

Title: The Efficacy of Omalizumab in Cutaneous Mastocytosis: A Case Series

Running head: Omalizumab for Cutaneous Mastocytosis

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Abstract:

Background: Mastocytosis describes a heterogeneous group of disorders arising from a clonal proliferation of mast cells. Given the lack of curative treatments for the cutaneous form, there is a significant need for superior therapies. Omalizumab is a recombinant DNA-derived humanized IgG monoclonal antibody that selectively binds to human immunoglobulin E (IgE). It represents a potential treatment for the treatment of cutaneous mastocytosis, which currently has no standard treatment.

Methods: Two patients were treated with subcutaneous omalizumab 300 mg every four weeks.

Discussion: Patient one experienced 50% reduction in cutaneous infiltration and moderate improvement in pruritus. Patient two underwent 90% complete clearance of cutaneous lesions and reported full resolution of pruritus. The median duration of treatment was 24 weeks and time to response was eight weeks. No significant changes in tryptase levels were observed. Both patients experienced injection site reactions.

Conclusion: We provide evidence from two cases supporting the efficacy of IgE-mediated therapy in the treatment of cutaneous mastocytosis. Even at a higher-than-standard dose (300mg versus 150mg), the drug was well-tolerated. As we await the results of pivotal clinical trials, omalizumab appears to be a promising treatment option in patients with cutaneous mastocytosis unresponsive to traditional therapies.

Introduction:

Cutaneous mastocytosis (CM) is a variant of mastocytosis, a heterogeneous disease group arising from abnormal proliferation and accumulation of mast cells in one or more organs. The majority of patients present with a point mutation in the c-KIT gene. (Valent, Akin & Metcalfe, 2017). The most common cutaneous presentation in adults is maculopapular cutaneous mastocytosis (historically called urticaria pigmentosa), which is caused by mast cell infiltration. The skin lesions elicit Darier's sign, or whealing and flushing on mechanical irritation). Symptoms include episodes of flushing, hives, urticaria, and pruritus. The number and distribution of the cutaneous lesions show individual variations but are typically chronic and recalcitrant to treatment

Treatment for mastocytosis is supportive and directed toward symptom control. Steroids and/or antihistamines are utilized. Currently, there is no definitive therapy for cutaneous mastocytosis. Research by Kawakami and Blank (2016) has reported the efficacy of omalizumabo in the management of mastocytosis.

Omalizumab is a recombinant humanized monoclonal antibody that conjugates free serum IgE and reduces binding to the high-affinity IgE receptor (FcεRI) on mast cells and basophils. The reduction in free IgE leads to a downregulation in the expression of FcεRI on mast cells and basophils, thereby stabilizing and reducing their reactivity. In addition, omalizumab may also accelerate the dissociation of the preformed IgE-FcεRI complex on the surfaces of mast cells and basophils, leading to a further impairment of the IgE-inflammatory signaling cascade. Omalizumab is currently approved for the treatment of IgE-mediated chronic diseases such as allergic asthma and chronic urticaria. Here, we report the efficacy of omalizumab in the treatment of two cases of cutaneous

mastocytosis. We provide further evidence for the role of anti-IgE therapy for cutaneous mastocytosis.

Case Presentation:

Case 1: A 51-year-old female with spinal stenosis and joint disease presented with a one-year history of hyperpigmented macules and papules beginning on the left arm and gradually involving the face, trunk, abdomen, and bilateral upper and lower extremities (Figure 1a). The patient noted a several-month history of occasional self-limited episodes of nausea and diarrhea. She was hospitalized three years previously for an anaphylactic episode after *Hymenoptera* envenomation. She has smoked one pack of cigarettes daily for 30 years. SM was verified by one major criterion and one minor WHO criterion: the presence of multifocal, collections of mast cells in bone marrow confirmed by tryptase immunohistochemical staining, and aspirate smear demonstrate accumulation of spindle-shaped mast cells(minor criterion). Physical examination revealed extensive maculopapular cutaneous mastocytosis. Laboratory workup was remarkable for slightly elevated tryptase of 13 mg/ml (normal: <11 mg/mL). A chest radiograph showed no evidence of cardiopulmonary disease. Cutaneous lesions failed to respond to both topical and oral corticosteroid therapy, and montelukast. Treatment with omalizumab 300 mg subcutaneously every four weeks was initiated. After two months, the patient reported moderate (25%) reduction in the hyperpigmentation of macules and papules, and no appreciable improvement in symptoms. After seven total injections, over seven months, the patient experienced a 50% reduction in skin involvement, in response to omalizumab (Figure 1b) and mild improvement of symptoms.

