

Omalizumab Treatment of Systemic Mast Cell Activation Disease: Experiences from Four Cases

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Abstract

We report on the outcome of 4 patients with therapy-resistant systemic mast cell activation disease (MCAD) treated with the anti-IgE monoclonal antibody omalizumab in compassionate use. Two patients achieved an impressive persistent clinical response to treatment with omalizumab. In the third patient symptoms gradually improved. In the fourth patient omalizumab treatment had to be discontinued due to intolerable mast cell mediator-induced symptoms. In conclusion, omalizumab can lessen the intensity of the symptoms of systemic MCAD. Hence, omalizumab should be considered as a therapeutic option in cases of systemic MCAD that are resistant to evidence-based therapy.

Key words: systemic mastocytosis, omalizumab, tryptase

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Introduction

Systemic mast cell activation disease comprises disorders characterized by an accumulation of mast cells in organs and tissues and an enhanced release of mast cell mediators. Such patients have a history of chronic and acute mediator-related symptoms such as diarrhoea, nausea, pruritus, flushing, tachycardia, palpitations, light-headedness, dizziness, shortness of breath, and headache. According to a recent diagnostic algorithm consensus (1) variant forms of systemic mast cell activation disease can be differentiated. On the one hand, there are disorders termed *systemic mastocytosis* which are characterized by certain pathological immunohistochemical laboratory findings [the WHO-criteria; (2)]. On the other hand, there are disorders termed *systemic monoclonal mast cell activation syndrome* that present the complex clinical picture of mast cell mediator-induced symptoms in combination with the exclusion of relevant differential diagnoses but lack pathognomonic immunohistochemical findings and laboratory biomarkers. Irrespective of the variant form of the systemic mast cell activation disease evidence-based therapy consists of trigger avoidance and/or a medica-

tion with antihistamine and mast cell membrane-stabilising compounds that should be supplemented, if required, by a medication adapted to individual mast cell mediator-induced symptoms. However, symptoms are frequently therapy resistant. Because anti-IgE treatment with the humanized murine mAb omalizumab has been successful in disorders in which mast cells are pathogenetically involved such as in allergic asthma (3), drug allergies (4), idiopathic angioedema (5) or chronic urticaria (6), therapy with this antibody in systemic mast cell activation disease seems worth considering. Here, we report on the efficacy and safety of anti-IgE therapy with omalizumab in four of our patients with systemic mast cell activation disease (2 with systemic mastocytosis and 2 with systemic mast cell activation syndrome) and the results are discussed in light of the literature facilitating collection of some generalized clinically relevant conclusions.

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Table 1. Characteristics of the Four Patients with Systemic Mast Cell Activation Disease of the Present Report

	Case #1 male, *1958	Case #2 female, *1947	Case #3 male, *1963	Case #4 female, *1981
Diagnosis according to the consensus criteria (1)	aggressive systemic mastocytosis	systemic monoclonal mast cell activation syndrome	indolent systemic mastocytosis	systemic monoclonal mast cell activation syndrome
Tryptase (µg/L) [<11.4 µg/L]	15.8 ¹ / 2.8 ²	3.7 ¹ / 4.0 ²	6.9 ¹	2.5 ¹ / 1.4 ²
Heparin (IU/mL)¹ [<0.02 IU/mL]	0.04	0.03	not determined	0.04
Genetic alterations in tyrosine kinase Kit	GNNK $\ominus$ /GNNK $\oplus$ $\geq 92\%$ ins Q252 del S715 del nt a2356 (codon 778) $\Rightarrow$ frame shift with stop codon at amino acid 814	GNNK $\ominus$ /GNNK $\oplus$ 58.0% ins Q252 del S715 stop codon at amino acid 475	not determined	GNNK $\ominus$ /GNNK $\oplus$ $>99\%$ ins Q252 del S715
Mast cell mediator-related symptoms	fatigue, asthenia, weight loss, GIT symptoms, CV symptoms, Npsy. symptoms, Hep. symptoms, Resp. symptoms, skeletal symptoms, Cut. symptoms, abnormal bleeding	fatigue, asthenia, weight loss, GIT symptoms, CVsymptoms, Npsy. symptoms, Hep. symptoms, Resp. symptoms, skeletal symptoms, Cut. symptoms, abnormal bleeding	fatigue, asthenia, weight loss, GIT symptoms, CV symptoms, Npsy. symptoms, Hep. symptoms, Resp. symptoms, abnormal bleeding	fatigue, asthenia, weight loss, GIT symptoms, CV symptoms, Npsy. symptoms, Hep. symptoms, Cut. symptoms, abnormal bleeding
Score value³ [<14]	≥ 46	≥ 28	≥ 24	≥ 21
Clinical manifestation	year 1996	year 2000	year 2003	year 2002
Total IgE (kU/L) [<100 kU/L]	$<2^{1/2}$	91-107 ¹	not determined	$<0.1^{1/2}$

