

Unpredicted Adverse Reaction to Omalizumab

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■ Abstract

Despite promising reports of the use of omalizumab as add-on therapy in patients with systemic mastocytosis and recurrent anaphylaxis during specific venom immunotherapy (VIT), unpredicted adverse effects may lead to therapy failure. We present the case of a patient with systemic mastocytosis and Hymenoptera venom allergy who was administered omalizumab as add-on therapy to improve VIT tolerability after repeated severe adverse reactions despite H₁/H₂-antihistamine prophylaxis. We describe an unexpected discontinuation of omalizumab following successful initiation of VIT in a patient with systemic mastocytosis, with subsequent lack of tolerability of VIT. An interesting aspect of this case is the correlation of basophil activation test results with both clinical tolerability and VIT intolerance.

Key words: Mastocytosis. Venom immunotherapy. Basophil activation test. Omalizumab.

■ Resumen

A pesar de los prometedores informes acerca del uso de omalizumab como tratamiento suplementario en pacientes con mastocitosis sistémica y anafilaxia recurrente durante la inmunoterapia con veneno (ITV) específica, los efectos adversos no previstos pueden conducir al fracaso terapéutico. Se presenta el caso de un paciente con mastocitosis sistémica y alergia al veneno de himenópteros al que se administró omalizumab como tratamiento suplementario para mejorar la tolerabilidad a la ITV, después de experimentar reacciones adversas graves en repetidas ocasiones pese a recibir profilaxis con antihistamínicos H₁/H₂. Se describe una interrupción inesperada del tratamiento con omalizumab después de un inicio satisfactorio de la ITV en dicho paciente con mastocitosis sistémica, con aparición posterior de intolerancia a la ITV. Un aspecto interesante de este caso es la correlación de los resultados de los tests de activación de basófilos tanto con la tolerabilidad clínica como con la intolerancia a la ITV.

Palabras clave: Mastocitosis; inmunoterapia con veneno; test de activación de basófilos; omalizumab.

Introduction

Venom immunotherapy (VIT) is an established, highly effective treatment of immunoglobulin (Ig) E-mediated Hymenoptera venom allergy, even in patients with concomitant systemic mastocytosis (SM) [1]. It may, however, be associated with immediate adverse reactions resulting in treatment withdrawal, which is of major concern in patients with SM. In recent years, omalizumab, a recombinant humanized monoclonal antibody, used as add-on therapy, has been shown to facilitate induction of VIT in individuals—and patients with SM in particular—who fail to reach maintenance doses because of recurrent allergic reactions [2,3]. Omalizumab selectively binds serum immunoglobulin (Ig) E at the same site of the Fc domain as the alpha chain of the high-affinity IgE receptor

(FcεRI) on mast cells and basophils, thereby blocking the interaction between unbound IgE and its receptor [4]. In consequence, reactivity to allergens is thought to be reduced. There have been few reports of omalizumab therapy failure in combination with VIT [5]. In this report we describe an unexpected discontinuation of omalizumab following successful initiation of VIT in a patient with SM.

Case Description

A 52-year-old nonatopic man with grade IV anaphylaxis (Mueller classification) due to an unidentified Hymenoptera sting in 2007 was suspected to have SM (positive skin and colon biopsy; serum tryptase, 93 µg/L [ImmunoCAP Phadia,

Uppsala, Sweden]). The patient declined a bone marrow biopsy. Endpoint intradermal skin tests were positive to both bee venom (BV) and yellow jacket venom (YJV) at 0.1 $\mu\text{g}/\text{mL}$. Specific serum IgE to BV and YJV was 0.47 and 0.36 kU/L, respectively. The basophil activation test (BAT) was strongly positive for both venoms. After repeated severe adverse reactions despite H_1/H_2 -antihistamine prophylaxis during the ultrarush up-dosing to both venoms in June 2008, therapy was modified to conventional weekly VIT. However, maintenance doses could not be reached because of recurring systemic reactions such as hypotension, dyspnea, and angioedema. Finally, VIT was discontinued in December 2008.

Subcutaneous omalizumab 150 mg (total IgE, 5 kU/L; 68 kg) (off-label use) was started 8 months later and 1 week before the resumption of VIT (YJV followed by BV 1 week later). Ultrarush treatment was uneventful in both cases, and the usual cumulative dose of 111.1 μg was successfully reached. Monthly dose repetitions were well tolerated in the case of

both venoms. Omalizumab treatment was continued monthly, 1 week before VIT.

