

Positive basophil activation test following anaphylaxis to pertuzumab and successful treatment with rapid desensitization

David González-de-Olano, MD^a, Jose M. Morgado, BSc^b,
Raquel Juárez-Guerrero, BS^a,
Laura Sánchez-Muñoz, MD, PhD^b,
Javier Letellez-Fernández, BS^c,
Diego Malón-Giménez, MD^d, and
Mariana C. Castells, MD, PhD^e



Clinical Implications

- The basophil activation test may be a useful tool for the diagnosis of allergic and anaphylactic reactions to monoclonal antibodies including pertuzumab. Treatment of these reactions with rapid desensitization enables patients to tolerate first-line therapy.

TO THE EDITOR:

Pertuzumab is a monoclonal antibody (MoAb) for the treatment of positive human epidermal growth factor receptor 2 (HER-2) breast cancer. In patients with HER2-positive metastatic breast cancer, the addition of pertuzumab to trastuzumab and docetaxel has resulted in a breakthrough, because its administration significantly increases the median overall survival over 15 months as compared with trastuzumab and docetaxel alone (56.5 months' median survival vs 40.8).¹ Pertuzumab was approved by the United States Food and Drug Administration in 2012, by the European Medicines Agency in 2013, and its use in Spain was started in 2014 once approved by the Spanish Medicines and Sanitary Devices Agency. To date, no cases of allergy to pertuzumab have been reported.

We report a 38-year-old Spanish woman with HER2-positive metastatic breast cancer who presented within 2-3 minutes of the second administration of pertuzumab (approximately 32 mg in 20 mL) pruritus in palms and soles, sudden epigastric pain, vomiting, dyspnea, wheezing, dizziness, and presyncope. Oxygen saturation decreased to 84% and blood pressure to 70/40 mm Hg. Prompt administration of 0.5 mL of intramuscular epinephrine (1 mg/mL) followed by 200 mg of hydrocortisone, 5 mg of dexchlorpheniramine, 1 L of fluids, 2.5 mL (5 mg) of nebulized salbutamol, and oxygen provided gradual recovery. A tryptase serum sample collected 2 hours after the onset of symptoms was 8.87 ng/mL (normal range, 0-11.4 ng/mL). She had previously received 4 cycles of adriamycin, docetaxel, and trastuzumab, without adverse reactions.

Two weeks after the reaction, the skin prick test to pertuzumab (1.6 mg/mL, the concentration used for the infusion) and intradermal (0.016 and 0.16 mg/mL) tests were negative with a good positive control. Both skin tests were performed again 8 weeks

later with negative result as well. A basophil activation test (BAT) was performed (1.6 mg/mL of pertuzumab) to further understand the mechanism of the reaction and the potential for desensitization. The BAT was found positive based on the increased expression of CD63 and CD203c (Figure 1).² Anti-IgE triggered a similar CD63 and CD203c expression in the patient and control, but pertuzumab triggered activation markers only in the patient and was negative in the control (Figure 1). Serum baseline tryptase at 2 weeks was found to be 2.03 ng/mL, indicating a significant elevation during the reaction. Because IgE, basophils, and likely mast cells were implicated in the reaction, rapid drug desensitization (RDD) was indicated and a 4-bag 16-step protocol³ was generated because of the severity of the initial reaction (Table 1). The patient was premedicated with montelukast 10 mg/24 h and acetylsalicylic acid 300 mg/24 h for 2 days—because both drugs had demonstrated to block mast cell mediator related symptoms during RDD⁴—20 mg of dexamethasone, and 10 mg of cetirizine 24 hours before and 10 mg of cetirizine 1 hour before the desensitization. The patient tolerated the full dose of pertuzumab without any adverse reaction. The patient has had 3 additional pertuzumab desensitizations with the same protocol at 3 weeks' intervals without significant side effects.

We report the first case of IgE-mediated anaphylactic reaction to pertuzumab with a successful outcome through RDD. Although the patient received steroids as premedication, these medications have not been successful at preventing anaphylaxis to other chemotherapies,⁵ and it is unlikely that they were solely responsible for the improved tolerance and increased safety during RDD. The mechanisms of acute reactions to MoAbs include IgE and non-IgE anaphylactic reactions, such as the activation of basophils through FcγRIII by IgG antibodies, and complement activation through IgG immunocomplexes.⁶ Non-antibody-mediated reactions such as cytokine release syndromes have also been proposed as the underlying mechanism of some reactions.⁷ The diagnosis of hypersensitivity to MoAbs is based on the timing of exposure, the clinical manifestations, and skin testing, but *in vitro* tests have been lagging to help identify the mechanism of the reaction in skin test negative patients.⁸ The BAT has been used in few cases of MoAb hypersensitivity, and expression of the activation surface markers (eg, CD63 and CD203c) has been shown to correlate with an IgE-mediated response.⁹ We demonstrate here that the BAT could be used as a sensitive tool to assess IgE sensitization to pertuzumab. It is possible that skin testing was negative because of the severity of the initial reaction and refractory period, but it is more likely that a metabolite not detected by skin testing was responsible for the anaphylactic reaction because skin tests repeated at 8 weeks were also negative. Tryptase was shown to have a greater than 20% increase above baseline plus 2 ng/mL within 2 hours of the reaction, which is considered a sufficient criterion for mast cell activation during the reaction.¹⁰ The case fulfills the criteria for an IgE mechanism as suggested by a positive BAT, and of mast cell activation by a significantly elevated tryptase.

