Omalizumab as a Desensitizing Agent and Treatment in Mastocytosis: A Review of the Literature and Case Report

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Patients with all forms of mastocytosis can experience urticaria, abdominal cramps, nausea, diarrhea, or hypotension due to release of mediators by mast cells. Patients with mastocytosis and Hymenoptera venom allergy can develop severe adverse reactions to Hymenoptera stings. In addition, patients with mastocytosis and on venom immunotherapy are at high risk for incomplete protection and fatal reactions. Recent literature has reported the use of omalizumab as an adjunctive treatment in patients with mastocytosis, used for both symptom improvement and to dampen adverse effects caused by venom immunotherapy. This article reviews the literature regarding omalizumab use in the treatment of mastocytosis and for protection against the adverse effects during venom immunotherapy. In addition, we report the case of a patient at high risk and with cutaneous mastocytosis, whose symptoms improved with concomitant administration of omalizumab and venom immunotherapy. © **2014 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2014;2:266-70)**

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We report a now 77-year-old man with a history of telangiectasia macularis eruptiva perstans (TMEP) for 2 decades, with significant skin lesions (Figure 1), his diagnosis was confirmed by skin biopsy (Figure 2). TMEP is an uncommon form of cutaneous mastocytosis. It usually is insidious in onset and may present with systemic involvement and hematologic manifestations. In addition to his diagnosis of TMEP, this patient also had critical aortic stenosis, coronary artery disease, and a recent severe reaction to a honeybee sting, with rapid vascular collapse and minimal hives. Shortly after his episode of anaphylaxis in early 2010, he was referred to our allergy clinic. He described syncope and low blood pressure immediately after the honeybee sting. He also reported being stung by a wasp in the recent past, which was accompanied by mild urticaria. Results of a physical examination were remarkable for a systolic ejection murmur at the left second intercostal space and numerous tan-red macules with telangiectasias on his skin. Laboratory testing results revealed a total IgE level of 806 IU/mL (reference range, 0-180 IU/mL), serum tryptase level at 15.5 μg/L (reference interval, 0.4-10.9 ug/L), and specific IgE level to honeybee venom markedly elevated at 94.20 kU/L (reference range $\leq$0.34 kU/L). Specific IgE to other stinging insects were highly positive as well. Specific IgE to aeroallergens were tested due to symptoms of allergic rhinitis, and most were elevated. Medications included antihistamines as well as a β-blocker; an angiotensin converting enzyme inhibitor; and aspirin for his history of coronary artery disease, aortic stenosis, and hypertension. His history of recent near-fatal reaction to a honeybee sting, underlying cutaneous mastocytosis, and aortic stenosis increased his mortality risk with another occurrence of anaphylaxis if the patient were stung again. Moreover, his history of aortic stenosis and use of β-blockers made the use of epinephrine to treat anaphylaxis more challenging. He enjoyed spending time outdoors, thus the likelihood of getting stung again was high. We decided to administer honeybee venom immunotherapy (VIT). However, given his age and other comorbidities, including cutaneous mastocytosis, cardiovascular disease, and a history of severe reaction to honeybee, we chose to administer omalizumab concurrently with VIT.

Before initiating therapy, bone marrow biopsy was performed to rule out systemic mastocytosis. A PCR-based test (sensitivity, <0.01) was negative for D816V mutation in the KIT gene, tryptase level was less than 20 ng/mL in blood, CD25, and/or CD2 were not coexpressed on $CD117^{+}$ cells by flow cytometry, and no morphologic evidence of mastocytosis was evident in an (albeit poor quality) bone marrow biopsy, which ruled out systemic mastocytosis. In April 2011, 375 mg omalizumab injections were started and administered every 2 weeks. He underwent aortic valve replacement in May 2011. Honeybee venom rush desensitization was initiated in September 2011 in an acute care setting, and he tolerated the procedure well. Before and during desensitization, his angiotensin converting enzyme inhibitor was stopped and his β-blocker dose was reduced by half, in concordance with his cardiologist's recommendations. After desensitization, he continued to receive twice monthly omalizumab injections and his maintenance honeybee VIT in the clinic without difficulty. Laboratory analysis in June 2012 revealed a tryptase level of 10.5 μg/L and specific IgE level to honeybee venom at 71.5 kU/L, both values decreased since initiation of combination immunotherapy and omalizumab. Wasp rush desensitization also was initiated in February 2013. He has not had another wasp or honeybee sting. He now receives

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Abbreviations used
TMEP- Telangiectasia macularis eruptiva perstans
VIT- Venom immunotherapy

375 mg omalizumab monthly. He continues on a β-blocker and an angiotensin converting enzyme inhibitor for his significant cardiovascular disease. Laboratory analysis in September 2013 revealed a tryptase level of 10.1 μg/L and specific IgE level to honeybee venom at 48.8 kU/L, again, both levels decreased as treatment with omalizumab and Hymenoptera immunotherapy continued. Interestingly enough, his skin lesions had dramatically improved.

