CASE REPORT

Severe Anaphylaxis to Bee Venom Immunotherapy: Efficacy of Pretreatment and Concurrent Treatment With Omalizumab

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Abstract

Immunotherapy is an established mode of treatment for Hymenoptera venom anaphylaxis, although adverse reactions may occur.
We report the case of a 33-year-old woman, the wife of a beekeeper, who experienced a systemic allergic reaction following a bee sting. Initial specific immunotherapy had to be stopped due to anaphylaxis (multiple immediate cardiovascular reactions).
We looked for an alternative treatment option, and repeated immunotherapy accompanied by the anti-immunoglobulin (Ig) E monoclonal antibody omalizumab. Our new protocol was well tolerated.
After 1 year of therapy, the patient was stung by a bee and developed only a slight local reaction, which resolved spontaneously. This result confirmed the success of our specific immunotherapy. We compared our results with those of 6 similar cases in the literature.
Anti-IgE has provided a treatment option for patients with severe IgE-mediated allergic disease that is difficult to treat. This case suggests that omalizumab may be able to prevent anaphylaxis during immunotherapy.

Key words: Bee venom allergy. Omalizumab. Immunotherapy.

Resumen

La inmunoterapia es una forma establecida de tratamiento para la anafilaxia por veneno de himenópteros, aunque pueden ocurrir reacciones adversas.
Informamos de un caso de una mujer de 33 años de edad, la esposa de un apicultor, que presentó una reacción alérgica sistémica tras una picadura de abeja. La inmunoterapia específica inicial tuvo que ser suspendida por anafilaxia (reacciones cardiovasculares inmediatas múltiples).
Buscamos una opción terapéutica alternativa, y repetimos la inmunoterapia acompañada del anticuerpo monoclonal anti-inmunoglobulina (Ig) E omalizumab. Nuestro nuevo protocolo fue bien tolerado.
Tras 1 año de la terapia, la paciente fue picada por una abeja y desarrolló sólo una reacción local leve, que se resolvió espontáneamente. Este resultado confirmó el éxito de nuestra inmunoterapia específica. Comparamos nuestros resultados con 6 casos similares en la literatura.
La anti-IgE ha proporcionado una opción terapéutica para pacientes con enfermedades alérgicas graves mediadas por IgE que son difíciles de tratar. Este caso sugiere que omalizumab podría ser capaz de prevenir la anafilaxia durante la inmunoterapia.

Palabras clave: Alergia a veneno de abeja. Omalizumab. Inmunoterapia.

Introduction

Hymenoptera venom anaphylaxis affects about 3% of the general population and a higher percentage of beekeepers. Venom-specific immunotherapy (VIT) is an established mode of treatment for this condition and, in 85-95% of cases, it offers long-term protection from further generalized reactions. However, anaphylaxis may occur with VIT and can lead to withdrawal of treatment. Omalizumab, a humanized nonanaphylactogenic monoclonal, anti-immunoglobulin (Ig) E antibody against the Cε3 domain of IgE, could prevent these reactions if administered before immunotherapy [1].

Case Description

We report the case of a 33-year-old woman, the wife of a beekeeper, who experienced a near fatal anaphylactic reaction to a bee sting. An allergy workup confirmed sensitization to bee venom. The intradermal skin test was positive at 0.1 μg/mL and the specific bee IgE level was 35 kU_A/L. The tryptase level was normal (2.4 μg/L), thus excluding systemic mastocytosis. VIT was strongly indicated. The first inpatient rush VIT [2] was initiated with antihistamine pretreatment, but this had to be stopped after 20 μg of venom due to anaphylaxis. One month later, a new modified rush VIT [2] was administered, but had to be stopped at 5 μg of venom, again due to anaphylaxis.

The patient-specific bee venom IgE level had increased to 100 kU_A/L. Treatment with omalizumab, which has been approved by the French regulatory agency (Agence française de sécurité sanitaire des produits de santé [AFSSAPS]), was proposed. This was begun 6 weeks before a new rush VIT by subcutaneous injection of 150 mg of Xolair (weight, 52 kg; total IgE, 321 kU_A/L) once every 2 weeks (Table 1). After 4 months, she was able to tolerate a dose of 150 μg for the maintenance dose, but failed to tolerate our target dose of 200 μg. This patient has been receiving treatment for the past 28 months. At month 12, she was stung by a bee and only presented local edema that resolved spontaneously, thus demonstrating that VIT was effective. After 24 months with this regimen, we decided to reduce the dose of omalizumab to 75 mg, but this led to an anaphylactic reaction within 30 minutes of the VIT (Table 1). The total serum IgE level decreased to 248 kU_A/L and intradermal skin tests became negative for 0.1 μg/mL and positive for 1 μg/mL; the specific bee venom IgE level remained positive at over 100 kU_A/L at 24 months.