¹ Value determined before starting treatment with omalizumab² Latest value under therapy with omalizumab³ The score value refers to the diagnostic questionnaire validated to identify mast cell mediator-related symptoms (24).

Reference values in brackets.

GNNK $\ominus$ /GNNK $\oplus$: ratio of the expression intensities of the oncogenic isoform of tyrosine kinase *Kit* with the deletion of the amino acids 510-513 (GNNK $\ominus$) over that without this deletion (GNNK $\oplus$). In healthy subjects a ratio of up to 75% has been found (25).

GIT – gastrointestinal; CV – cardiovascular; Npsy. – neuropsychiatric; Hep. – hepatic;

Resp. – respiratory; Cut. – cutaneous

Case Report

Patient 1

A Caucasian man was diagnosed with *aggressive systemic mastocytosis* according to the WHO-criteria (Table 1; C-findings: malabsorption with weight loss, osteolysis with pathological bone fractures, hepatopathy). His medications at the time of initiation of omalizumab therapy included regular prednisolone, cromolyn sodium, ranitidine, fexofenadine, ketotifen, montelukast, ascorbic acid, pantoprazol, valsartan, α -lipoic acid, macrogol and risedronic acid. Before omalizumab therapy, his tryptase and heparin levels in blood were increased; his serum IgE level was in the low normal range. In the autumn of 2007, the patient began receiving 150 mg subcutaneous injections of omalizumab in compassionate use, the first two injections biweekly and after this

initial treatment he has continued receiving the same dose as maintenance therapy, once every four weeks up to the present day. After approximately 6 months of treatment with omalizumab the patient started to achieve a clear persistent clinical response as indicated by decreased symptom intensity and by a reduced number and doses of drugs necessary to control the disorder (Fig. 1). Under therapy serum tryptase declined to a normal value (Table 1). In general, the drug has been well tolerated with the exception of paresthesia and pruritus (grade 1 according to the *Common Terminology Criteria for Adverse Events v4.03*) after two of the injections. In the beginning of the omalizumab injections, flare-ups of intestinal (grade 1-2) and cutaneous (grade 1) fungal infections were observed which could later be prevented by prophylactic treatment with nystatin and bifonazole.

