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Omalizumab therapy for mast cell-mediator symptoms in patients with ISM, CM, MMAS and MCAS

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Abbreviations

CEREMAST: French National Reference Center for Mastocytosis

CM: cutaneous mastocytosis

CR: complete response

IgE: immunoglobulin E

ISM: indolent systemic mastocytosis

MCA: mast cell activation

MCAS: Mast Cell Activation Syndrome

MMAS: Monoclonal MCAS

MR: major response

PR: partial response

SM: systemic mastocytosis

SM-AHN: systemic mastocytosis with associated hematologic neoplasm

Key words: omalizumab, mast cell disorders, mastocytosis, IgE

Highlights boxes

1. What is already known about this topic?

Clinical experience of omalizumab in mast cell disorders is limited, with mainly case-reports and a 14-patients retrospective series testifying for its efficacy in recurrent anaphylaxis, venom immunotherapy and mast cell activation symptoms.

2. What does this article add to our knowledge?

We prospectively surveyed 56 patients with a systemic mast cell disorder receiving omalizumab, following the same administration scheme. The overall response rate was 76.8% with a very favorable safety profile.

3. How does this study impact current management guidelines?

This real-life study describes the symptoms which encompass the best response, the median time to response and it provides guidelines about optimal modalities of omalizumab administration in mast cell disorders.

Abstract

Background. Patients with mast cell diseases may suffer from various distressing symptoms, which can be insufficiently controlled with available therapies, severely affecting their quality of life. There is a need for new and safe treatment options for these patients.

Objectives. We aimed to evaluate safety and efficacy of omalizumab administration in patients with a symptomatic mast cell disorder.

Methods. We included 55 patients with a mast cell disorder associated with debilitating symptoms who received omalizumab treatment between January 2015 and December 2017, after a multidisciplinary team meeting at the French National Reference Center for Mastocytosis (CEREMAST).

Results. A complete response was achieved for 1 patient (1.8%), a major response for 30 patients (54.5%) and a partial response for 12 patients (21.8%), resulting in an overall best response rate of 78.2% (43/55 patients). The response was persistent at least 3 months in 33/43 (76.7%) responding patients. At last follow-up, the final overall response rate was 58.2% (32/55 patients). Median time to first response was 2 months and median time to best response was 6 months. Omalizumab was dramatically effective on all superficial and general vasomotor symptoms and on most gastrointestinal or urinary symptoms, and partially effective on most neuropsychiatric symptoms. Safety profile was acceptable, except for one severe adverse event (edema of the larynx and dyspnea after the first injection of omalizumab). Side effects were reported in 16 patients (28.6%), mainly of low to mild intensity, yet causing interruption of treatment in 6 patients (10.7%).

Conclusion. Omalizumab seems to be a useful therapeutic option to control mast cell-mediator symptoms and displays a favorable safety profile.

Introduction

Mast cells are effector cells involved in allergic and inflammatory reactions (1-3). They derive from myeloid stem cells, then migrate in tissues and organs (1). Mast cells are a well-known source for many proinflammatory mediators (such as histamine, tryptase, prostaglandin D2, platelet-activating factor, leukotrienes, various cytokines and chemokines) and express the high-affinity IgE receptor FcεRI (1-3). Once activated by an allergen that aggregates IgE and FcεRI complexes, or by non-IgE related stimuli, mast cells self-activate and release their mediators, which can cause many local and systemic symptoms.

Systemic mastocytosis (SM) is a heterogeneous hematological neoplasm characterized by clonal expansion and accumulation of mast cells in different tissues, including the bone marrow, the skin, the gastrointestinal tract, the liver and the spleen (1). SM is opposed to cutaneous mastocytosis where only the skin is involved, even though most adult patients with cutaneous mastocytosis have SM. SM is further divided in several subcategories of increasing severity: indolent SM (ISM), smoldering SM (SSM), SM with associated hematologic neoplasm (SM-AHN), aggressive SM (ASM) and mast cell leukemia (MCL) (4). Some patients display typical clinical symptoms of mast cell activation (MCA), but do not meet the criteria for mastocytosis: these patients are diagnosed with another mast cell disorder called Mast Cell Activation Syndrome (MCAS), which can be clonal (if *KIT* mutation (mandatory) +/- aberrant phenotype (CD2 and/or CD25) is proven) (MMAS) or non clonal (5).

