IgE- mediated anaphylaxis and successful desensitization to Pertuzumab: a first case with positive skin test

Anafilaksja mediowana mechanizmem IgE-zależnym i desensytyzacja Pertuzumabem: pierwszy przypadek z dodatnimi testami skórnymi

Bavbek Sevim, Hakan Yeşil, Nilay Orak Akbay

Department of Pulmonary Medicine, Immunology and Allergy Clinic, Ankara University, Cebeci, Ankara, Turkey

Summary

IgE-related hypersensitivity reactions (HSRs) to pertuzumab may occur and limit their practicality. Pertuzumab related infusion reactions are not surprising, but HSRs are less common. We report a 58-year-old female with the diagnosis of metastatic breast cancer. She experienced itching, pruritus, flushing, sweating, tachycardia, chest tightness and collapse within 2-3 minutes of pertuzumab administration. Following positive skin test results with pertuzumab, she was successfully desensitized with rapid drug desensitization protocol, despite having a history of pertuzumab-induced Grade 3 anaphylaxis.

Keywords: *Pertuzumab, Anaphylaxis, Hypersensitivity, Drug desensitization, Skin tests*

Streszczenie

Podanie pertumuzabu niesie ze sobą ryzyko wystąpienia anafilaksji mediowanej mechanizmem IgE-zależnym, co ogranicza praktyczność stosowania leku. W pracy opisano przypadek 58-letniej kobiety z rozpoznaniem raka piersi z przerzutami. W ciągu 2-3 minut od podania pertumuzabu doświadczyła świądu, zaczerwienienia się, pocenia się, tachykardii, ucisku w klatce piersiowej i zapaści. Po pozytywnych wynikach testów skórnych z pertuzumabem pacjentka została skutecznie odczulona zgodnie z protokołem desensytyzacji pomimo wcześniejszego przebycia anafilaksji 3-go stopnia wywołanej przez pertuzumab.

Słowa kluczowe: *pertuzumab, anafilaksja, nadwrażliwość, desensytyzacja, testy skórne*

© **Alergia Astma Immunologia 2019, 24 (4): 170-172**
www.alergia-astma-immunologia.pl

Adres do korespondencji / Address for correspondence

INTRODUCTION

Pertuzumab is a humanized monoclonal antibody (MoAb), successfully used for the treatment of human epidermal growth factor receptor-2 (HER2)-positive metastatic breast cancer in combination with trastuzumab and docetaxel [1]. Monoclonal antibodies, in general, can induce cytokine releases, but IgE-related hypersensitivity reactions (HSRs) may also occur and limit their practicality [2]. Rapid drug desensitization (RDD) was developed for the delivery of biologic agents that cause immediate HSRs by inducing temporary tolerance. However, desensitization protocols for MoAbs are seldom used [2]. We have been using RDD, as developed at the Brigham and Women's Hospital, for patients who experience immediate HSRs [2, 3].

Pertuzumab related infusion reactions are not surprising but HSRs are less common due to their lack of mouse antibody parts. In keeping with that very few immediate HSRs to pertuzumab and desensitization attempts have been reported [4, 5].

Here we report a patient who was skin test positive to pertuzumab, and could be successfully desensitized with RDD despite having a history of pertuzumab-induced Grade 3 anaphylaxis.

CASE DESCRIPTION

A 58-year-old female with the diagnosis of metastatic breast cancer was given four cycles of pertuzumab, trastuzumab and docetaxel in oncology department. The patient experienced itching, pruritus, flushing, sweating, tachycardia, chest tightness and collapse within 2-3 minutes of pertuzumab administration. The drug infusion was stopped immediately, and intramuscular pheniramine (45.5 mg) and intravenous methylprednisolone (40 mg) were administered. The patient developed the same symptoms during the subsequent infusion, and the infusion was stopped and patient was referred to the allergy department.

