release reaction [2].

To our knowledge, there are no previous reports on RDD with isatuximab. We present the first case of a patient with anaphylactic shock due to isatuximab grade III/severe (EAACI severity system) with positive biomarkers (tryptase and skin test) suggesting a Type I hypersensitivity reaction treated with successful RDD. The patient successfully underwent a 16-step desensitization protocol with 4 dilutions with no disruptive reactions. The second, third and fourth desensitization were carried out with three dilutions without incident. It is planned that the fifth and sixth desensitization will be carried out with a single dilution.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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Table 1. Desensitization protocol of 16 steps corresponding to 620 mg of isatuximab (100% dose needed) modified on that described by Sloane (8)

	STEPS	ml/hour	Time (minutes)	Total ml	mg/passed
SOLUTION -1-					
100 ml					
1/1000 dilution (0.62 mg)	**1**	2	15	0.5	0.0031
0.0062 mg/ml	**2**	4	15	1	0.0062
		TOTAL =	**30**	**1.5**	**0.093**
SOLUTION -2-	**3**	0.8	15	0.2	0.012
100 ml	**4**	2	15	0.5	0.031
1/100 dilution (6.2 mg)	**5**	4	15	1	0.062
0.062 mg/ml	**6**	8	15	2	0.124
		TOTAL =	**60**	**3.7**	**0.229**
SOLUTION -3-	**7**	2	15	0.5	0.310
100ml	**8**	4	15	1	0.620
1/10 dilution (62 mg)	**9**	8	15	2	1.240
0.62 mg/ml	**10**	16	15	4	2.480
		TOTAL =	**60**	**7.5**	**4.650**
SOLUTION -4-[§]	**11**	5	15	1.25	3.07
	12	10	15	2.5	6.15
250ml	**13**	20	15	5	12.30
1/1 dilution (615 mg)	**14**	40	15	10	24.60
2.46 mg/ml	**15**	80	15	20	49.20
	16	140	90,5	211,25	519,67
		TOTAL Min =	**315.5**	**250**	**615**
		TOTAL Hours =	**5.25**	TOTAL mg =	**620**

[§]Milligrams administered from bags 1, 2 and 3 have been removed from the total dose in the bag 4 (615 mg)

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