In ISM, SSM, some SM-AHN, MMAS or non clonal MCAS, clinical symptoms caused by MCA are often in the foreground, and can be very diverse ranging from chronic mild pruritus, musculoskeletal pain, fluctuating abdominal cramping and diarrhea, to acute episodes of potentially life-threatening anaphylaxis (1, 5). Patients with mast cell disorders can also present neuropsychiatric symptoms with unknown pathophysiological mechanisms.

Several pharmacologic agents can target MCA symptoms such as antihistamines, corticosteroids, cromolyn sodium or leukotriene inhibitors. When those agents are insufficient to control symptoms, targeting mast cells with tyrosine kinase inhibitors, immunomodulatory or cytoreductive therapies such as imatinib, masitinib, alpha-interferon or cladribine can be necessary (4, 6, 7) and some patients can relapse, experience adverse events, or become refractory to these therapies. However, these therapies should only be used in patients with mastocytosis and not in other mast cell disorders. Uncontrolled MCA symptoms can severely affect the quality of life of patients, and there is a great need for alternative and safe treatment options (8).

Omalizumab is a humanized anti-IgE monoclonal antibody already approved for the treatment of allergic asthma and chronic spontaneous urticaria (9-11). In these diseases, omalizumab binds to free IgE, decreases the expression of FcεRI and therefore increases the threshold for degranulation of mast cells and basophils (10).

Clinical experience of omalizumab in mast cell disorders is limited, with mainly case-reports testifying for its efficacy in recurrent anaphylaxis (12-19). It has also been shown to help control reactions to venom immunotherapy (17). In some cases, a “flare” effect has been observed after injection of omalizumab (20), which pleads for a first in-hospital administration. More recently, a 14-patients cohort study evaluated the efficacy and safety of omalizumab in SM (21). This study reported a promising efficacy of omalizumab in SM, especially in anaphylaxis but with improvement of other MCA symptoms and quality of life as well, along with a favorable safety profile.

We aimed to confirm these results by analyzing our national cohort of 55 patients who received omalizumab since January 2015, within the institutional framework of the French National Reference Center for Mastocytosis (CEREMAST).

Methods

Patients. From January 2015 to December 2017, the national multidisciplinary expert team from the CEREMAST recommended treatment with omalizumab for 65 patients with symptomatic mast cell disorder, treated in 11 different centers in France and Belgium. Patients had severe or debilitating symptoms refractory to classical treatments of mast cell disorders, including antihistamines, cromolyn sodium or leukotriene inhibitors. According to CEREMAST rules of functioning, patients with such treatment decision were prospectively surveyed in the CEREMAST national database, in order to record efficacy and safety data. The use of this computerized database (22) to store personal information was authorized by the French National Data Protection Commission (CEREMAST authorization: CNIL: No1445939 (October 29, 2010)).

In January 2018, we screened these 65 eligible patients, and the different centers were contacted in order to update data with last follow-up. We included patients who received at least one injection of omalizumab. Nine patients who did not receive omalizumab, who were lost from follow-up or for whom data was deemed insufficient were excluded from this study. One patient with SM-AHN was also excluded for this study. We retained 55/65 patients with a confirmed diagnosis of mast cell disorder according to the World Health Organization (WHO) criteria (23) (n=40 patients) and with clonal and non clonal MCAS (n= 1 and n=14 patients). MCAS was diagnosed according to recommendations, by the association of typical clinical symptoms, increase in serum total tryptase by at least 20% above baseline plus 2 ng/ml during or within 4 hours after a symptomatic period, and response of clinical symptoms to histamine receptor blockers (HR1 +/– HR2 inverse agonists) or ‘MC-targeting’ agents like cromolyn 1 (5).

