

Educational & Teaching Material

Case Report



Received: Aug 25, 2017

Accepted: Jan 8, 2018

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Combination of omalizumab and bee venom immunotherapy: does it work?

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ABSTRACT

Bee venom immunotherapy (b-VIT) can be combined with omalizumab therapy in order to suppress systemic reactions developing due to b-VIT itself. Omalizumab acts as a premedication and gains time for the immunotherapy to develop its immunomodulatory effects. However, the combination of omalizumab and b-VIT is not always effective enough. Herein we present a patient in whom successful immunotherapy cannot be achieved with combination of omalizumab to b-VIT.

Keywords: Anaphylaxis; Venom immunotherapy; Omalizumab

INTRODUCTION

Bee venom is one of the allergens that can cause local or systemic reactions. Bee venom immunotherapy (b-VIT) is the most effective method to prevent bee venom anaphylaxis in those with such a history [1, 2]. However, although rare, adverse effects of immunotherapy (IT) can also be seen. Mild or severe systemic reactions ranging from urticaria to anaphylaxis can develop, often in the form of IgE-mediated early-type hypersensitivity reactions [3], but none of these reactions are an indication to discontinue b-VIT [2].

Once these systemic reactions that generally develop in the buildup phase of IT are treated, IT can be continued from a lower dose (based on the severity of the reaction). With dose adjustment, the patients mostly become tolerant to the dose that caused the reaction and can reach and continue a maintenance dose without a problem. However, small number of patients can still develop recurrent anaphylaxis episodes even with dose adjustment. Recently, b-VIT has been administered together with omalizumab for this patient group [4-7]. The aim here is to suppress the allergic reaction developing due to b-VIT and therefore make venom IT tolerable for the patient. In other words, omalizumab is used as a premedication to gain time for the immunomodulatory effect of IT to appear. We present a case that developed recurrent anaphylaxis episodes in the buildup phase of *apis mellifera* IT administered together with omalizumab.

CASE REPORT

A 49-year-old male patient was referred to our clinic with a history of severe anaphylaxis (urticaria, angioedema, dyspnea, and hypotension) after a honeybee sting. Sensitization to *apis mellifera* was confirmed with both skin prick test and serum specific IgE and conventional IT for *apis mellifera* (Alutard SQ, ALK-Abelló, Hørsholm, Denmark) was initiated. Five minutes after the injection of 0.4-mL dose of the 4th vial (100,000 SQ units/mL) in the buildup phase, he developed anaphylaxis (flushing, itching, shortness of breath, and nausea). One week later, IT was continued with 0.1 mL of the 4th vial. An anaphylaxis episode similar to the previous one developed 5 minutes after the dose of 0.4 mL of the 4th vial in the patient whose IT dose was being increased 0.1 mL every week. This time the 3rd vial was started 1 week later by decreasing it by 0.6 mL. A systemic reaction similar to the previous one developed again at a dose of 0.4 mL of the 4th vial in our case who was continued IT at doses increased by 0.1 mL every week. We decided to combine IT with omalizumab 150 mg/2-week treatment due to these reactions. The omalizumab dosing scheme with b-VIT is not standardized and various dosing schedules have been used [4-7]. The scheme administered to our case is shown in **Table 1**. With IT + omalizumab combination, he was able to tolerate the buildup doses with which he had experienced anaphylaxis previously, and the maintenance dose (1 mL of the 4th vial) was reached. Omalizumab was discontinued and no reaction was observed with the maintenance dose administered 1 month later. However, after the maintenance dose of the 2nd month symptoms of itching, urticaria, cough, and dyspnea developed within 15 minutes. Adrenaline 0.5 mg intramuscular (IM) twice with an interval of 5 minutes, diphenhydramine 45.5 mg (Avil, Sandoz Ilac Sanayii A.S., Istanbul, Turkey) IM and methylprednisolone 40 mg (Prednol, Mustafa Nevzat Ilac Sanayii A.S., Istanbul, Turkey) intravenous were administered. Two weeks later, 150 mg of omalizumab was administered first and IT was administered 4 hours later by decreasing the dose to 0.4 mL of 4th vial. A reaction similar to the previous one occurred about half an hour after this dose. Patients who experienced significant bee anaphylaxis and have recurrent anaphylaxis episodes with b-VIT, must be evaluated regarding basal serum tryptase levels and mastocytosis [8, 9]. The basal serum tryptase level was 63 ng/mL in our case (reference range < 11.5 ng/mL). The case had no mastocytosis skin findings and no history of chronic itching or urticaria. He did not describe a history of anaphylaxis with another allergen. The patient refused to be undergone bone marrow biopsy. Both IT and omalizumab treatments were terminated. Protection measures and how to use an epinephrine auto-injector were explained again.

