

Successful rapid desensitization to atezolizumab in delayed hypersensitivity confirmed with lymphocyte transformation test

Margarita Giraldo-Tugores, MD^{a,*},
Carlos Fernández-Lozano, MSc^{b,c,*},
Alejandra Carrón-Herrero, MD^a, Pablo Gajate, MD^d,
Javier Martínez-Botas, PhD^{b,e},
Cristina Pueyo-López, PharmD^f,
Emilio Solano-Solares, MD^a, and
María Pilar Berges-Gimeno, MD, PhD^{a,g}



Clinical Implications

This is the first case of type IV hypersensitivity reaction to atezolizumab confirmed with positive drug provocation and a lymphocyte transformation test. To the authors' knowledge, there are no previously reported cases of successful rapid desensitization in a patient with delayed hypersensitivity reaction to atezolizumab.

Atezolizumab is a humanized IgG1 checkpoint inhibitor (CPI) mAb that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This release of PD-L1/PD-1 includes the activation of T cell-mediated antitumor immune response. It is currently approved by the US Food and Drug Administration for several indications, such as locally advanced or metastatic urothelial carcinoma, non-small cell lung cancer, and triple-negative breast cancer.^{1,2}

Cutaneous adverse reactions to atezolizumab have been observed in more than one-third of treated patients in clinical trials, and rash was the most common manifestation.² After the increased use of atezolizumab in clinical practice, some cases of immediate drug hypersensitivity reaction (DHR), including life-threatening anaphylaxis, were reported, most recently in Gonzalez-Diaz SN et al³ and Bian et al.⁴ Maculopapular rash is the most frequent non-immediate DHR (NI-DHR) induced by this CPI. Severe cutaneous reactions may occur, although they are rare. Only one case of Stevens-Johnson syndrome induced by atezolizumab has been recently published.⁵

Despite limited experience, rapid drug desensitization (RDD) to CPIs appears to be a safe and effective option for patients who experience DHRs to continue on first-line therapy.⁶ To date, there is no available information on desensitization to atezolizumab in nonsevere NI-DHRs.

We present the case of an 82-year-old man with the diagnosis of metastatic urothelial carcinoma. In 2019, he was treated with nivolumab as a clinical trial followed by six cycles of carboplatin and gemcitabine. Progression of liver metastases was evidenced in January 2021, and he started second-line treatment with atezolizumab. Two weeks after the second cycle, he developed pruritus and maculopapular exanthema on the face, neck, chest, and arms with facial edema. He was treated with oral prednisone and

dexchlorpheniramine for 5 days. The symptoms disappeared 15 days later without leaving residual lesions. After the second cycle, a computed tomography scan showed partial response of liver metastases.

Because of the good response of the patient to atezolizumab, the medical oncologist (MO) decided to continue the same drug and the patient was referred to our allergy department. He gave written informed consent, and 2 weeks after the initial reaction, he underwent a skin prick test and intradermal test with atezolizumab. The skin prick test at concentrations of 0.6, 6, and 60 mg/mL were negative. The intradermal test at 0.6 mg/mL was negative upon immediate and delayed readings³ compared with the positive control (histamine, 10 × 10 mm). The patient was considered for a drug provocation test (DPT); he had a mild delayed reaction and negative skin test (ST). He accepted undergoing this procedure after being informed by his allergist about the risks and the indication by his MO to continue the treatment. The DPT was performed according to our hospital protocol; no alterations of the standard premedication were made on the DPT.⁷ Non-immediate reactions occurred. However, a week later, the DPT reproduced the original symptoms. The MO decided to continue with atezolizumab, and we performed a three-bag RDD with a 10-step protocol,⁷ starting with an initial concentration of 1:500 of the total dose, increasing every 15 minutes until the full dose was administered (Table 1). No breakthrough reactions were reported during the desensitization. The patient remained under home observation for 2 weeks and no adverse reactions were observed.

