Anaphylaxis to Mepolizumab and Omalizumab in a Single Patient: Is Polysorbate the Culprit?

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The past decade has seen an increase in the use of biological agents such as mepolizumab and omalizumab for the treatment of severe asthma. These agents reduce the frequency of exacerbations, allow for reduced oral corticosteroid use, and increase quality of life. Their safety profile is generally very good. Beside local adverse effects, which are comparable in placebo-controlled clinical trials, there are very few reports on anaphylactic reactions to these biologics [1,2].

Pivotal studies indicate that the anti-IL-5 antibody mepolizumab is well tolerated, with no reports of anaphylaxis or treatment-related deaths [2]. The anti-IgE monoclonal antibody omalizumab binds to the constant region of free IgE only and, therefore, does not cause mast cell degranulation. However, omalizumab has been reported to cause anaphylaxis in <0.1% of patients, with reactions being delayed in many cases [3]. The mechanism for these reactions is, however, unclear [3]. Here, we report an anaphylactic response after 13 months of treatment with mepolizumab and following the subsequent first injection of omalizumab in a patient with severe asthma.

The patient was a never-smoking woman (born 1989) who, since childhood, had had allergic asthma due to sensitization to cat and dog dander, house-dust mite, and tree and grass pollen. Sublingual immunotherapy for chronic rhinosinusitis without polyps due to mite allergy was attempted but discontinued because of unwanted adverse effects. There were no other clinically relevant comorbidities. During the 12 months before starting mepolizumab, the patient experienced 4 serious asthma exacerbations despite using a high-dose inhaled corticosteroid (fluticasone 1500 µg), a long-acting ß mimetic, a long-acting muscarinic antagonist, and a leukotriene receptor antagonist. Her symptoms were severe, with nightly awakening (3-5 times/wk) and exercise-induced dyspnea after climbing about 20 stairs.

Before starting mepolizumab on November 1, 2017, the patient had a total blood IgE of 1109 kU/L, sIgE against grass pollen (class 4), tree pollen (class 5), and *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (class 6). Her eosinophil count was 540/µL (without oral corticosteroids). FEV_1 was 2.5 L (65% predicted). Following initiation of

mepolizumab (100 mg/mo), she was able to discontinue corticosteroids and experienced no exacerbations for 13 months. Her FEV_1 increased to 3.1 L (78% predicted).

On December 12, 2018, about 30 minutes after her 13th injection of mepolizumab 100 mg, the patient developed dry cough and dyspnea, with a fall in blood pressure to 90/60 mm Hg, a heart rate of 140 bpm, and respiratory distress. Her FEV_1 decreased from 2.4 L (62% predicted) to 1.6 L (41% predicted), and she hyperventilated (pO_2, 84 mm Hg; pCO_2, 22 mmHg). She was treated with 250 mg prednisolone intravenously and inhaled salbutamol and ipratropium bromide. She was hospitalized with a diagnosis of status asthmaticus and treated with inhaled adrenaline, subcutaneous terbutaline, and noninvasive intermittent ventilation therapy. Her laboratory results 8 days later were as follows: eosinophils, 0.3% (30/μL); C-reactive protein, 0.2 mg/dL; and tryptase, 6.7 μg/L.

The patient herself and the attending pulmonary physician assumed that this was probably not a reaction to mepolizumab but an asthma exacerbation that had occurred many times before the biologic. She was subsequently referred to us with a request to continue mepolizumab therapy for severe asthma in our center. Three weeks later, after discussion with the patient, we performed a prick test with undiluted mepolizumab. As the test was negative after 20 minutes, we injected mepolizumab 0.3 mL (about 35 mg) subcutaneously. Thirty minutes later, she developed dry cough, dyspnea, and wheezing, with a decrease in blood pressure. She was treated immediately with prednisolone 250 mg intravenously, terbutaline subcutaneously, salbutamol, and oxygen. After 20 minutes she recovered slowly and was not hospitalized.