RDD has been successfully used to treat IgE and non-IgE hypersensitivity reactions and anaphylaxis to MoAbs such as rituximab, trastuzumab, and infliximab.¹¹ We present here the first successful RDD to pertuzumab, which enabled the patient

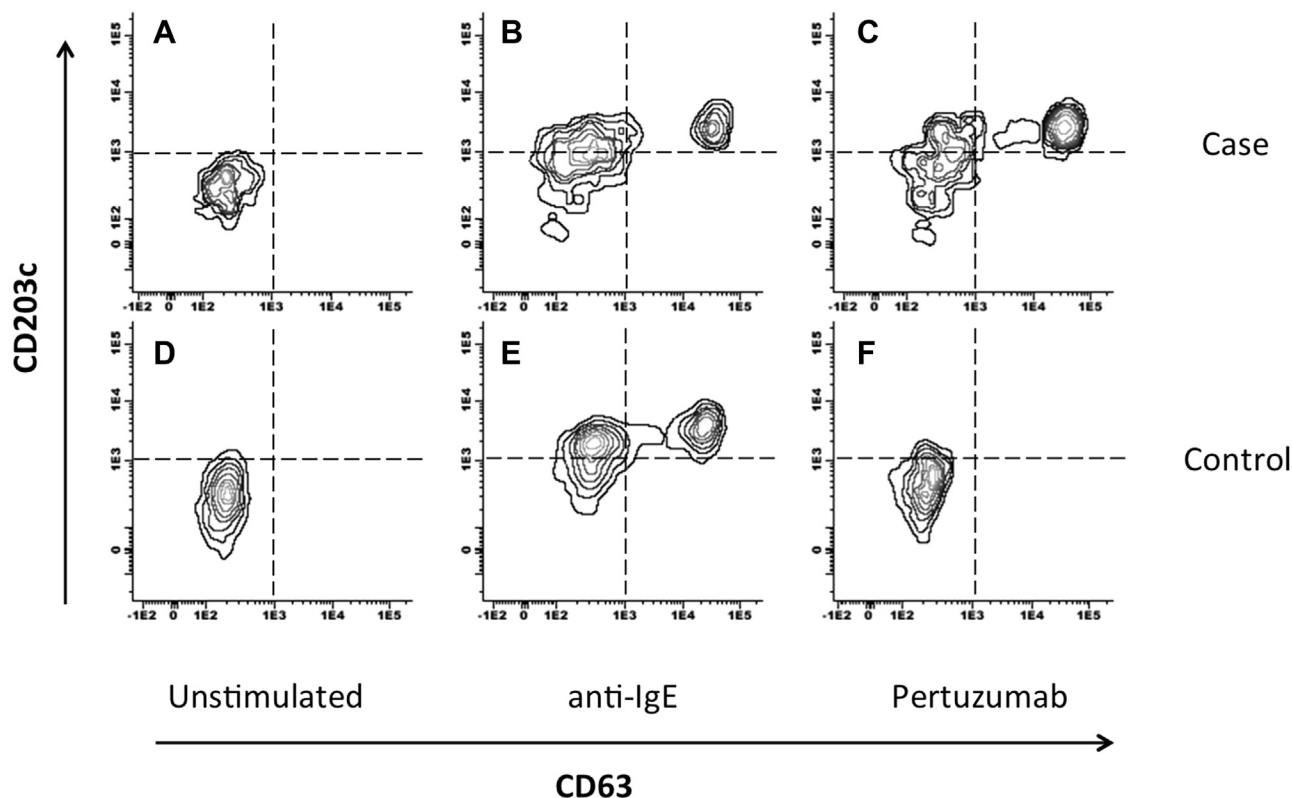


FIGURE 1. Flow cytometry density plots representing the basophil activation test (BAT) analysis. The expression of CD203c and CD63 was analyzed for each condition. **A-C**, Plots showing the results of the patient analysis; **D-F**, plots showing the control study. **A** and **D** correspond to unstimulated sample, **B** and **E** to anti-IgE (1 mcg/mL), and **C** and **F** to pertuzumab 1:500 (from a concentration of 1.6 mg/mL).