All 55 patients were informed that they received a drug non registered neither for mastocytosis nor MCAS, but that could be prescribed after recommendation from a multidisciplinary team meeting at the CEREMAST. All patients gave their consent for this prospective survey.

Clinical and biological data were collected from the CEREMAST database for all 55 patients, and completed with medical files and with a descriptive questionnaire sent to the clinician in charge of the treated patient(s). The study was conducted according to the Declaration of Helsinki.

Omalizumab therapy. The recommended starting dose of omalizumab was 150 mg every 2 weeks subcutaneously, without taking into account patient weight nor total IgE level. Patients were strongly encouraged to continue their conventional therapy during omalizumab therapy. First injection was always performed at the hospital, and the following doses could be injected at home. The rhythm of physician's supervision was every four to six weeks during the first three months then every three to six months depending on tolerance and efficacy. A dose escalation to a maximum of 300 mg every two weeks was allowed in order to improve a partial efficacy. A weekly administration of omalizumab was permitted (150 mg/week), in case of reoccurrence of symptoms prior to the following dose of omalizumab, in a patient responding to therapy. This reappearance of symptoms a few days before the following dose of omalizumab was assessed by the patient and its physician. It should be noted that there is no proof of the efficacy of these regimens (dose escalation or weekly dosing) and that they are not recommended outside of a clinical trial. Treatment was given as long as it was effective and well-tolerated.

Efficacy assessment: symptoms improvement. All symptoms were assessed before and during treatment, from medical files and/or via an assessment questionnaire sent to the clinician in charge of the treated patients. We collected all symptoms present before treatment, and attributed the number 1 for all existing symptoms at baseline. Then, for each symptom, we determined the evolution on treatment, including time to first response and time to best response.

To semi-quantitatively evaluate the symptoms evolution, we established a "symptom score" summing up the response for each symptom under omalizumab therapy:

- 1.5: Worsening of the symptom.
- 1: No change.
- 0.75: Slight improvement.
- 0.5: Substantial improvement.
- 0.25: Dramatic improvement.
- 0: Complete disappearance of the symptom.

Quality of life assessment with classical forms was not mandatory in this real-life study; thus effect of omalizumab on quality of life was not assessable.

Efficacy assessment: depth of response. Responses were assigned at time of best response, from the "symptom score". A complete response (CR) was defined as the resolution of all preexisting symptoms. A major response (MR) was defined as a decrease superior to 50% of preexisting symptoms, according to symptom score. A partial response (PR) was defined as a decrease of 10% to

50% of preexisting symptoms, according to symptom score. Absence of response was defined as a decrease of less than 10% of preexisting symptoms, according to symptom score, or worsening of preexisting symptoms or apparition of new symptoms.

Efficacy assessment: biological effects of omalizumab. Blood parameters such as tryptase and total IgE levels were analysed as in daily practice in the different centres. They were collected at diagnosis, and in some cases before and during treatment with omalizumab.

Safety assessment. All physicians following patients under omalizumab therapy were requested to report all adverse events occurring under therapy, following the in-law daily practice reporting system**.**

Statistical analyses. All analyses were performed with the GraphPad Prism 7.00 software. Differences in the symptom score between baseline and follow-up under omalizumab therapy were calculated using Wilcoxon signed rank test. Tests were performed two-tailed. Mean tryptase and total IgE levels were compared with paired Student T tests. Reported p-values were considered statistically significant if below 0.05.

Results

Patients. 55 patients with a confirmed diagnosis of mast cell disorder according to the World Health Organization (WHO) criteria and treated with omalizumab were included in this study. Median age at diagnosis was 41 years [2-87] and median age at treatment with omalizumab was 48 years [17-93].

The diagnoses were: indolent systemic mastocytosis (ISM; 29 patients, 52.7%), mast cell activation syndrome (MCAS; 15 patients, 27.3%) and cutaneous mastocytosis (CM; 11 patients, 20%). Forty-nine patients/55 were evaluated for *KIT* mutation; *KIT* D816V mutation was found in 27/49 patients (55.1%): 23/28 (82.1%) patients with ISM, 3/9 (33.3%) patients with CM and 1/12(8.3%) patient with MCAS.