DISCUSSION

This case report suggests that adding omalizumab to venom IT creates a powerful premedication effect and had no effect on immune modification. There are previous reports in which patients experiencing recurrent anaphylaxis with b-VIT have successfully completed until the maintenance phases under omalizumab. Omalizumab were completely discontinued or reinitiated again because of an anaphylaxis with IT afterwards in these reports [4-7]. In patients without a systemic reaction after omalizumab discontinuation, it can be said that successful immunomodulation effect of IT was achieved. However, it is debatable regarding both cost and patient comfort whether omalizumab treatment should be continued in patients experiencing a reaction to b-VIT after omalizumab discontinuation

Table 1. Apis mellifera immunotherapy (IT) + omalizumab combination administration scheme of our case

Administration date (wk)	Omalizumab dose	IT dose	Reaction
0	150 mg	Not administered	
2	150 mg (4 hours before IT)	4th vial 0.4 mL (0.2 mL to both arms in divided doses with an interval of half an hour)	None
3	Not administered	4th vial 0.5 mL (0.25 mL to both arms in divided doses with an interval of half an hour)	None
4	150 mg (4 hours before IT)	4th vial 0.6 mL (0.3 mL to both arms in divided doses with an interval of half an hour)	None
5	Not administered	4th vial 0.7 mL (0.35 mL to both arms in divided doses with an interval of half an hour)	None
6	150 mg (4 hours before IT)	4th vial 0.8 mL (0.4 mL to both arms in divided doses with an interval of half an hour)	None
7	Not administered	4th vial 0.9 mL (0.45 mL to both arms in divided doses with an interval of half an hour)	None
8	150 mg (4 hours before IT)	4th vial 1 mL (0.5 mL to both arms in divided doses with an interval of half an hour)	None
10	Not administered	4th vial 1-mL single dose	None
13	Not administered	4th vial 1-mL single dose	None
17	Not administered	4th vial 1-mL single dose	Facial erythema and itching, uvula edema, nausea and dyspnea 15 minutes after administration
19	150 mg (4 hours before IT)	4th vial 0.4 mL	Facial erythema and itching, uvula edema, nausea and dyspnea 25 minutes after administration

or dose reduction. In contrast, informing the patient about protective measures, and prescribing antihistamines and an epinephrine auto-injector seems to be a logical solution in terms of cost-effectiveness. It is also debatable to insist on IT + omalizumab therapy in patients with milder systemic reaction than before with b-VIT + omalizumab. Because, the combination of IT and omalizumab can have some adverse effects in addition to IgE-mediated hypersensitivity reactions [6]. Another point is that it may not be possible to have a successful response with the IT + omalizumab combination in systemic mastocytosis patients with recurrent anaphylaxis episodes [6, 10]. Although the mastocytosis diagnosis was not confirmed in our case, the high basal tryptase levels indicate such a possibility. On the other hand, discontinuation of IT in this cases also means that there will always be a risk of anaphylaxis with bee stings. We therefore evaluated the risk/benefit ratio with the patient and decided to stop IT and omalizumab, and monitor him with an adrenaline auto-injector and protective measures.

A successful IT cannot always be achieved in patients experiencing recurrent systemic reactions with b-VIT even after a successful period with the combination of omalizumab and IT. The decision to resume or discontinue IT and omalizumab in this patient group should be made by evaluating the possible risks and benefits after a discussion between the physician and the patient.

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