TABLE I. Desensitization protocol to pertuzumab

Step	Solution	Rate (cc/h)	Time (min)	Administered dose (mg)	Cumulative dose (mg)
1	1	1	15	0.0004	0.0004
2	1	2	15	0.0010	0.0014
3	1	5	15	0.0021	0.0035
4	1	10	15	0.0042	0.0077
5	2	2	15	0.0084	0.0161
6	2	5	15	0.0210	0.0371
7	2	10	15	0.0420	0.0791
8	2	20	15	0.0840	0.1631
9	3	5	15	0.2100	0.3731
10	3	10	15	0.4200	0.7931
11	3	20	15	0.8400	1.6331
12	3	40	15	1.6800	3.3131
13	4	10	15	4.1654	7.4785
14	4	20	15	8.3308	15.8093
15	4	40	15	16.6616	32.4709
16	4	75	186	387.3815	420.0000
Total time	411				

Solution 1: 0.42 mg of pertuzumab in 250 cc of saline solution (0.002 mg/mL).
Solution 2: 4.2 mg of pertuzumab in 250 cc of saline solution (0.017 mg/mL).
Solution 3: 42 mg of pertuzumab in 250 cc of saline solution (0.168 mg/mL).
Solution 4: 416.5 mg of pertuzumab in 250 cc of saline solution (1.666 mg/mL).

to receive and safely tolerate first-line therapy and may result in a significant increase in her life expectancy as shown in the initial studies.¹ RDD is demonstrated here to address reactions to pertuzumab consistent with type I hypersensitivity reactions, including anaphylaxis.^{3,11} This case illustrates a promising new tool for the diagnosis of IgE-mediated hypersensitivity to pertuzumab such as the BAT and the utility of RDD in overcoming severe hypersensitivity symptoms such as anaphylaxis.

^aAllergy Unit, Hospital Universitario de Fuenlabrada, Madrid, Spain

^bInstituto de Estudios de Mastocitosis de Castilla La Mancha (CLMast), Hospital Virgen del Valle, Toledo, Spain

^cPharmacy Department, Hospital Universitario de Fuenlabrada, Madrid, Spain

^dOncology Department, Hospital Universitario de Fuenlabrada, Madrid, Spain

^eAllergy and Immunology Department, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts.

Received for publication August 6, 2015; revised September 16, 2015; accepted for publication October 12, 2015.

Available online December 24, 2015.

Corresponding author: David González-de-Olano, MD, Allergy Unit, Hospital Universitario de Fuenlabrada, Camino del Molino 2, 28942 Fuenlabrada, Madrid, Spain. E-mail: dgolano@yahoo.es.

2213-2198

© 2015 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2015.10.007>

REFERENCES

1. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015;372:724-34.
2. González-de-Olano D, Álvarez-Twose I, Morgado JM, Esteban López MI, Vega Castro A, Díaz de Durana MD, et al. Evaluation of basophil activation in mastocytosis with hymenoptera venom anaphylaxis. *Cytometry B Clin Cytom* 2011;80:167-75.
3. Castells M. Rapid desensitization for hypersensitivity reactions to chemotherapy agents. *Curr Opin Allergy Clin Immunol* 2006;6:271-7.
4. Breslow RG, Caiado J, Castells MC. Acetylsalicylic acid and montelukast block mast cell mediator—related symptoms during rapid desensitization. *Ann Allergy Asthma Immunol* 2009;102:155-60.
5. Kadoyama K, Kuwahara A, Yamamori M, Brown JB, Sakaeda T, Okuno Y. Hypersensitivity reactions to anticancer agents: data mining of the public version of the FDA adverse events reporting system, AERS. *J Exp Clin Cancer Res* 2011;5:30-93.
6. Vultaggio A, Castells M. Hypersensitivity reactions to biologic agents. *Immunol Allergy Clin North Am* 2014;34:615-32.
7. Maggi E, Vultaggio A, Matucci A. Acute infusion reactions induced by monoclonal antibody therapy. *Expert Rev Clin Immunol* 2011;7:55-63.
8. Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International Consensus on drug allergy. *Allergy* 2014;69:420-37.
9. Kleine-Tebbe J, Erdmann S, Knol EF, MacGlashan DW Jr, Poulsen LK, Gibbs BF. Diagnostic tests based on human basophils: potentials, pitfalls and perspectives. *Int Arch Allergy Immunol* 2006;141:79-90.
10. Valent P, Akin C, Arock M, Brockow K, Butterfield JH, Carter MC, et al. Definitions, criteria and global classification of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. *Int Arch Allergy Immunol* 2012;157:215-25.
11. Brennan PJ, Rodríguez Bouza T, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *J Allergy Clin Immunol* 2009;124:1259-66.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.