Discussion

Omalizumab was developed for the treatment of severe allergic asthma. It blocks binding of free IgE to its corresponding FcεRI receptor on basophils and mast cells, thus inhibiting their activation by allergens. It is associated with a marked lowering of free IgE levels and downregulation

Table 1. Protocol for Administration of Bee Venom Immunotherapy and Omalizumab

Beginning of Treatment With Omalizumab
Week 0: 1 subcutaneous injection of omalizumab 150 mg
Week 2: 1 subcutaneous injection of omalizumab 150 mg
Week 4: 1 subcutaneous injection of omalizumab 150 mg
Initiation of VIT Combined With Omalizumab
Week 5: rush VIT 1 + 5 + 10 μg bee venom (well tolerated)
Week 6: 1 subcutaneous injection of omalizumab 150 mg and, after 1 hour, 10 + 20 + 30 μg bee venom (well tolerated)
Week 7: VIT 30 + 50 μg bee venom (well tolerated)
Week 8: 1 subcutaneous injection of omalizumab 150 mg and, after 1 hour, VIT 50 + 50 μg bee venom (well tolerated)
Week 9: VIT 50 + 100 μg bee venom (well tolerated)
Week 10: 1 subcutaneous injection of omalizumab 150 mg and, after 1 hour, VIT 100 μg bee venom (well tolerated)
Week 11: VIT 200 μg bee venom (well tolerated)
Maintenance Phase: VIT Combined With Omalizumab Monthly
Month 4: 1 subcutaneous injection of omalizumab 150 mg and, after 15 minutes, VIT 200 μg bee venom (well tolerated)
Month 5: 1 subcutaneous injection of omalizumab 150 mg and, after 15 minutes, VIT 200 μg bee venom (reaction with palm pruritus, facial urticaria, rhinitis, nausea)
Month 5 + 15 days: 1 subcutaneous injection of omalizumab 150 mg and, after 15 minutes, VIT 100 μg bee venom (well tolerated)
Month 6: 1 subcutaneous injection of omalizumab 150 mg and, after 15 minutes, VIT 150 μg bee venom (well tolerated)
Month 7: 1 subcutaneous injection of omalizumab 150 mg and, after 15 minutes, VIT 150 μg bee venom (well tolerated)
Continuation of the Protocol

Abbreviations: VIT, venom immunotherapy.

Table 2. Characteristics of Hymenoptera Venom –Allergic–Patients Treated by Specific Immunotherapy and Omalizumab

Patient Characteristics[a]	Reaction	Risk Factors	Skin Tests and Specific IgE	VIT Trial and Results	Omalizumab Trial	Comments
M 66 Germany [3]	Severe anaphylaxis to honey bee sting	Mastocytosis (blood tryptase, 60 mg/L)	IgE to bee +	Initiation: Moderate reaction Maintenance: After 10 monthly injections of bee venom, the patient was stung by a yellow jacket and experienced severe anaphylaxis – Bee VIT was later, the dose was increased to 100 µg, and severe anaphylaxis followed within 5 minutes. – Four weeks later, the dose was increased to 100 µg, and severe anaphylaxis followed within 5 minutes. – Several weeks later, VIT was reintroduced at 40 µg. Severe epinephrine-resistant anaphylaxis followed. – VIT was administered again some weeks later at 40 µg and was followed by severe nausea, flushing, and hypotension	– 1 dose of omalizumab (150 mg) – 1 week later: ultra rush bee VIT (well tolerated) and 10 maintenance	1 injection of omalizumab enabled ultra rush bee VIT and maintenance dose at 100 µg Patient not on omalizumab after 5 months of follow-up
	Anaphylactic shock after wasp stings 3, 7, and 11 years ago					
M 15 Germany [4]	Systemic allergic reaction to honey bee sting	Son of a beekeeper Normal blood tryptase levels	IgE to bee: 13.3 IU/mL IgE to wasp +	Initiation: 10 µg bee VIT followed by immediate cardiovascular reaction. Next day: new rush bee VIT (hypotension at 10 µg)	– 1 dose of omalizumab (300 mg) – 2 weeks later, a new ultra rush bee VIT was administered (well tolerated) – Maintenance dose reached (100 µg), carried on for 1 year – Slight reaction after being stung	1 dose of omalizumab prevented anaphylaxis during rush bee VIT Patient not on omalizumab after 12 months of follow-up
F 37 Germany [5]	Grade III anaphylaxis to wasp sting	Normal blood tryptase levels	IgE to wasp: 12.6 IU/mL	Initiation: ND Maintenance: urticaria, paresthesia, hypotension after 50 µg wasp VIT	– 1 dose of omalizumab (300 mg) was administered 32 months later and 4 weeks before a new ultra rush wasp VIT – Omalizumab 300 mg every month for 3 months. Wasp VIT was well tolerated at the maintenance dose of 100 µg for a total follow-up of 7 months	4 doses of omalizumab enabled rush wasp VIT and maintenance dose at 100 µg Patient not on omalizumab after 7 months of follow-up

