Omalizumab for prevention of anaphylactic episodes in a patient with severe mosquito allergy

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Abstract

Mosquito allergy can rarely give raise to severe clinical manifestations.Here we describe the case of a patient suffering from relapsing anaphylaxis after mosquito bites, who completely responded to off label therapy with anti-IgE monoclonal antibody.This is the first demonstration of the efficacy of omalizumab in such unusual life-threatening allergy.

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Key Clinical Message

Anaphylaxis after mosquito bite is rare, but life-threatening. To date, no approved preventive therapy is available, but omalizumab could be a promising therapeutic option for reduction of risk and improvement of quality of life in these patients.

Abstract

Mosquito allergy can rarely give raise to severe clinical manifestations. Here we describe the case of a patient suffering from relapsing anaphylaxis after mosquito bites, who completely responded to off label therapy with anti-IgE monoclonal antibody. This is the first demonstration of the efficacy of omalizumab in such unusual life-threatening allergy.

Introduction and Background

Several immune mediated disorders are triggered by mosquito bites (Table 1).[1,2] All of these are quite uncommon, including mosquito allergy. In this latter case, sensitized individuals usually develop immediate or delayed large local reactions, but in exceptional circumstances anaphylactic episodes have been described.[3]

Mosquitoes belong to the order Diptera, family Culicidae, which consists of three subfamilies, namely Toxorhynchitinae, Anophelinae and Culicinae. In Italy, three main mosquito species have been detected: common mosquito (Culex pipiens), tiger mosquito (Aedes albopictus) and the newly emerged korean mosquito (Aedes koreicus); Anopheles mosquitoes is also present but it rarely bites humans.[4]

To date, studies conducted primarily on Aedes aegypti (the yellow fever mosquito), which is present in tropical, subtropical and temperate regions throughout the world, identified a total of 22 salivary allergens and only four body allergens, including a tropomyosin (Aed a 7); among them, Aed a 1, Aed a 2 and Aed a 4 are potentially genuine allergens[5]

Moreover, the mosquito hyaluronidase has been identified as cross reactive with that of wasp's venom, giving rise to the so-called wasp/mosquito syndrome,[6] and a recent study correlates mosquito (Aedes communis) and bee allergy.[7]

In most cases, mosquito allergy is due to the presence of saliva-specific IgE, and mosquitoes' saliva has been confirmed as the main allergen source.[8] Even more uncommonly, hypersensitivity reactions can take place in sensitized individuals after inhalation of suspended allergens derived from mosquitoes' bodies and emanations.[3]

The prolonged exposure to mosquitoes' bites seems to be protective against the risk of developing hypersensitivity, due to a natural desensitization: in these cases, mosquitoes' specific-IgE levels could increase but together with specific IgG1 and IgG4.[9]Hence, mosquito allergy is more frequent in children than in adults.

The few existing studies regarding mosquito venom immunotherapy (VIT) are limited to little groups and have used whole-body extracts.[10–13]

Their results were promising, but it has to be noted that their primary endpoint was reduction of local reactions and eventually even respiratory symptoms, that could depend, as previously mentioned, on mosquito body allergens.[10,11]. Two subjects who developed anaphylaxis after mosquito bite were given mosquito VIT using mosquito body extracts: complete resolution was achieved in just one of them.[14]

Of interest, vaccines against mosquito salivary proteins have been tested to protect against mosquito-borne disease rather than allergies. The interaction of the host with saliva of vectors (in this case, mosquitoes) seems to favor the transmission of pathogens; the efficacy of such vaccines could deeply change the approach of preventing severe infectious diseases.[15]

On the other hand, interest toward mosquito allergy gradually faded over time, both from a scientific and pharmaceutical point of view, so that today VIT products for mosquito allergy are not commercially available anymore.

Even if less than thirty cases of anaphylaxis to mosquito bites have been reported to date worldwide,[8,14,16–19] management of risk and quality of life (QoL) is exceedingly challenging in these patients.

Case report

Here we report the case of a 51-year-old man, living in Tuscany, Italy (an endemic region for the presence of mosquitoes) who had already begun VIT for Polistes dominula and Vespa crabro after experiencing systemic reactions (grade III according to Muller et al).[20]

More recently, he experienced two anaphylactic episodes characterized by urticaria, presyncope and ascertained hypotension, during dinner outdoor in summertime.

After a detailed medical history, the patient referred that both reactions took place just after receiving several mosquito bites, which previously provoked only large local reactions. Therefore, mosquito allergy

was suspected.

Since skin tests with mosquito extract are no longer available in Italy, specific IgE against Aedes communis were evaluated and resulted increased (0.53 kUA/l, n.v. $<$ 0.35 kUA/l, total IgE 300 kU/l, n.v. $<$ 100 kU/l; ImmunoCAP, ThermoFisher Scientific, Uppsala, Sweden).

Of note, the allergen source of the mosquito ImmunoCAP kit is the insect whole body, instead of its saliva, and this could explain the weak positivity in our patient.

Therefore, the two anaphylactic episodes were interpreted as Mueller IV reactions to mosquito bites.

The allergologic workup included IgE against potential cross-reactive allergens such as tropomyosin and cross-reactive carbohydrate derminants (CCD), which gave negative results.