A few weeks after the ultrarush treatment with BV, the patient noted sleep disturbances and had progressive difficulty falling asleep at night. He later developed vertigo, exercise intolerance, diffuse myalgia, joint pain without effusions, and debilitating fatigue. These complaints had not been present during the previous VIT. In contrast, pruritus and diarrhea—symptoms thought to be associated with SM—improved. The addition of fexofenadine 180 mg 3 times daily did not improve his general condition. Clinical examination was unremarkable and laboratory test results (blood cell count, liver enzymes, renal function, C-reactive protein) were within normal ranges. Since it was suspected that the reactions might be adverse reactions to omalizumab, the drug was stopped after the seventh dose. VIT with both venoms, however, was continued. Within weeks, the patient's fatigue improved but exercise intolerance, diffuse myalgia, and joint pain persisted.

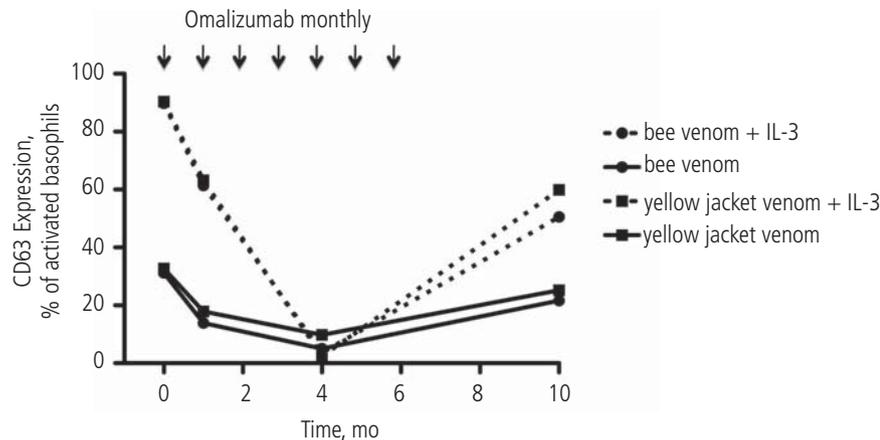


Figure 1. CD63 expression shown as percentage of activated basophils for bee venom and yellow jacket venom at a concentration of 55 ng/mL during and after omalizumab treatment. Dotted line, interleukin (IL) 3 stimulation; solid line, no IL-3 stimulation.

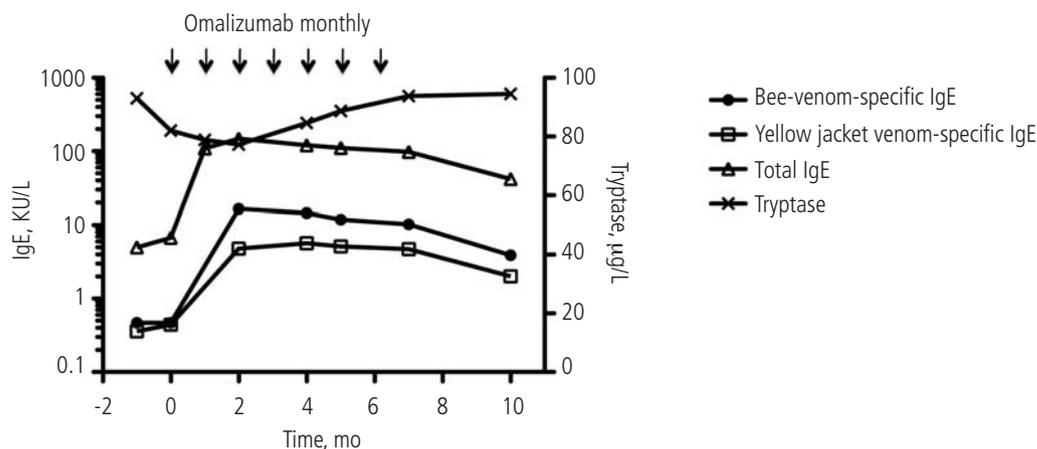


Figure 2. Immunoglobulin (Ig) E and tryptase levels during and after omalizumab treatment.