Table 2. Continued

Patient Characteristics[a]	Reaction	Risk Factors	Skin Tests and Specific IgE	VIT Trial and Results	Omalizumab Trial	Comments
M 45 Greece [6]	Near fatal anaphylaxis to honey bee	Indolent systemic mastocytosis	IgE to bee: 42.5 IU/mL	Initiation: ND Maintenance: 36 bee VIT injections at 28-day intervals: 97% with systemic reactions. Severe anaphylactic reaction at 18th month	– 1 dose of omalizumab (300 mg) – 1 week later: ultra rush bee VIT: 150 µg cumulative dose well tolerated – Omalizumab repeated each month from 19th to 26th months, 7 days to 1 hour before bee VIT injection	Omalizumab injections every month enabled ultra rush bee VIT and maintenance dose at 150 µg Patient not on omalizumab after 8 months of follow-up
F 47 Greece [6]	Near fatal reaction to vespid stings, twice in 2 years	ND	IgE to bee: class 0 IgE to yellow jacket: class 3 IgE to white faced hornet: class 2 IgE to yellow and European hornet: class 1	ND	– 1 dose of omalizumab – 2 weeks later: new ultra rush wasp VIT well tolerated (only large local reaction)	1 dose of omalizumab enabled wasp VIT, but only 2 weeks of follow-up
F 32 France [our case]	Near fatal reaction to honey bee sting	Beekeepers' wife Normal blood	IgE to bee: 35 IU/mL	Initiation: First rush bee VIT stopped at 20 µg (anaphylactic reaction). Second rush bee VIT stopped at 5 µg (severe anaphylactic reaction)	– 3 doses of omalizumab: 150 mg every 2 weeks – 6 weeks later: rush bee VIT completed – Omalizumab 150 mg repeated every month from 1st to 26th months (30 min before bee VIT); maintenance dose at 150 µg well tolerated. – At 27th and 28th month, decrease in dose of omalizumab to 75 mg (anaphylactic reaction)	Omalizumab injections enabled ultra rush bee VIT and maintenance dose at 150 µg. Failure to reduce omalizumab dose and to stop it. Patient still on omalizumab 150 mg before each 150 µg bee VIT after 28 month of follow-up
M 32 Germany [7]	Near fatal reaction to honey bee sting	ND	IgE to bee: ND	Initiation: No reaction Maintenance: No reaction at the beginning. A sting challenge performed to assess efficacy led to a systemic anaphylactic reaction. Afterwards, the patient repeatedly developed systemic anaphylactic reaction to further bee VIT injections.	– 2 doses of omalizumab (150 mg) at 2-week intervals – 1 week later: ultra rush bee VIT completed. – Omalizumab 150 mg repeated 3 times every 4-6 weeks before bee VIT: injections and challenge test were well tolerated.	5 doses of omalizumab enabled rush bee VIT and maintenance dose. Patient not on omalizumab after 8 months of follow-up.

Abbreviations: F, female; Ig, immunoglobulin; M, male; ND, no data; ST, skin tests; VIT, venom immunotherapy.
[a] Sex, age (years), country of origin, reference.

of IgE receptors on circulating basophils [1]. In our search of the literature, we found 6 case reports that examine the protective effect of omalizumab against adverse VIT reactions [3-7] (Table 2). The treatment protocols (rush VIT and omalizumab) were quite different: in 2 cases [3,4], a single omalizumab injection was sufficient to cover rush VIT and the maintenance dose. In a further 2 case reports, 1 [5] or 2 [7] doses of omalizumab were administered before rush VIT (as pretreatment) and 3 doses were administered during rush and maintenance VIT. In 1 case, omalizumab was repeated each month during the maintenance phase, as in our case report, but follow-up lasted only 7 months, with no information regarding the end of the treatment. Our case provides the longest follow-up period to date, and once again emphasizes both the efficacy of anti-IgE for this indication and its main limitation: omalizumab could not be stopped. The question remains as to how much longer omalizumab needs to be maintained and what the consequences might be, especially for this patient, for whom VIT is indicated for life.

The combination of omalizumab and VIT may be a valid option for patients who do not tolerate VIT alone and are at high risk of anaphylaxis. Nevertheless, an analysis of the literature reveals a wide range of responses between individuals in terms of dosage and duration of therapy.

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