She had no history of atopic diseases and was negative to skin prick testing with inhalant allergens. Prick test with

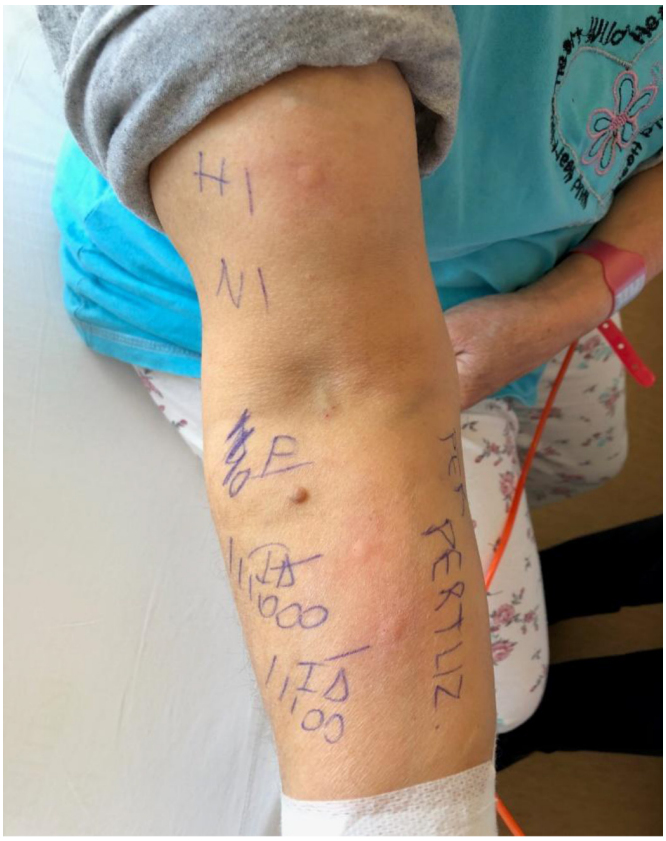

Fig. 1. Skin tests, prick and intradermal (ID) tests with Pertuzumab

the culprit drug was negative at 1:1 (30 mg/mL) dilution, but intradermal skin tests (IDTs) were positive at concentrations of 1:1000 (0.03 mg/mL) and 1:100 (0.3 mg/mL) of (30*mg/mL pertezumab per vial)* (Fig 1). Two healthy controls were negative in IDTs to these culprit drug dilutions.

The drug induced reaction was defined as Grade 3 according to the Brown Classification, which indicates severe HSR [6]. Considering severity of the initial reaction, and taking approval of her oncologist, a 12-step rapid RDD protocol was developed for half dose of (420 mg) of. The same protocol would be giving in the second day to reach the final does (840 mg). The patient was premedicated with montelukast, acetylsalicylic acid, H1 and H2 blockers, with systemic steroids and was desensitized by an experienced allergist using established protocols (Table I). The basal tryptase level was 1.65 μg/L. At the 12th step of the protocol, she developed sweating, dizziness, nausea, chest tightness. At immediate examination, she was severely pale, with hypotension, and tachycardia (blood pressure: 90/70 mm Hg, oxygen saturation: 94%, pulse: 97 beat/min) but no wheezing, thus, desensitization was interrupted and treatment including 0.6 mL of intramuscular epinephrine (0.5 mg/mL), pheniramine hydrogen maleate (22.7 mg), methylprednisolone (40 mg), IV fluid infusion were administered. The infusion was restarted without adverse effects.

The same protocol, but with addition of IV Fluid (Dextroz 5% infusion, 100 cc/hour) and addition of pheniramine hydrogen maleate (22.7 mg) infusion at the beginning of step 9 was giving in the next day. However, the patient developed the same clinical presentation of breakthrough

Table I. Pertuzumab Desensitization Protocol (modifications are in bold)

Step	Solution	Rate (mL/h)	Time (min)	Volume/Step (mL)	Total Dose (mg)
1	1	2.5	15	0.60	
2	1	5.0	15	1.25	
3	1	10.0	15	2.50	
4	1	20.0	15	5.00	
					0.158
5	2	5.0	15	1.25	
6	2	10.0	15	2.50	
7	2	20.0	15	5.0	
8	2	40.0	15	10.0	
					3,308
9	3	10.0	15	2.5	**Feniramin hidrojen maleat 22.7mg infusion mg in 250 cc Dextroz 5%**
10	3	20.0	15	5.00	
11	3	40.0	15	10.00	
11a	**3**	**50**	**15**	**12,5**	
12	3	60.0	240	221.50	420