A large majority of these patients already received all classical therapies against symptoms related to mast cell activation, including antihistamines, cromolyn sodium or leukotriene inhibitors. 45/55 patients (82%) continued at least one of the classical therapies that they were receiving before initiation of omalizumab. Some patients already received multiple tyrosine kinase inhibitors, immunomodulatory or cytoreductive treatments. Patients' characteristics at inclusion, including previous treatments, are detailed in Table 1.

Best response rates. Among the 55 patients, we observed a CR for 1 patient (1.8%), a MR for 30 patients (54,5%) and a PR for 12 patients (21.8%), resulting in symptom improvement for 43 patients (overall response rate of 78,2%).

The overall response rate was 82.9% among the 41 patients with primary MCAS, and 68.7 among the 14 patients with idiopathic MCAS. Detailed response rates are presented in Table 2.

Time to first response and duration of response.

Median time to response was 2 months and median time to best response was 6 months. Regarding specific symptoms improvement, median time to first symptom improvement was 1 month [1 – 3 months] for general vasomotor symptoms (anaphylaxis, malaise, palpitations) and improvement required 2 to 3 months for all the others symptoms [1 – 10 months].

At last follow-up, 32 patients (58.2%) remained on omalizumab therapy. Median duration of omalizumab therapy was 9 months for the whole cohort, and 11 months for responding patients, i.e. reaching at least a PR [2 – 36 months]. Median duration of therapy was 2 months for non responding patients, 10 months for patients in PR, 11 months in patients with MR and 17 months for the patient in complete response.

Response was persistent in most responding patients, with a sustained response of at least 3 months in 33/43 patients (76.7%). Only 4 patients lost their acquired response under omalizumab, after 2 to 13 months of treatment.

Among the 43 responding patients, 11 have stopped therapy because of: loss of response (4 patients), intolerance (3 patients), loss from follow-up (2 patients), pregnancy intent (2 patients).

The 12 patients who did not respond to omalizumab all stopped treatment, after 1 to 6 months: 9 patients (75%) stopped for lack of efficacy while 3 patients (25%) stopped for intolerance. Follow-up data are summarized in Figure 2.

Separated follow-up data for patients with primary MCAS (ISM + CM + MMAS) and non clonal idiopathic MCAS patients are presented in supplemental Figures E3 and E4.

Response rate at last follow-up. At last follow-up, 32 patients were still on therapy. Among these 32 patients, 1 patient was still in CR (1.8%), 23 in MR (41.8%) and 8 in PR (14.5%), resulting in a persistent overall response rate of 58.2%. Detailed final response rates are presented in Table 2.

Dose modifications. In 15/55 patients (27.3%), a dose escalation was prescribed in order to try to improve symptom control with omalizumab, according to CEREMAST initial recommendations (up to 300 mg every 15 days for 14 patients, and up to 600 mg every 15 days for 1 patient, which was not a recommended schedule and without objective measures to substantiate efficacy). Among these 15 patients, 14 patients (93%) improved their response, with 6 patients (40%) reaching a MR and 8 patients (53.3%) improving their PR.

In our cohort, 3 patients (5.5%) had a reoccurrence of symptoms prior to the following dose of omalizumab administered every two weeks. In these patients, omalizumab's therapy was modified to a weekly schedule, to reduce the dose interval to one week – this weekly schedule is however not FDA-approved and should not be prescribed outside of a clinical trial. Among these 3 patients, 2 patients improved their response, reaching 1 MR and 1 PR, and 1 patient was not improved with closer administration and stopped omalizumab.

Symptoms improvement. Symptoms and numbers of patients with each symptom are indicated in Figure 1 for ISM and MCAS patients. The mean number of symptoms per patient was 11.

Omalizumab was dramatically effective on all general and superficial vasomotor symptoms, and on most gastrointestinal or urinary symptoms. Omalizumab was also, but often partially, effective on most neuropsychiatric symptoms. Some patients had an improvement of their musculoskeletal pains or headaches. Clinical efficacy data are presented in Figure 1.