Mastocytosis and venom hypersensitivity

Mastocytosis or mast cell disease is a diverse group of disorders characterized by clonal proliferation and accumulation of mast cells in different tissues, most commonly in the skin and also the skeletal, hematopoietic, gastrointestinal, cardiopulmonary, and central nervous systems. It can appear in several forms, including systemic mastocytosis and cutaneous mastocytosis. Patients with all forms of mastocytosis often have urticaria, abdominal cramps, nausea, diarrhea, or hypotension due to release of mediators by mast cells. Mast cell mediator release typically occurs through a non−IgE-mediated mechanism, at times triggered by physical stimuli, aspirin, stress, and alcohol consumption.[1] Patients with mastocytosis are subject to anaphylactic events due to Hymenoptera venom. Patients with a mast cell disorder also are subject to more severe adverse reactions to Hymenoptera venom.[2] A serum tryptase level higher than 11.4 μg/L is an indication that a mast cell disorder may underlie an anaphylactic event due to a Hymenoptera sting.[3] In addition, patients with mastocytosis and who are on VIT are at high risk for incomplete protection and fatal reactions.[3] Recent literature has reported the use of omalizumab as an adjunctive treatment in patients with mastocytosis, used for both symptom improvement and to dampen adverse effects caused by VIT.[1,4-14]

Omalizumab used as a treatment for mastocytosis

Omalizumab is a humanized murine mAb that conjugates with free serum IgE, which reduces binding to the high-affinity FCεRI on mast cells and basophils, thereby stabilizing and reducing the potential reactivity of these cells. There are several case reports that suggest that omalizumab may decrease symptoms of mastocytosis, including hypotensive events.[1,4-9] Prior studies and case reports have also demonstrated the protective effect of omalizumab in patients with mastocytosis, both in systemic and cutaneous forms, who are on immunotherapy.[10-14]

In 2007, the first report of omalizumab improving symptoms in mastocytosis was published.[4] Two patients with biopsy-confirmed systemic mastocytosis and severe unprovoked episodes of anaphylaxis were reported to improve after initiation of omalizumab therapy.[4] In addition, both patients tolerated the drug well, with only local swelling at the site of injection; however, serum tryptase levels did not decrease in either patient in this report.[4] In 2010, a case was reported of a man with indolent systemic mastocytosis and severe anaphylactic episodes, both unprovoked and related to bee stings. Interestingly, this patient had undetectable specific IgE *in vivo* and *in vitro* to all Hymenoptera venoms. He was treated with monthly omalizumab injections with a decrease in tryptase levels and absence of recurrence of anaphylactic episodes. Since initiation of omalizumab, he also tolerated 1 bee sting, 2 unknown Hymenoptera stings, 100 μg of bee venom subcutaneously, and controlled bee sting challenge without any adverse reactions.[5] Yet another article, published in 2010, reported the case of a woman with indolent systemic mastocytosis, elevated serum tryptase levels, and severe unprovoked anaphylactic episodes who demonstrated significant improvement with omalizumab therapy. Her tryptase level had decreased, and she had not had an episode of anaphylaxis since initiating therapy.[6]

In 2011, 4 German patients with systemic, therapy-resistant mast cell activation syndrome received omalizumab as an adjunctive treatment. Two of the patients achieved an impressive persistent clinical response to omalizumab as evidenced by a decrease in symptom intensity, a decreased need for concomitant medication use, and a decrease in the serum tryptase level in one of the patients. In the third patient, symptoms gradually improved; however, the patient could not reduce the number or dosage of the other medications he received for his mast cell disorder. The drug was well tolerated in this patient. In the fourth patient, omalizumab was discontinued due to severe headaches, nausea, and dizziness immediately after several injections.[7] However, it must be noted that these patients, although reported to have clonal mast cell activation syndrome, were not diagnosed according to consensus algorithms and did not carry the c-kit D816V mutation.

In 2012, an 11-year old pediatric patient with mast cell activation syndrome was reported to improve with omalizumab. Before starting omalizumab injections, he experienced episodes of headache, flushing, diarrhea, abdominal pain, urticaria, and fatigue in addition to episodic anaphylactoid reactions refractory to maximal antihistamine therapy. He also had an elevated serum tryptase level. The patient was prescribed omalizumab as a steroid-sparing agent, and experienced immediate improvement in his symptoms. This case does not report changes in serum tryptase level since initiation of therapy.[8]

In April of 2013, the case of a 25-year-old man with cutaneous mastocytosis, elevated serum tryptase levels, and skin biopsy that revealed diffuse mast cell infiltration was reported to improve after initiation of omalizumab therapy. His significant skin lesions, episodes of anaphylaxis, mast cell infiltration on skin biopsy, and serum tryptase level all improved. In addition, he had no adverse effects from therapy.[1] Most recently, in November of 2013, a pediatric patient with cutaneous mastocytosis was reported to improve after receiving therapy with omalizumab. Although diagnosed at birth, by the age of 12 years, the patient was experiencing almost daily unprovoked generalized urticaria and frequent anaphylactic episodes. She was treated with high doses of antihistamines and oral corticosteroids; however, her urticaria remained refractory to this therapy. Interestingly, in this case report, the patient responded to only 3 injections of omalizumab—once a month for 3 months, with a complete disappearance of symptoms and no need for any other medications. The absence of symptoms persisted for 12 months of follow-up. This was the first case to report such a short course of this therapy.[9]

Omalizumab used for patients with mastocytosis and on VIT

In 2007, the first case report that suggested the protective effect of omalizumab against VIT was published.[11] A 15-year-old