Patient 2

A Caucasian woman was diagnosed with *systemic monoclonal mast cell activation syndrome* (Table 1). At the commencement of therapy, medications included cromolyn sodium, ranitidine, cetirizine, montelukast, pantoprazol, azathioprine, risedronic acid, Pankreatin, vitamin D, calcium and magnesium. Before omalizumab therapy, normal tryptase concentration was detected in her blood and her serum IgE level was normal to slightly increased (Table 1). In autumn of 2007, omalizumab therapy was initiated at 300 mg every 4 weeks in compassionate use and has now continued for 106 weeks. After about 6 months of treatment with omalizumab the patient started to achieve an impressive persistent clinical response: hives, aphthas and flushes vanished, the intensity of fatigue and the other symptoms decreased, gain in weight occurred, the intake of azathioprine could be discontinued and doses of other drugs necessary to control the disorder could be reduced. At the same time her diet, which was restricted to millet, quinoa, manioc, lamb and Chinese leaves due to induced/accompanied multiple food allergies, could be expanded e.g. to dairy products. The urinary excretion of methylhistamine which had been continuously increased before omalizumab treatment became normal (Fig. 2). Omalizumab has been well tolerated with only occasional transient swelling of the mucosa in nose and auditory tube, cough, hoarseness and aphthas of the tongue (grade 1). In temporal relation with the omalizumab application thrush in the mouth (grade 1) was observed.

Patient 3

A Caucasian man was afflicted with *indolent systemic mastocytosis* according to the WHO criteria (Table 1). Because symptoms were not relieved sufficiently by evidence-based therapy with ranitidine, cetirizine, ketotifen and omeprazol, the patient began receiving 150 mg injections of omalizumab in compassionate use in July 2009 on a bi-weekly schedule up to the present day. During the 18 weeks of treatment with omalizumab (9 injections) the patient has felt an improvement of his health manifested by a gain in weight, an intake of a normal diet and almost steady digestion, but the number and doses of drugs could not yet be reduced. To date, the drug has been well tolerated.

Patient 4

A Caucasian woman was diagnosed with a *systemic monoclonal mast cell activation syndrome* (Table 1). The evidence-based therapy with cromolyn sodium, ranitidine, fexofenadine, ascorbic acid, ketotifen, supplemented with montelukast, tropisetron, risedronic acid and omeprazol, did not sufficiently relieve her symptoms. Continuous therapy with prednisolone and azathioprine moderately but not sufficiently improved the intensity of the symptoms, whereas methotrexate and imatinib had been completely ineffective. Therefore, in March 2009, the patient began receiving 150

mg injections of omalizumab biweekly in compassionate use. Right after the first injection intolerable mast cell mediator-induced symptoms (headache, nausea, dizziness) occurred which increased in intensity after the subsequent 2 injections (grade 2-3) and therefore omalizumab therapy was discontinued.

Discussion and Conclusions

In accordance with previous findings in four case reports in the literature comprising 5 patients (8-11) the present data demonstrate that omalizumab application is an effective treatment for systemic mast cell activation disease. Omalizumab reversibly binds to the Fc portion of the IgE molecule, thereby forming small, biologically inert, noncomplement-fixing complexes which are cleared with a terminal half-life of 26 days [for review on its pharmacokinetics, see (12)]. Complexation of free serum IgE reduces IgE binding to the high affinity FcεRI on mast cells and basophils, followed by rather fast down-regulation of FcεRI expression by basophils (13) and a slower down-regulation by (dermal) mast cells (14), thereby reducing the potential reactivity of these cells. The slow development of improvement of symptoms by omalizumab in patients with mast cell activation disease argues in favour of a predominant action of omalizumab at mast cells in those patients.

In the previous case reports, serum tryptase was reported to decrease under omalizumab therapy in two mastocytosis patients (8, 9) but it remained unchanged in two other patients (5). In the present patients we observed a decline of the mast cell mediators tryptase and methylhistamine, respectively, in two of them. These observations could indicate rather an interference of omalizumab with a differential mast cell mediator release process (15, 16) than with mast cell degranulation. In this context, it is interesting to note that genome-wide gene expression profiling of human mast cells revealed substantial changes in gene expression already in response to monomeric IgE (17). Genes coding for three cytokines and five chemokines were upregulated in mast cells by binding of monomeric IgE beside upregulated expression of several genes for other receptor and proteins involved in immune response. Thus, binding of monomeric IgE to mast cells may not only prime the mast cells for a subsequent antigene challenge, but may by itself enable mast cells to trigger other immune effector cells by selective mediator synthesis and release (17 and references therein)]. Omalizumab may antagonize this trigger effect in vivo by decreasing circulating monomeric IgE. The conclusion that omalizumab did not down-regulate the activity of mast cells as a whole would also be in line with the previous observation that omalizumab therapy did not result in a decrease of the mast cell number in the patients (11, 14) which would be expected to occur as a consequence of a reduced total activity of mast cells. In addition to its effects at mast cells, it is likely that regulatory influences of omalizumab on basophils (18, 19) as well as numerous other pharmacologic and