We performed separate analyses for symptoms improvement in patients with primary MCAS (ISM + CM + MMAS) and non clonal idiopathic MCAS patients (supplemental Figures E1 and E2). The response profile to omalizumab therapy does not seem to be different between these entities, except for some symptoms with only low number of patients leading to lower statistical power.

Safety. Overall, safety profile was acceptable. Sixteen patients (29%) presented side effects, among whom 6 patients interrupted omalizumab therapy because of these side effects. One patient (1.8%) developed a severe adverse event with edema of the larynx and dyspnea 30 minutes after the first injection of omalizumab. Symptoms were controlled after corticosteroids, antihistamine and β2 mimetics therapy, but persisted moderately around 3 weeks according to the patient. Three patients (5.5%) presented a significant "flare" effect with accentuation of their symptoms on therapy, requiring omalizumab discontinuation. Other side effects included: fatigue (3 patients), fever (3 patients), headache (2 patients), malaise (2 patients), nausea (2 patients), abdominal pain (2 patients), bleeding (increased menstruations and epistaxis for 1 patient, ecchymosis for 1 patient) pruritus (1 patient), local rash (1 patient), sweating (1 patient).

Biological effects. Blood tests during therapy were not mandatory in this survey, but 15 patients were tested for serum tryptase before and on omalizumab therapy and 15 patients were tested for serum total IgE level before and on omalizumab therapy.

We did not observe any significant modification of the tryptase level on therapy with omalizumab, with a mean value of 30.3 ng/mL before omalizumab and 32 ng/mL on therapy (after at least 3 months of treatment).

We observed an increase in total IgE levels on therapy, with a mean value of 235.1 UI/mL [3.5 – 1616] before omalizumab and 772.8 UI/mL [6.6 – 4356] on therapy. Among the 15 tested patients, 11 (73,3%) presented an increase of total IgE level while the 4 remaining patients (26,7%) presented stable total IgE levels. The evolution of total IgE levels was not correlated with treatment efficacy or tolerance in this small tested sub-group of patients.

Tryptase and total IgE levels evolutions on therapy are presented in supplemental Figure E5.

Discussion

This study presents data on the efficacy and safety of omalizumab in mast cell disorders, mainly primary MCAS (ISM, CM and MMAS) and non clonal idiopathic MCAS. We included 55 patients in this analysis, which is to our knowledge the largest cohort to date since only 29 patients with SM treated omalizumab have been reported so far, in 10 different series (12-21).

We observed an overall response rate of 78.2% in our series, which is in line with the overall response rate of 78.6% recently published by Broesby-Olsen et al. (21) in their 14-patients cohort.

In this series and when compiling single-cases observations, omalizumab seemed especially efficient on recurrent anaphylaxis. In our study, we observed that omalizumab had a very positive effect on all general and superficial vasomotor symptoms, including but not restricted to anaphylaxis, and on most gastrointestinal or urinary symptoms. Regarding anaphylaxis, 13/14 patients had an improvement of their symptoms, reaching independence of epinephrine after beginning of omalizumab; but anaphylaxis worsened in one patient, which remains unexplained.

Efficacy seems more modest for musculoskeletal pains, headaches or neuropsychiatric symptoms, yet a few patients significantly improved their symptoms on therapy. These results were similar to those reported by Broesby-Olsen et al.: in their series, the lowest response rate was observed for musculoskeletal pains and neuropsychiatric symptoms (21).

In our study, omalizumab's efficacy was rapidly observed with a median time to first response of 2 months and a median time to best response of 6 months. Time to response nevertheless ranged from 1 to 10 months, depending on the patient and on the symptom considered. Consistently with available data, the most rapid effect of omalizumab was observed on general vasomotor symptoms, including anaphylaxis. We also observed persistent responses, with an ongoing maximum duration of 36 months at last follow-up. Only 4 patients lost their response, after 2 to 13 months of treatment.

Interestingly, we observed a possible improvement of symptoms with dose adjustment and/or closer administration. Even if we did not observe a clear relationship between omalizumab dosing and depth of response in the whole cohort, these observations claim for a dosing effect, which seems variable over time and which remains to be explored.