In the suspicion of a mast cell disorder, serum basal tryptase was evaluated and resulted within normal range; a hematological consultation was performed but bone marrow biopsy was not indicated due to the low probability of a clonal mast cell disorder according to the REMA score (+1).[21]

The patient was advised to always carry two epinephrine autoinjectors; however, the potential risk of sudden severe allergic reactions to mosquito bites, along with the difficulty in avoiding them, had a major impact on this patients' QoL.

Therefore, the need for a prophylactic therapy was considered, but its choice was challenging.

The effectiveness of antihistamines has been demonstrated in reducing itching and wheal and large local reactions but not in preventing systemic ones.[22,23] An immunotherapy with mosquito extract was not feasible, since its evidence is weak[10,11] and, anyway, it is no longer available.

In the absence of other therapeutic options, the patient started off-label therapy with the anti-IgE monoclonal antibody omalizumab, 300 mg subcutaneously every 4 weeks, from August to October 2020.

In this period, he received several mosquito bites without experiencing neither anaphylactic episodes nor mild hypersensitivity reactions.

Given the good result, the therapy was started again in March this year (March to October is the period considered more at risk for mosquito bites in Tuscany), without relapses to date. In parallel, the patient was able to resume outdoor activities and reported a significant reduction of psychological burden of disease.

Discussion

VIT has been defined as a disease modifying treatment, since it can target the pathogenic pathways of allergic response altering its natural history and inducing tolerance to allergens.[24]

In the case of hymenoptera venom allergy, in which risk of anaphylaxis is elevated, VIT is responsible for a strong reduction of risk and a significant improvement in QoL.[24]

The lack of an immunotherapy for mosquito allergy, or other therapeutic options capable of reducing the risk of analphylaxis for at-risk patients living in mosquito endemic area, could result in a failure of management of risk and QoL, as seen in other allergic conditions.[25]

Looking for other drugs targeting the underlying pathophysiology, anti-IgE monoclonal antibody was judged the most suitable choice.

Omalizumab is a recombinant humanized monoclonal anti-IgE antibody approved in Europe for the treatment of severe allergic asthma and chronic spontaneous urticaria refractory to standard therapies.[26,27]

Its efficacy is explained with the established omalizumab mechanism of action of binding free IgE and subsequent downregulation of Fc RI on mastcells, basophils, eosinophils and antigen presenting-cells.[27,28] Moreover, some Authors postulated an apoptotic effect of omalizumab on mastcells.[29–31]

Even if omalizumab use is off-label for this indication, it resulted capable of reducing incidence of anaphylaxis triggered by different allergens in clinical trials and real-life settings,[32]and evidence is increasing in this regard.

In the context of food allergy, previous studies demonstrated that peanut allergic adults receiving omalizumab showed a 56-fold increase in the threshold challenge dose, in most cases this change emerged early after the beginning of the treatment.[33]

When using omalizumab before and during peanut desensitization protocols, tolerance was achieved faster and to higher amounts of food compared to those receiving placebo.[34]

Its capacity in increasing the tolerability towards offending allergens has been demonstrated even in the context of Hymenoptera venom allergy. Those experiencing severe reactions during the build-up phase of Hymenoptera VIT did not relapse if premedicated with omalizumab,[35–37] and this effect was confirmed also in patients with mast cell disorders.[31,38]

Moreover, omalizumab showed a favourable effect in reducing the risk of idiopathic anaphylaxis, even in the context of IgE-independent reaction and in patients with mast-cell disorders.[32,39–44]

These subjects sometimes do not exhibit specific IgE against Hymenoptera venom nor positive skin tests despite life threatening anaphylactic reactions. Since VIT is not indicated when venom hypersensitivity is not demonstrable, Omalizumab was successfully used to mitigate relapsing episodes in two cases.[39,40]

In these studies, a quick achievement of protection was observed[42] and the dosage of 300 mg/monthly was considered effective[41], while 150 mg every second week was associated with lower degree of protection.[42]

To date, there is no established protocol for the use of omalizumab in the prevention of anaphylaxis, especially regarding dosage. However, based on the aforementioned publications, in our patient we chose a dosage of 300 mg every 4 weeks, which proved effective in guaranteeing a protective effect against anaphylaxis episodes after mosquito bite.

Although a therapy with omalizumab in preventing severe allergic reactions after mosquito bite in a mastocytosis patient was already proposed by Reiter N et al.,[16] to our knowledge this is the first reported case in which omalizumab was used and proved to be effective in relapsing anaphylaxis after mosquito bite.

Author contributions

ME was in charge of clinical management, all the Authors contributed to manuscript preparation and critical revision.

Table 1. Uncommon clinical conditions related to mosquitoes' bite.

Clinical Condition	Clinical Picture
Skeeter syndrome	Large local reaction (more than 3 cm) associated with fever and som
Wells syndrome	Eosinophilic cellulitis
Chronic active Ebstein-Barr virus (CAEBV) disease	In patients with Epstein-Barr virus-associated T/natural-killer cell-as
IgE-mediated allergy	From mild wheal and flare reactions or large local reactions to systen

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