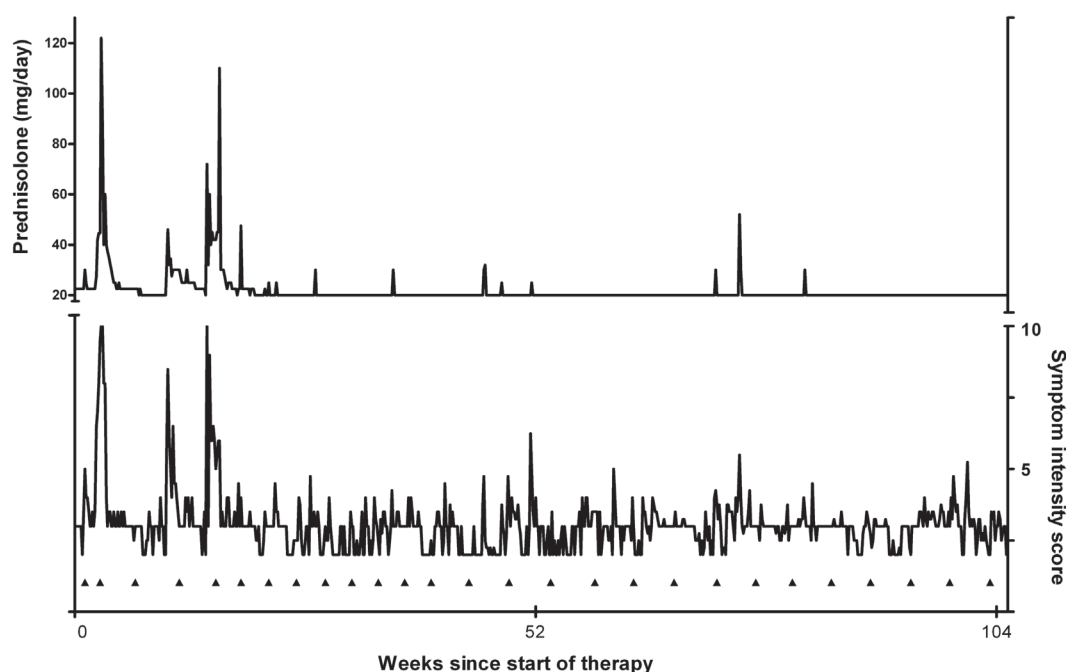


Figure 1. Omalizumab treatment resulted in the reduction of intensity of symptoms of systemic mastocytosis in patient #1. Upper panel: daily prednisolone dose necessary to alleviate symptoms. Lower panel: scoring of disease intensity by the patient on a 10-point visual analog scale (0 = no mast cell mediator-related symptoms, 10 = excruciating mast cell mediator-related symptoms). Arrows indicate the time points of omalizumab injections.