Solution	Total Volume	Concentration
1	250 mL	0.0168 mg/mL
2	250 mL	0.168 mg/mL
3	250 mL	1.662mg/mL

Premedication: 12 hours ago:10 mg montelukast PO, 300 mg acetylsalicylicacid PO: 30 minutes ago: 10 mg montelukast PO, 10 mg cetirizine PO, 50 mg ranitidine IV, 40 mg methylprednisolone IV, 300 mg acetylsalicylic acid PO, IV Fluid: SF or Dextroz 5% infusion, 100 cc/hour, steps between 1-8 PO: peroral, IV: intravenous

reaction, the infusion was then interrupted and the patient treated accordingly, then infusion was restarted. A month later we modified the desensitization protocol with addition of step 11a with a infusion rate 50 cc/hour and increased dextroz 5 % infusion to 250 cc/hour at step 9 for the rest of desensitization (bold in Table I) The patient perfectly tolerated this protocol. She received 4 RDDs with two breakthrough reactions developed during the first two desensitizations, but no reaction occurred during third and fourth desensitization. The desensitization protocol is ongoing.

DISCUSSION

The data about HSR to pertuzumab are very limited and in keeping with that successful RDD to pertuzumab has been reported only in two references [4, 5]. An IgE-mediated HSR suggested by a positive basophile activation test and increased tryptase levels, was reported in a 38-year-old woman with breast cancer on her second infusion with pertuzumab. She was safely re-exposed to the drug through 4-bag 16-step protocol because of the severity of the initial reaction. Skin prick and IDT were negative in this case [5]. In the recent paper about HSRs to 16 MoAbs, there were two cases with HSRs to pertuzumab and only one was skin tested and resulted in negative [5].

Skin testing with the offending agent, specific serum IgE measurement along with elevated serum tryptase level during the acute reaction can be used for IgE-mediated HSR [8]. We are not aware the presence of specific in vitro test for the measurement of IgE to pertuzumab. Instead we performed skin tests. Skin tests with MoAbs have not been standardized but as used in the recent article [5], we used 1:1, 1:10- 1: 1000 dilutions for prick and IDTs. To our knowledge, our case is the first with a positive IDT result to pertuzumab. Dose reduction is used to tolerize patients to their target dose when initial desensitizations are not successful [2, 7], We preferred to use half dose of the drug in the initial desensitization along with augmented premedication because of the severity of initial reaction. Despite that the patient reacted with grade 3 anaphylaxis during the first two desensitizations. Unfortunately a blood sample for tryptase levels was not taken during the reactions but we were able to manage the further desensitizations with modification of the protocol.

In conclusion pertuzumab can induce IgE-mediated anaphylaxis and can be successfully managed with RDD.

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.

References

1. Santos RB, Galvão VR. Monoclonal Antibodies Hypersensitivity: Prevalence and Management. Immunol Allergy Clin N Am 2017; 37: 695-711.
2. Brennan PJ, Rodriguez Bouza T, Hsu FI, et al. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. J Allergy Clin Immunol 2009; 124: 1259-66.
3. Bavbek S, Kendirlinan R, Çerçi P, et al. Rapid drug desensitization with biologics: a single-center experience with four biologics. Int Arch Allergy Immunol 2016; 171: 227-33.
4. Gonza´lez-de-Olano D, Morgado JM, Jua´rez-Guerrero R, et al. Po sitive basophil activation test following anaphylaxis to pertuzumab and successful treatment with rapid desensitization. J Allergy Clin Immunol Pract 2016; 4: 338-40.
5. Isabwe GAC, Neuer MG, 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.
6. Brown SG. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol. 2004; 114: 376-81.
7. Castells M. Drug Hypersensitivity and Anaphylaxis in Cancer and Chronic Inflammatory Diseases: The Role of Desensitizations. Front Immunol 2017; 8: 1472.