Two Immediate Hypersensitivity Reactions to Isatuximab Confirmed by the Complement Activation Test and Treated With Successful Rapid Desensitization

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Isatuximab is a novel IgG1 κ monoclonal antibody used for the treatment of refractory multiple myeloma (MM) [1]. It binds to CD38, a transmembrane glycoprotein that is highly expressed in MM. Polysorbate 80 is added to the formulation of isatuximab.

Two cases of type I reaction to isatuximab treated with successful rapid drug desensitization (RDD) were recently published [2,3]. Torres Gorriz et al [2] reported a patient who experienced anaphylactic shock caused by isatuximab and whose positive intradermal test (IDT) result was highly suggestive of an IgE-mediated reaction. Hutten et al [3] reported the case of a patient with underlying indolent systemic mastocytosis who developed anaphylaxis to isatuximab after retreatment and had a positive basophil activation test result.

We report 2 cases of immediate drug hypersensitivity reactions (DHRs) to isatuximab caused by direct activation of the complement system. Written consent was obtained from the patients for their participation in the study and the publication of the results.

The first patient was a 50-year-old man with IgG κ MM. During his first cycle of isatuximab, he developed dyspnea, pharyngeal pruritus, and dizziness after infusion of 46.8 mL. Treatment was stopped. His oxygen saturation was 88% and blood pressure 40/60 mmHg. Dexchlorpheniramine, methylprednisolone, and oxygen were administered. The symptoms improved after 1 hour. Tryptase levels were not measured.

Skin tests with isatuximab were performed 2 weeks later. The results of skin prick tests (SPTs) (20 mg/mL, 2 mg/mL, and 0.2 mg/mL) and IDTs (20 mg/mL, 2 mg/mL, and 0.2 mg/mL), were negative. A drug provocation test (DPT) with premedication (paracetamol, dexchlorpheniramine, dexamethasone) yielded a negative result.

The hematologist confirmed that isatuximab was the only available treatment. DPT was ruled out after risk stratification, and an intravenous 3-bag, 10-step RDD procedure with isatuximab was performed according to the Ramon y Cajal University Hospital (RCUH) protocol [4]. The patient underwent 14 cycles of desensitization without breakthrough reactions.

The second patient was a 68-year-old man with IgA λ MM. During his first cycle with isatuximab, he developed pruritic hives on the abdomen, back, thighs, and right arm. His vital signs were normal. The infusion was stopped, and hydrocortisone and dexchlorpheniramine were administered. The symptoms resolved after 10 minutes, and the infusion was restarted at 25 mL/h, with new hives appearing on the left shoulder. The infusion was stopped again, and dexchlorpheniramine was administered.

Skin tests were performed 2 weeks later. SPTs (20 mg/mL, 2 mg/mL, and 0.2 mg/mL) and IDTs (20 mg/mL, 2 mg/mL, and 0.2 mg/mL) were negative. DPTs with premedication (paracetamol, dexchlorpheniramine, and dexamethasone) were negative. DPT was not performed with isatuximab because the patient did not give his consent, since he had already experienced 2 reactions.

The hematologist confirmed that isatuximab was the preferred treatment. A 3-bag, 10-step RCUH RDD protocol with isatuximab was used. To date, the patient has tolerated 10 cycles without breakthrough reactions.

An in vitro complement activation test (CAT) was carried out in both patients at baseline and, in one case, after desensitization. The CAT followed the recommendations of Weiszhár et al [5] and Szebeni et al [6]. The increase in C3a, C5a, and SC5B9 was measured using enzyme-linked immunosorbent assay (ELISA) kits from BD Biosciences (Figure). Isatuximab (50 µg/mL) and polysorbate 80 (4.4 µg/µL) were incubated with patient serum in a water bath with manual shaking every 10 minutes for 1 hour at 37°C at a 1:5 ratio. After incubation, the reaction was stopped by adding 20 volumes of phosphate-buffered saline containing 2 mM EDTA, 25 mg/mL bovine serum albumin, 0.05% Tween 20,