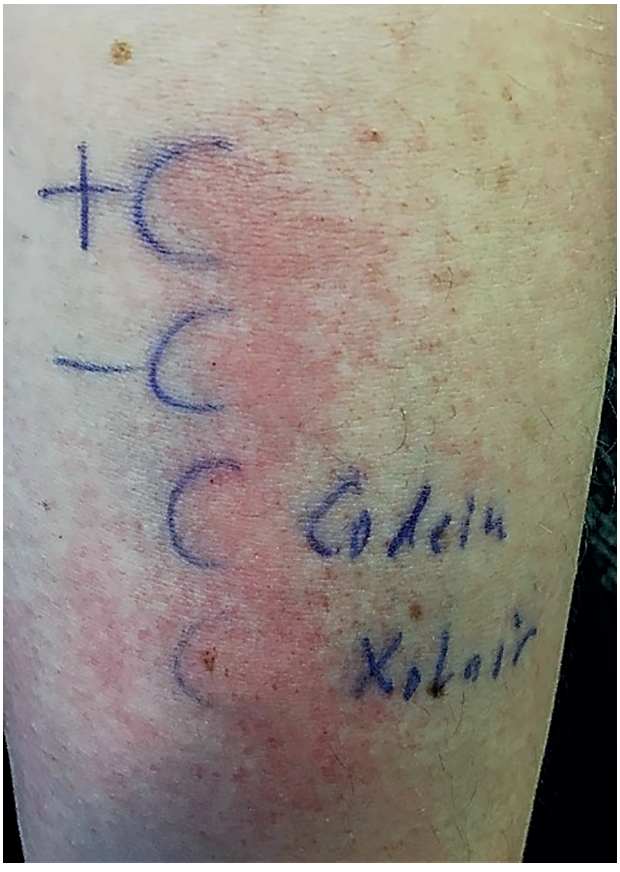

Figure. Skin prick test with histamine (0.1%), saline (0.9%), codeine (0.9%), and omalizumab (Xolair, undiluted) after 45 minutes.

Since the patient fulfilled the indication for omalizumab, we responded to her request to start taking the drug, although we wanted to clarify her tolerability in advance. On February 21, 2019, we performed skin prick tests with omalizumab, mepolizumab, benralizumab, and polysorbate (all undiluted). Given that all tests were negative after 15 minutes, we injected omalizumab 0.1 mL subcutaneously. However, about 10 minutes later, the test with polysorbate became positive, with a wheal of 4 mm, and the test with omalizumab became positive after about 45 minutes (Figure). About 20 minutes following the omalizumab injection, the patient developed a dry cough, dyspnea, dizziness, and obstruction with no signs of hyperventilation or any other stress-induced reaction. The reaction was moderate. Following inhalation of salbutamol and a subcutaneous terbutaline injection, the dyspnea resolved, and the patient's breathing returned to normal.

No cases of mepolizumab-induced anaphylaxis have been reported to date. In contrast, anaphylactic responses minutes following administration of omalizumab after more than a year of uneventful treatment have been described in 2 patients [4]. However, the authors concluded that this was not due to sensitization to the monoclonal antibody, as neither IgE nor IgG antibodies to omalizumab could be found. Instead, they concluded that polysorbate 20, an excipient in omalizumab, was the most likely cause of these reactions. Interestingly, polysorbate is also an excipient in mepolizumab.

Polyoxyethylene-sorbitan-20-monolaurate (also known as polysorbate 20 and Tween 20) is a solubilizing agent used ubiquitously in many medical preparations. With respect to the biologics used to treat asthma, polysorbate 20 is an excipient in omalizumab and benralizumab, as is polysorbate 80 in mepolizumab and dupilumab but not in reslizumab. Polysorbate 20 and 80 have no differences as inducers of anaphylactic reactions. In a patient experiencing multiple anaphylactic responses to an intravenously administered vitamin product, polysorbate 80 was identified as the causative agent [5]. Furthermore, polysorbate 80 has been considered the causative agent in anaphylaxis to intramuscular corticosteroids [6] and in anaphylaxis in a teenager receiving omalizumab containing polysorbate 20 [7]. The fact that antipolysorbate IgE molecules were not found in any of these reports suggests that the response was nonallergic anaphylaxis. A clue to the possible mechanism has been suggested in experiments in beagle dogs, in which polysorbate 80 was shown to activate the complement cascade, resulting in mast cell degranulation [8]. Polysorbates are structurally related to polyethylene glycols, which are also frequently used as excipients and which are reported as a cause of anaphylaxis [9].

We have since performed skin prick tests to polysorbate 20 in 8 healthy adults and 7 patients with severe asthma receiving mepolizumab or benralizumab for more than 3 months. All results were negative.

In conclusion, we show the development of hyperresponsiveness to mepolizumab 13 months after successful treatment and apparent cross-reactivity with

omalizumab. We believe that in both cases, the cause was a non–IgE-mediated anaphylactic response to the excipient polysorbate, which was used in both agents.

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Conflicts of Interest

Dr. Zuberbier reports the following conflicts outside the work submitted: personal fees from AstraZeneca, AbbVie, ALK, Almirall, Astellas, Bayer Health Care, Bencard, Berlin Chemie, FAES, HAL, Leti, Meda, Menarini, Merck, MSD; grants and personal fees from Novartis; and personal fees from Pfizer, Sanofi, Stallergens, Takeda, Teva, UCB, Henkel, Kryolan, L'Oréal. Dr. Zuberbier's organizational affiliations include the following: Committee Member of the WHO-Initiative "Allergic Rhinitis and Its Impact on Asthma" (ARIA); Member of the Board of the German Society for Allergy and Clinical Immunology (DGAKI); Head of the European Centre for Allergy Research Foundation (ECARF); Secretary General of the Global Allergy and Asthma European Network (GA2LEN); and Member of the Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO).

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The remaining authors declare that they have no conflicts of interest.

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