Desensitization to Pertuzumab With a Positive Skin Test Result in a Mixed-Phenotype Hypersensitivity Reaction

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J Investig Allergol Clin Immunol 2022; Vol. 32(4): 320-321
doi: 10.18176/jiaci.0761

Key words: Monoclonal antibodies. Hypersensitivity reaction. Desensitization.

Palabras clave: Anticuerpos monoclonales. Reacción de hipersensibilidad. Desensibilización.

Pertuzumab is a humanized monoclonal antibody that binds to the dimerization domain of human epidermal growth factor receptor 2 (HER2), thus inhibiting its heterodimerization with other receptors of the HER family. It has been approved for combination with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer and improves survival. The most common adverse effects include grade III or IV febrile neutropenia and diarrhea [1]. Hypersensitivity reactions to monoclonal antibodies are possible, and recognizing them is important for subsequent therapeutic management [2]. A case of a hypersensitivity reaction to pertuzumab reported in the literature, demonstrates the importance of diagnosis and therapeutic management of these reactions [3], including desensitization as a therapeutic tool [4]. We present a case of a hypersensitivity reaction to pertuzumab with a positive intradermal test and a successful 13-step desensitization protocol.

A 56-year-old woman with a personal history of pollinosis and high blood pressure was diagnosed with HER2-positive breast cancer. Treatment with trastuzumab-pertuzumab-docetaxel was started. Within 10-15 minutes after the first dose of pertuzumab after premedication with dexamethasone and ondansetron (as per the oncologist's protocol), she developed chills, headache, and low-grade fever (37.5°C). The infusion was stopped, paracetamol was administered, and the condition described resolved in approximately 40 minutes. The infusion was continued at a slower rate until the full dose was reached, followed by docetaxel and trastuzumab without incident. At 3 weeks, 5 minutes after starting the infusion of the second dose of pertuzumab, the patient developed persistent cough, facial flushing, and headache. The infusion was suspended, and paracetamol, dexamethasone, and dexchlorpheniramine were administered; the symptoms resolved after approximately 30 minutes. She subsequently tolerated trastuzumab and docetaxel without incident. The tryptase curve was not measured in either of the reactions.

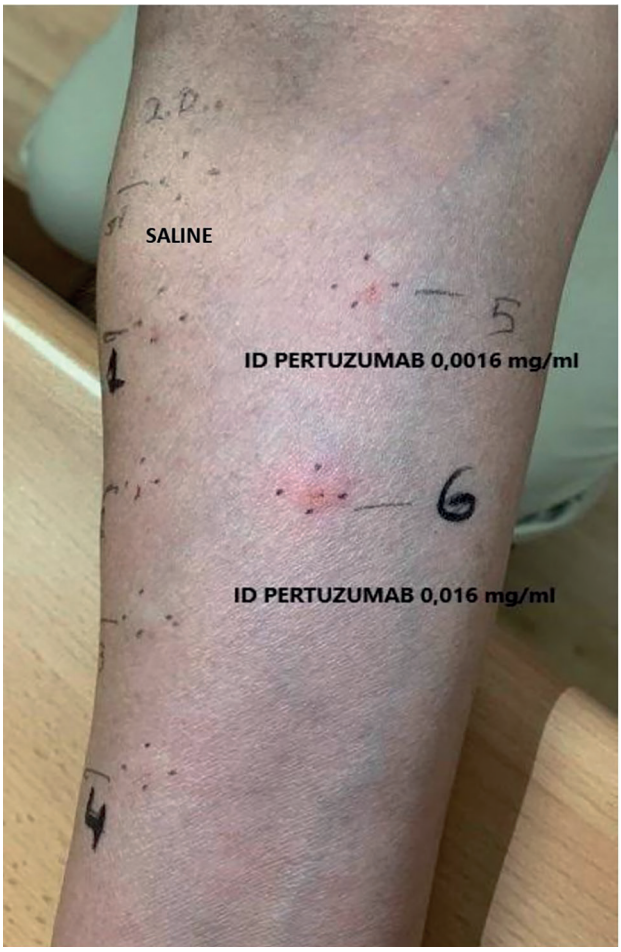

Figure. Intradermal skin tests results.

Given that treatment with the pertuzumab-trastuzumab-docetaxel regimen improved prognosis and survival, we performed an allergy study 2 weeks after the second reaction, during the patient's visit to the oncology department. This involved a prick test to evaluate pertuzumab at a concentration of 1.6 mg/mL and an intradermal test at 0.016 mg/mL and 0.0016 mg/mL (positive result at 0.016 mg/mL) (Figure). The results of the prick and intradermal skin tests with ondansetron and dexamethasone were negative. The decision was made to desensitize the patient to pertuzumab using a 13-step, 3-bag protocol (online supplementary table), with the last step administered at a rate of 120 mL/h. Premedication was administered the night before with montelukast 10 mg, acetylsalicylic acid 500 mg, dexamethasone 20 mg, and cetirizine 10 mg. The doses of acetylsalicylic acid 500 mg and dexamethasone 20 mg were repeated 1 hour before desensitization. Dexchlorpheniramine 5 mg, ranitidine 50 mg, paracetamol 1 g, and ondansetron 8 mg were added as part of the premedication protocol by the oncologist, and pertuzumab was administered without incident. The patient received 1 additional cycle of pertuzumab as part of the desensitization protocol, without incident.

We present the case of a patient who presented with an immune-mediated reaction after the first and second doses

of her pertuzumab cycle. Based on her clinical symptoms (chills, headache, low-grade fever, cough, facial flushing, and headache), we believe the reaction was due to cytokine release. After the allergology study, we confirmed a positive intradermal reaction at a concentration of 1/100. The clinical presentation and the results of the in vivo tests led us to suspect a mixed-phenotype hypersensitivity drug reaction. The symptoms of reactions presenting in the mixed phenotype can be controlled by desensitization protocols [5], indicating that administration via desensitization is successful.

Further cases of hypersensitivity reactions to monoclonal antibodies have been reported, with different mechanisms involved. In addition to the classic IgE-mediated mechanism underlying the hypersensitivity reaction, de Las Vecillas and Castells [6] commented on possible non–IgE-mediated mechanisms (IgG-mediated or cytokine release) associated with hypersensitivity reactions to biologics and discussed how sometimes IgE-mediated and non–IgE-mediated mechanisms can coexist, as in the case we present, where the clinical symptoms were consistent with cytokine release syndrome and the result of an in vivo test. We believe that the positive skin test result was due to exposure to pertuzumab and consequent sensitization. It is important to recognize and classify such patients to ensure appropriate management, with desensitization being an effective therapeutic option [5,7,8].

Various published protocols have successfully achieved desensitization to these drugs, although in some cases, the authors were unable to demonstrate the mechanism involved using an objective test. González de Olano et al [3] were the first to report a case of anaphylaxis after the administration of pertuzumab and demonstrate an IgE-mediated mechanism using the basophil activation test, thanks to which it was possible to administer the desensitization protocol. As in the case of these authors, we opted for the administration of additional corticosteroid doses as premedication to prevent the symptoms caused by the release of mast cell mediators.

Our findings highlight the increasing frequency of hypersensitivity reactions to monoclonal antibodies and stress the need for a timely allergology study. It is important to be able to classify drug hypersensitivity reactions into different phenotypes and endotypes to optimize therapeutic management. Desensitization is a useful option for management of hypersensitivity reactions to drugs with different underlying mechanisms.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Manuscript received July 19, 2021; accepted for publication October 28, 2021.

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