To clarify the underlying mechanism, 5 months after the reaction, we performed a lymphocyte transformation test (LTT) with atezolizumab. Mononuclear cells were isolated from peripheral blood using LymphoPrep (STEMCELL Technologies, Vancouver, BC) gradient centrifugation. We added 200 µL of cell suspensions (10⁶ cells/mL) in AIM V medium (Thermo Fisher Scientific, Madrid, Spain) to each culture plate well and stimulated them with increasing concentrations of atezolizumab, provided by the hospital pharmacy. Cells were also stimulated with Dynabeads (Thermo Fisher Scientific, Madrid, Spain; CD3/CD28, 1 µL/well) as a positive control. Negative control was composed of cells with no stimulation. Cultures were performed in triplicate and incubated for 4 days in a humidified incubator (37°C, 5% CO₂ in air). On day 4, the culture plates were centrifuged and 100 µL of each well was replaced with fresh AIM-V medium containing 10 µCi of 3H-thymidine. On day 6, cells were harvested with a vacuum manifold and radioactivity incorporation into DNA was measured using a liquid scintillation counter. The stimulation index (SI) was calculated as the ratio between the mean of triplicate disintegrations per minute of the drug-stimulated cultures and the mean of triplicate disintegrations per minute of the negative controls.

As standard criteria, an SI greater than 3 in at least one concentration was considered positive.⁸ The patient had a positive reading at concentrations of 5,000 and 500 µg/mL of atezolizumab. The results of LTT with atezolizumab were negative in two controls; one patient was receiving treatment with atezolizumab without reactions and the other had no previous exposure (Figure 1).

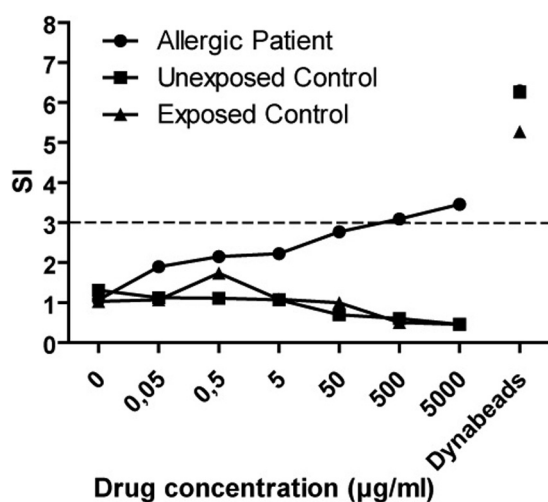
TABLE 1. Ramon y Cajal University Hospital standard rapid desensitization protocol adapted for total dose of 1,200 mg atezolizumab diluted in 250-mL volume of 0.9% saline solution

Total dose	1,200 mg	Solution concentration, mg/mL	Total dose in each solution, mg	Drug
Solution A	250 mL	0.096	24	Atezolizumab
Solution B	250 mL	0.96	240	Atezolizumab
Solution C	250 mL	4.06	1,015	Atezolizumab

Step	Solution	Administered volume, mL	Rate, mL/h	Time, min	Administered dose, mg	Fold increase per step	Approximative cumulative dose infuse, mg
1	A	22	88	15	0.0	NA	0.0
2	A	25	100	15	2.4	×2.4	2.4
3	A	50	200	15	4.8	×2	7.2
4	A	100	400	15	9.6	×2	16.8
5	B	22	88	15	0.0	NA	16.8
6	B	25	100	15	24	×2.5	40.8
7	B	50	200	15	48	×2	88.8
8	B	100	400	15	96	×2	184.8
9	C	22	88	15	0.0	NA	184.8
10	C	250	125	120	1015	×2.6	1,200

NA, not applicable.

Total infusion time was 255 minutes (4.15 h).

**FIGURE 1.** Cell stimulation index according to atezolizumab concentration. All patients had a normal response to Dynabeads CD3/CD28. The patient in the study had a positive lymphocyte transformation test (LTT) result with concentrations of 5,000 and 500 µg/mL and a negative LTT result with the lower concentrations because the proliferative capacity of the patient decreased. Controls showed no proliferative responses in LTT with atezolizumab. SI, stimulation index.