Case 2: A 36-year-old female with no significant past medical history presented with a seven-year history of generalized cutaneous hyperpigmented macules. SM was verified by one major criterion and two minor WHO criteria: the presence of multifocal, collections of mast cells in bone marrow confirmed by tryptase immunohistochemical staining (major criterion) and aspirate smear demonstrate accumulation of spindle-shaped mast cells and elevated serum tryptase of 31 ng/mL (minor criteria). The lesions started as erythematous-brown macules on the chest and arms that gradually spread to the neck, back, and thighs (Figure 2a). While some lesions remained chronically stable, most lesions appeared intermittently during exacerbations accompanied with itching, fatigue, nausea, headache, dizziness, and palpitations. These acute episodes developed on a daily basis and were not associated with any identifiable triggers. She had been previously treated with cromolyn sodium and PUVA without improvement. Omalizumab therapy was initiated at 300 mg every four weeks. The patient reported 100% resolution of her symptoms after two months and sustained 90% improvement from baseline of her skin lesions after five months (Figure 2b).

Discussion:

There are reported multiple cases in the literature of successful treatment of systemic mastocytosis with omalizumab. Pitt, Cisneros, Kalicinsky, and Becker (2010) report a case of idiopathic anaphylaxis in an adolescent with an excellent response. As well, Douglass et al., (2010) in a nonatopic patient; all cases reported fewer anaphylactic episodes. There are two reported cases of cutaneous mastocytosis in which treatment with

omalizumab was successful, as defined by reduction in skin symptoms such as pruritus, wheals, flushing, and hives(Paraskevopoulos et al., 2013; Kibsgaard, Skjold, Deleuran & Vestergaard, 2014;) Phase II and III clinical trials evaluating the safety and efficacy of omalizumab for mastocytosis were completed in January 2016; however, results have not yet been published.(National Institute of Health, 2016)

Although the mechanism whereby omalizumab decreases symptoms of both cutaneous and/or systemic mastocytosis is not established, it has been described that the reduction in mast cell activity caused by omalizumab alleviates symptoms. Molderings et al., (2011) support that effective treatment of cutaneous mastocytosis does not appear to be a result of reduction of mast cell infiltration. As well, serum tryptase levels in both of our patients with mastocytosis did not significantly change(>5-10mg) in response to omalizumab treatment. However, a significant decrease in serum free IgE and downregulation of FcεRI on the surface of basophils has been observed shortly after initiation of omalizumab therapy (MacGlashan.,et al 1999). The mechanisms underlying clinical and symptomatic improvement with omalizumab, in patients with cutaneous mastocytosis, are still not fully understood.

New treatment options are available for cutaneous mastocytosis, drugs include, mast cell cytoreductive therapy (2-CdA or IFNalpha) and KIT- Inhibitors (Masitinib). (Vaes, Benghiat & Hermine, 2017). Additionally, NB-UVB and PUVA are useful as a second line therapy.(Brazzelli, et al, 2016)

Although, lower doses of omalizumab has been shown reduced cutaneous symptoms. We report two cases of cutaneous mastocytosis in which treatment with a higher dose of omalizumab was well tolerated and observed to produce varying degrees of efficacy, thereby supporting the notion of IgE mediated therapy in the treatment of cutaneous mastocytosis. Larger scale studies and longer observation periods may help determine the role of omalizumab in the treatment of mast cell disorders and further elucidate its mechanism of action in clinical improvement and providing symptomatic relief.

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Figure 1. Comparison of case 1 with CM (a) before and (b) after seven doses of subcutaneous Omalizumab 300mg one time every four weeks for seven months.

Figure 2. Comparison of case 2 with CM (a) before and (b) after five doses of subcutaneous Omalizumab 300mg one time every four weeks for five months.