With respect to omalizumab's safety, a "flare" effect has previously been described at the beginning of therapy in some patients with mastocytosis (20). Among our 55 patients, 3 patients presented a similar "flare" effect, which has rapidly resolved without sequelae. However, in one patient, the flare effect was severe with edema of the larynx and dyspnea occurring 30 minutes after the first injection. Apart from this case, safety profile was acceptable, with mainly mild side effects yet leading to termination of the treatment in 6 patients (10.9%). Broesby-Olsen et al. also reported an overall favorable tolerance of omalizumab, with subjective side-effects of moderate severity in 3 patients, leading to termination of the treatment in 2 out of 14 patients (14.3%) (21). Although omalizumab's safety profile appears manageable in these series, the rate of side effects seems higher than expected as compared to other diseases such as chronic idiopathic/spontaneous urticaria (24). However, most of severe adverse events occurred after the first injection, which justifies the need for at least day care hospitalization at the beginning of therapy.

Concerning omalizumab's biological effects, similarly to Broesby-Olsen et al., we did not find any improvement in tryptase levels under therapy (21), demonstrating as expected that anti-IgE therapy is

not cytoreductive. We observed an increase in total IgE levels in 11 patients among the 15 tested patients. This effect might be due to stabilization of total IgE (which includes free and omalizumab-bound fractions), as previously reported in allergy patients (25) and in chronic spontaneous urticaria (26). Total IgE levels did not seem to correlate to clinical efficacy nor tolerance in our series. In allergic diseases already routinely treated with omalizumab, a reduction of inflammatory mediator release by omalizumab requires a 95% reduction in serum free IgE levels to modify allergen responses via receptor downregulation (25, 27, 28). Therefore, in allergic asthma, doses of omalizumab are adapted to serum total free IgE level and body weight to achieve this reduction in free IgE (29, 30). In symptomatic chronic idiopathic/spontaneous urticaria, which is not a classic allergen-driven disease, dose of omalizumab is fixed and measurement of total or free IgE level under therapy is not necessary (9, 24, 31, 32). Omalizumab's mechanism of action in symptomatic chronic idiopathic/spontaneous urticaria is however not entirely understood (26, 33). Further studies remain necessary to better understand how omalizumab therapy results in improvement of mast cell disorders symptoms, and whether and how free or total IgE levels are correlated with clinical efficacy.

There are some limitations to our study, mainly due to the absence of use of validated scoring test as well as quality of life assessment in this real-life evaluation. Moreover, as this was not a randomized study, patients were all aware of the treatment that they were given. Some of the responses, and especially temporary responses, may thus be due to a placebo effect. It should also be noted that dosing of omalizumab was not adapted on serum total IgE level nor on body weight, and that some schedules of treatment used in our study (dose escalation and weekly schedule) are not recommended in FDA approval for asthma and chronic urticaria.". Despite these limitations, this study provides valuable information on omalizumab therapy in patients with mast cell disorders, in which clinical experience is very limited. A few recommendations could directly derive from our real-life experience : 1/ Omalizumab can improve all symptoms but is most effective on general and superficial vasomotor and gastrointestinal symptoms; 2/ Efficacy is usually quick and persistent in responding patients; 3/ Even if rare, the risk of severe side effects exists at therapy initiation and thus the first(s) administration(s) should be performed in-hospital; 4/ In case of insufficient efficacy, increasing the dose up to 300 mg every 15 days can improve the response in majority of the cases.

Author contributions

Conception and design: RL, GF, LF, SB, DC, LL, JR, MA, OL, OH

Collection and assembly of data: RL, GF, LT, MV, CBL, LL

Data analysis and interpretation: RL, GF, JR, MA, OL, OH

Manuscript writing – original draft: RL, GF, JR, MA, OL, OH

Manuscript writing – review, editing, and final validation of the manuscript: RL, GF, OH

Table 1. Patients' characteristics.