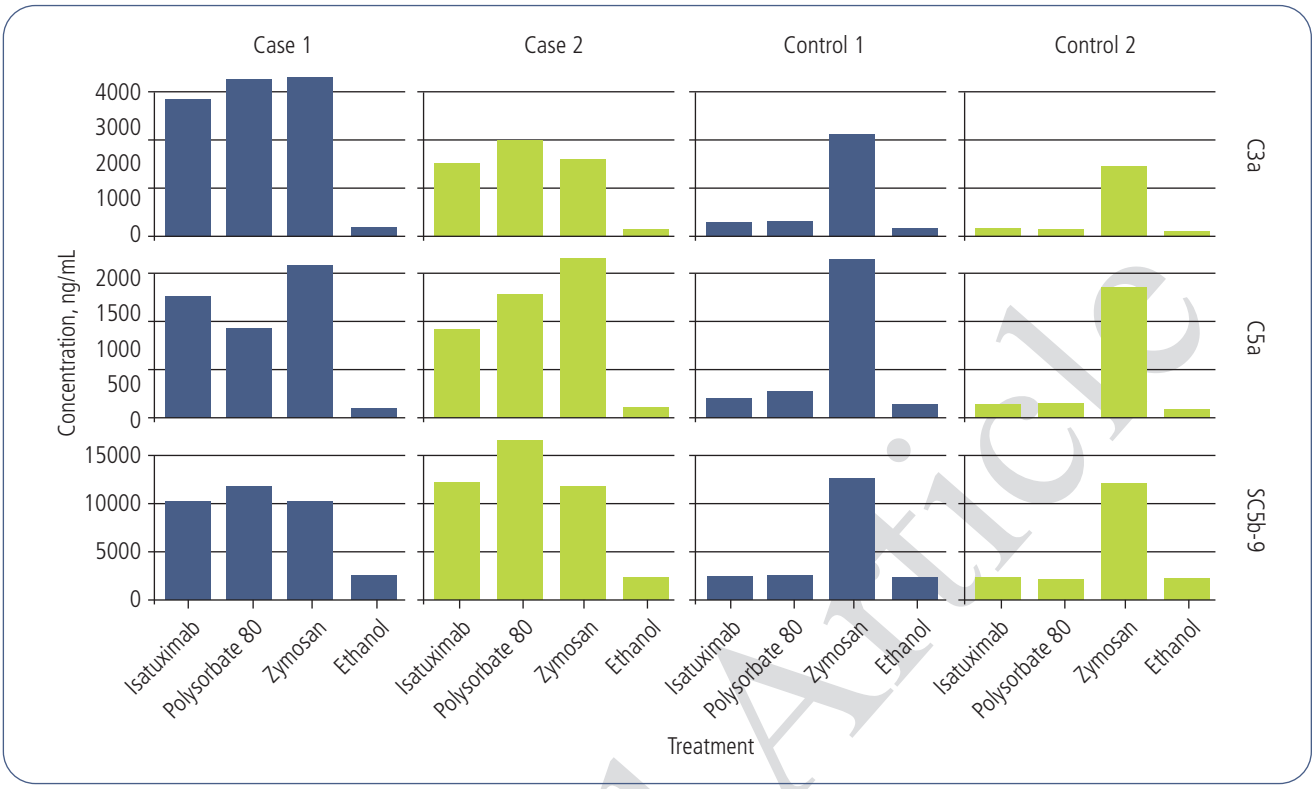

Figure. In vitro complement activation test. Isatuximab (0.4%), polysorbate 80 (4.4 µg/µL), Zymosan A (300 µg/µL), and ethanol (0.4%) were incubated with patient serum. Complement C3a, C5a, and SC5B-9 was measured using enzyme-linked immunosorbent assay. Zymosan A was used as a positive control of complement activation and 0.4% ethanol was used as a negative control.

and 0.01% thimerosal (pH, 7.4). Zymosan A (300 µg/µL) was used as positive control of complement activation, and 0.4% ethanol was used as a negative control. Quantifications were performed using commercial human C5b-9 (BD Biosciences, Cat. No.558315), C3a (BD Biosciences, Cat. No. 550499), and C5a (BD Biosciences, Cat. No. 557965) ELISA kits according to the manufacturers' instructions. The presence of soluble complement receptor after RDD to isatuximab was assessed with 100 µL of serum from pre- and post-RDD samples using the soluble human complement receptor 1 (sCR1) ELISA kit (Biomatik, Cat. No. EKU03431-96T) (Supplementary Figure). Isatuximab and polysorbate 80 activated C3a, C5a, and sC5b-9 in vitro in both cases. Adding polysorbate 80 to the isatuximab formulation induced complement activation. To exclude the possibility of false-positive results, CAT was performed in 2 patients exposed to isatuximab who had not developed a reaction. Complement from these patients was not activated with isatuximab or polysorbate 80 (Figure). In patient 2, we observed an increase in sCR1 after desensitization. There was no increase in sCR1 after administration in control 1 (Supplementary Figure).