Three months after the last omalizumab injection and some minutes after VIT with both venoms, the patient felt intense heat over his trunk and face. One month later, he developed erythema on his face and neck 20 minutes after VIT. The therapy was stopped and 2 months later he recovered and was able to resume exercise.

One month after the first omalizumab injection and the completion of VIT up-dosing with both venoms, BAT revealed a marked decrease in reactivity to both venoms, even at high concentrations (Figure 1). At week 12, reactivity to the venoms was barely detectable but 2 months after discontinuation of omalizumab, it was even higher than before therapy initiation. The lowest serum tryptase level was measured at month 2 of omalizumab treatment (77 µg/L), but levels returned to pretherapy values after discontinuation of omalizumab (94.5 µg/L; Figure 2). The skin test results remained unchanged. As expected, as a consequence of the immune-complex formation, total IgE increased after the second dose of omalizumab (148 kU/L). Specific IgE peaked after 2 months in the case of BV (16.5 kU/L; Figure 2) and after 4 months in the case of YJV (5.69 kU/L, Figure 2). Total and specific IgE to both venoms decreased after omalizumab was stopped.

Discussion

Patients with SM are at risk for more severe Hymenoptera stinging anaphylaxis [1,6], but VIT has been shown to be effective in treating IgE-mediated Hymenoptera anaphylaxis in such patients. Despite a relatively high risk of adverse reactions during the build-up phase, VIT is recommended because it provides protection against anaphylaxis [7]. Our case report highlights 3 issues: (1) the return of Hymenoptera venom hypersensitivity to VIT after discontinuation of omalizumab; (2) a correlation between BAT and clinical tolerability as well as recurrence of hypersensitivity to VIT in relation to omalizumab use; and (3) unpredicted omalizumab-related adverse reactions during VIT.

The initially favorable response to VIT with both Hymenoptera venoms subsequent to omalizumab might be explained by a downregulation of FcεRI-expression on basophils and probably also on mast cells [8]. The reduction of basophil FcεRI-receptors, in fact, has been shown to occur within 7 days of omalizumab administration [8] and is reversible once omalizumab is discontinued [8]. Given the rapid kinetics of FcεRI-expression, we decided to administer the first omalizumab injection 1 week before VIT resumption. We might have recognized the adverse reactions sooner if omalizumab had been administered earlier, as has been described in reports of asthmatic patients [9]. However, due to differences in pathomechanisms and course of disease (eg, asthma and mastocytosis), a comparison of VIT with specific immunotherapy containing aeroallergens is difficult to conduct. Based on reports published to date, optimal timing and duration of concomitant omalizumab or intervals to VIT vary. Thus, no valid conclusions can be drawn for general recommendations for combined use. No long-term follow-up studies have attested to the efficacy of VIT after discontinuation of omalizumab,

even in individuals with SM [3]. This present case indicates that caution should be exerted when omalizumab is stopped.

BAT has been shown to have excellent diagnostic sensitivity and specificity in Hymenoptera venom allergy [10]. It has also been shown to be a useful complementary diagnostic tool in patients with SM and Hymenoptera venom allergy, and it may contribute to predicting or confirming this fatal reaction, especially before discontinuing VIT in patients with negative skin tests or specific IgE or in patients with low total IgE levels [11].

A novel aspect in this report is the close correlation between BAT and both clinical tolerability and VIT intolerance (Figure 1). Also noteworthy was the significant increase in BAT levels for both venoms in parallel to the patient's recurring hypersensitivity to VIT. Since flushing is a relatively common symptom in SM, BAT may be a promising tool in VIT to distinguish between signs of SM and adverse effects of VIT [12].

Reports of VIT failure in patients with SM treated with omalizumab are rare [5]. Whereas arthralgia and myalgia are common adverse events associated with omalizumab, no statistical differences have been detected in this respect between omalizumab-treated and placebo-treated patients [13]. The main reason for discontinuing omalizumab in our patient was his crippling fatigue and feebleness. Even though continuous mast cell activation with accordant symptoms due to SM could be hypothesized, treatment with high-dose antihistamines, H₂-blockers and leukotriene receptor blocking agents was ineffective. Since the patient recovered slowly and steadily after discontinuation of omalizumab, we suspect a real but rare adverse reaction attributable to omalizumab, although the mechanisms are not clear. Half a year after stopping omalizumab and VIT all the symptoms disappeared completely, and the patient's life has returned to normal.

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