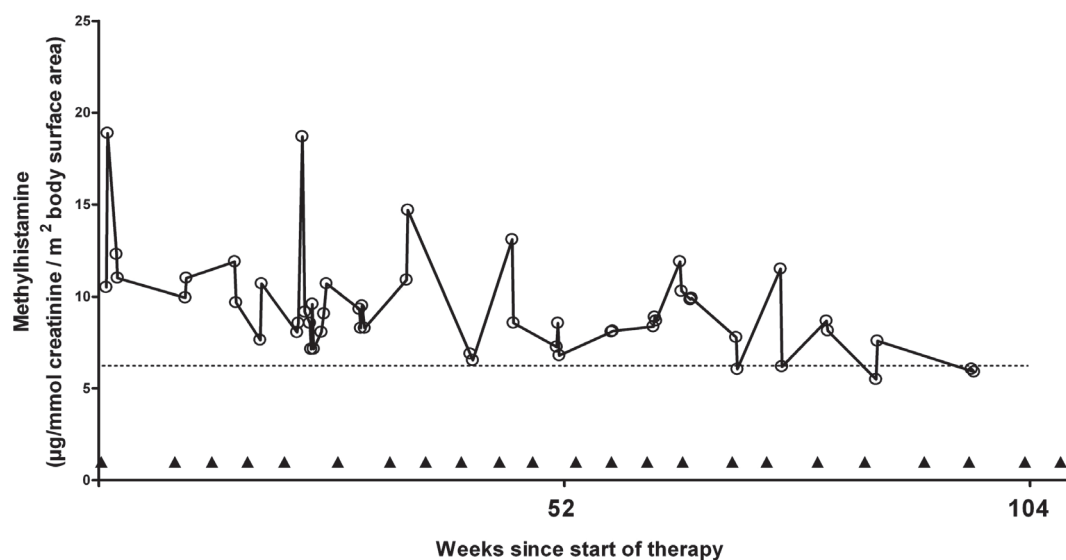


Figure 2. Omalizumab treatment resulted in the reduction of intensity of symptoms of the systemic monoclonal mast cell activation syndrome in patient #2 which was paralleled by a decrease of urinary methylhistamine excretion. The dotted line represents the upper limit of the normal range. Arrows indicate the time points of omalizumab injections.

immunoregulatory effects of omalizumab independent of an interaction with IgE contribute to its efficacy in systemic mast cell activation disease (20, 21).

In the therapy of allergic asthma with omalizumab the level of circulating IgE is used to calculate the necessary omalizumab dose. In mast cell activation disease omalizumab therapy was effective even when the levels of circulating unspecific IgE before treatment were not pathologically

increased (present study and 10, 11) which, however, does not necessarily imply an independence of efficacy from circulating IgE (for review, see 22).

As omalizumab targets components of the immune system, therapy may have the potential to increase the risk of infection or neoplasm as a result of long-term immunosuppression. In addition, monoclonal antibodies of murine origin may be associated with a risk of anaphylactic reactions.

However, the safety data from treatment studies on patients with allergic asthma have indicated that omalizumab is well tolerated (for review, see 23). Consistent with these studies no severe adverse effects (only local swelling at the site of injection) were observed in the previous case reports on omalizumab treatment of systemic mastocytosis. In the present study, omalizumab was also well tolerated by 3 of our 4 patients. However, two findings are noteworthy for clinical practice: 1) Transient mild to moderate mast cell mediator-induced symptoms can occur within several hours after injection which seem to indicate an activation of mast cells. Their occasional occurrence may point to an allergic reaction subsequently to the pathologically increased mast cell activity, outbalancing the effects of a direct inhibition of mast cells by omalizumab. In the worst case an intolerance of omalizumab with intense mast cell mediator-induced symptoms can occur as seen in the present patient #4. 2) Under omalizumab therapy clinically significant flare-ups of intestinal and cutaneous fungal infections were observed possibly reflecting derogated immune system activity.

Taken together, our data are in concert with those reported in the literature indicating that omalizumab treatment can successfully alleviate high intensity symptoms of systemic mast cell activation disease (either *systemic mastocytosis* or *systemic monoclonal mast cell activation syndrome*) but that it is not a curative therapy. Since treatment with omalizumab has an acceptable risk-benefit-profile, it should be considered at an early stage as an experimental therapeutic option in cases of systemic mast cell activation disease resistant to evidence-based therapy.

The authors state that they have no Conflict of Interest (COI).

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