Searching for new biomarkers to identify the underlying endotype of DHR to monoclonal antibodies is crucial for the diagnosis and management of type I reactions. The currently available biomarkers for identifying the drug involved in type I (IgE-mediated) reactions are skin testing and the basophil activation test. DPT is considered the gold standard [7,8]. Measurement of tryptase during the acute phase enables assessment of mast cell degranulation, and determination of IL-6 indicates cytokine release reactions, although it has not proven useful for identifying the culprit drug [9]. We provide evidence that isatuximab may activate C3a, C5a, and sC5b-9 in vitro, specifically by polysorbate 80 [10]. These findings could offer a novel approach to diagnosing non–IgE-mediated type I reactions as a step before DPT, especially in the case of life-threatening reactions. It is important to be aware of the limitations of CAT, which remains unvalidated. Studies with larger numbers of patients and controls are needed.

In one patient, we demonstrated that RDD induces tolerance, which is associated with an increase in sCR1 after desensitization (Supplementary Figure). sCR1 is a potent inhibitor of complement activation, acting by inhibiting C3 and C5 convertase [6] and, therefore, potentially modulating complement activation. Our findings shed light on the indication of RDD in patients with DHR due to complement activation.

To our knowledge these are the first 2 cases of DHR to isatuximab confirmed in vitro using the CAT with polysorbate 80. RDD enables safe administration in patients who experience reactions to isatuximab induced by complement activation..

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Conflicts of Interest

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References

1. Richardson PG, Beksaç M, Špička I, Mikhael J. Isatuximab for the treatment of relapsed/refractory multiple myeloma. Expert Opin Biol Ther. 2020;20:1395-404.
2. Torres Górriz MC, Borrás Cuartero J, Germán Sánchez A, Pesántez Méndez CG, Stein Coronado CI, Fernández-Delgado M, et al. Anaphylactic Shock due to Isatuximab and Successful Desensitization. J Investig Allergol Clin Immunol. 2024;34:200-2.
3. Hutten EM, Roeloffzen WWH, Lambeck AJA, van den Born-Bondt T, Oude Elberink HNG, van de Ven AAJM. Successful isatuximab desensitization in a patient with refractory multiple myeloma and indolent systemic mastocytosis. Reply to: Anaphylactic Shock due to Isatuximab and Successful Desensitization. J Investig Allergol Clin Immunol. 2024;34:216-7.
4. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Ferreiro-Monteagudo R, Guillen-Ponce C, Pueyo C, et al. Hypersensitivity and desensitization to antineoplasticagents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. Allergy. 2013;68:853-61.
5. Weiszhár Z, Czúcz J, Révész C, Rosivall L, Szebeni J, Rozsnyay Z. Complement activation by polyethoxylated pharmaceutical surfactants: Cremophor-EL, Tween-80 and Tween-20. Eur J Pharm Sci. 2012;45(4):492-8.
6. Szebeni J, Muggia FM, Alving CR. Complement activation by Cremophor EL as a possible contributor to hypersensitivity to paclitaxel: an in vitro study. J Natl Cancer Inst. 1998;90:300-6.
7. Madrigal-Burgaleta R, Bernal-Rubio L, Berges-Gimeno MP, Carpio-Escalona LV, Gehlhaar P, Alvarez-Cuesta E. A Large Single-Hospital Experience Using Drug Provocation Testing and Rapid Drug Desensitization in Hypersensitivity to Antineoplastic and Biological Agents. J Allergy Clin Immunol Pract. 2019;7:618-32.
8. Alvarez-Cuesta E, Madrigal-Burgaleta R, Broyles AD, Cuesta-Herranz J, Guzman-Melendez MA, Maciag M, et al. Standards for practical intravenous rapid drug desensitization & delabeling: a WAO Committee Statement. World Allergy Organization J. 2022;15:1-66.
9. Isabwe GAC, Garcia Neuer M, de Las Vecillas Sanchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: Phenotypes and endotypes. J Allergy Clin Immunol. 2018;142:159-70.
10. Fernandez-Bravo S, Palacio Garcia L, Requena-Robledo N, Yuste-Montalvo A, Nuñez-Borque E, Esteban V. Anaphylaxis: Mediators, Biomarkers, and Microenvironments. J Investig Allergol Clin Immunol. 2022;32:419-39.

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