Drug hypersensitivity reactions to mAbs include infusion-related reactions; cytokine-release reactions; and type I, III, and delayed type IV reactions comprising 3% of the initial reaction phenotypes.⁹ Non-immediate DHRs to mAbs are difficult to recognize when the timing of exposure is long. The diagnosis is based on the clinical history, ST, and DPT. The DPT is considered the reference standard for confirming or excluding a diagnosis of DHR. This procedure is indicated in selected patients with nonsevere delayed DHR or negative ST, and in low-risk patients.^{7,9}

The LTT is currently the most well-used test for the diagnosis of T cell–mediated hypersensitivity, especially in β -lactam and anticonvulsant DHRs.⁸ The LTT has not been used in mAbs. We demonstrate here that the LTT could be useful to elucidate the hypersensitivity mechanism of NI-DHRs and to arrive at a diagnose for patients with a negative ST. We found a good dose-response in the patient of 50 to 5,000 µg/mL atezolizumab, although the lower concentration did not reach the SI cutoff. The LTT itself does not diagnose T-cell hypersensitivity reactions, but along with an appropriate clinical history and positive DPT, it supports a T-cell mechanism. Nevertheless, further research is needed to evaluate the role of the LTT in the diagnosis of NI-DHRs to mAbs, including atezolizumab.

To our knowledge, this is the first case of type IV hypersensitivity reaction to atezolizumab, confirmed with a positive DPT and LTT, and successful RDD. This case illustrates the LTT as a promising new tool for the diagnosis of T cell–mediated DHR to atezolizumab.

^aAllergology Department, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain

^bBiochemistry Research Department, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria, Madrid, Spain

^cAlcalá University, Madrid, Spain

^dMedical Oncology Department, Hospital Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria and Centro de Investigación Biomédica en Red Cáncer, Madrid, Spain

^eBiochemistry Research Department, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria and Centro de Investigación Biomédica en Red Cáncer, Madrid, Spain

^fPharmacy Department, Hospital Universitario Ramón y Cajal, Madrid, Spain

^gRedes de Investigación Cooperativa Orientadas a Resultados en Salud, Madrid, Spain

^hBoth authors contributed equally and are co-first authors.

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Corresponding authors: Emilio Solano-Solares, MD, Hospital Universitario Ramón y Cajal, Servicio de Alergología, 2D, Carretera de Colmenar Km 9, 28034 Madrid, Spain. E-mail: emilio.solano.solares@gmail.com. Or: María Pilar Berges-Gimeno, Hospital Universitario Ramón y Cajal, Servicio de Alergología, 2D, Carretera de Colmenar Km 9, 28034 Madrid, Spain. E-mail: berges.pilar@gmail.com. Or: Margarita Giraldo-Tugores MD Hospital Universitario Ramón y Cajal, Servicio de Alergología, 2D, Carretera de Colmenar Km 9, 28034 Madrid, Spain. E-mail: mgiraltug@gmail.com.

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REFERENCES

1. Kim HS, Seo HK. Immune checkpoint inhibitors for urothelial carcinoma. *Investig Clin Urol* 2018;59:285-96.
2. U.S. Food and Drug Administration. Highlights of prescribing information. Atezolizumab prescription information. Accessed December 25, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761034s018lbl.pdf
3. Gonzalez-Diaz SN, Villarreal-Gonzalez RV, De Lira-Quezada CE, Rocha-Silva GK, Oyervides-Juarez VM, Vidal-Gutierrez O. Desensitization protocol to atezolizumab and bevacizumab after severe anaphylaxis in the treatment of lung adenocarcinoma. *J Investig Allergol Clin Immunol* 2021;31:265-7.
4. Bian LF, Zheng C, Shi XL. Atezolizumab-induced anaphylactic shock in a patient with hepatocellular carcinoma undergoing immunotherapy: a case report. *World J Clin Cases* 2021;9:4110-5.
5. Chirasuthat P, Chayavichitsilp P. Atezolizumab-induced Stevens-Johnson syndrome in a patient with non-small cell lung carcinoma. *Case Rep Dermatol* 2018;10:198-202.
6. Labella M, Castells M. Hypersensitivity reactions and anaphylaxis to checkpoint inhibitor-mono-clonal antibodies and desensitization. *Ann Allergy Asthma Immunol* 2021;126:623-9.
7. Madrigal R, Bernal L, Berges MP, Carpio LV, Gehlhaar P, Alvarez 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. Pichler WJ, Tilch J. The lymphocyte transformation test in the diagnosis of drug hypersensitivity. *Allergy* 2004;59:809-20.
9. Isabwe GAC, Garcia Neuer M, de Las Vecillas Sánchez L, Lynch DM, Marquis K, Castells M. Hypersensitivity reactions to therapeutic monoclonal antibodies: phenotypes and endotypes. *J Allergy Clin Immunol* 2018;142:159-170.e2.