		N = 55
General characteristics		
Age at diagnosis, years, median (range)		41 (2 – 87)
Age at omalizumab treatment, years, median (range)		48 (17 – 93)
Time from diagnosis to omalizumab treatment, median (range)		3 years (2 months - 37 years)
Sex ratio (M/F)		0.44
Disease classification in the whole cohort		
Primary MCAS (N=41)	**Indolent Systemic Mastocytosis (ISM), N (%)**	29 (52.7)
	- *KIT* D816V mutation positive, N	23
	- *KIT* D816V mutation negative, N	5
	- *KIT* D816V mutation not evaluated	1
	Cutaneous Mastocytosis (CM), N (%)	11 (20)
	- *KIT* D816V mutation positive, N	3
	- *KIT* D816V mutation negative, N	6
	- *KIT* D816V mutation not evaluated	2
	Mast Cell Activation Syndrome (MCAS), N (%)	15 (27.3)
	- *KIT* D816V mutation positive (=MMAS), N	1
Idiopathic MCAS (N=14)	- *KIT* D816V mutation negative, N	11
	- *KIT* D816V mutation not evaluated	3
WHO 2016 criteria		
Multifocal dense infiltrates of MCs (≥15 MCs in aggregates) in BM biopsies and/or in sections of other extracutaneous organ(s) (n=23 evaluated)		13 (56%)
25% of all MCs are atypical cells (type I or type II) on BM smears or are spindle-shaped in MC infiltrates detected on sections of visceral organs (n=39 evaluated)		39 (44%)
KIT point mutation at codon 816 in the BM or another extracutaneous organ (n=49 evaluated)		27 (55.1%)
MCs in BM or blood or another extracutaneous organ exhibit CD2 and/or CD25 (n=34 evaluated)		18 (53%)
Baseline serum tryptase level >20 ng/mL (n=55 evaluated)		21 (38%)
Disease presentation		
Involved skin, N (%)		35 (63.6)
	Maculopapular cutaneous mastocytosis, N (%)	31 (56.4)
	Histological criteria, N (%)	28 (50.9)
	KIT D816V mutation, N (%) (n= 22 evaluated)	14 (63.6)

Involved bone marrow, N (%)(n=49 evaluated)		28 (57,1)
	Histological criteria, N (%)	13 (26)
	Cytological criteria, N (%)	16 (32.7)
	Phenotypical criteria, N (%)	17 (34.7)
	KIT D816V mutation, N (%)	22 (44.9)
Decreased bone density, N (%)		17 (30.9)
Tryptase and total IgE levels at diagnosis (N=15)		
Tryptase (ng/mL), mean (range)		30.1 (2.5 – 145)
Total IgE (UI/mL), mean (range)		151.2 (2 – 1616)
Previous lines of therapy		
Symptomatic therapies		55 (100)
	H2 antihistamine, N (%)	50 (90.9)
	H1 antihistamine, N (%)	49 (89)
	Montelukast, N (%)	39 (70.9)
	Sodium cromoglycate, N (%)	27 (49)
Cytoreductive or targeted therapies (restricted to mastocytosis patients)		17 (30.9)
	Cladribine, N (%)	11 (20)
	Masitinib, N (%)	8 (14.3)
	Imatinib, N (%)	5 (8.9)
	Rapamycine, N (%)	3 (5.4)
	Interferon, N (%)	2 (3.6)

Table 2. Response rates.

	All patients (N=55)	Primary MCAS (N=41)				Idiopathic MCAS (N=14)
		All (N=41)	ISM (N=29)	CM (N=11)	MMAS (N=1)	
Best response						
ORR, N (%)	**43 (78.2)**	**34 (82.9)**	**23 (79.3)**	**10 (90.9)**	**1 (100)**	**9 (64.3)**
CR, N (%)	1 (1.8)	1 (2.4)	1 (3.4)	0	0	0
MR, N (%)	30 (54.5)	22 (53.7)	16 (55.2)	5 (45.45)	1	8 (57.1)
PR, N (%)	12 (21.8)	11 (26.8)	6 (20.7)	5 (45.45)	0	1 (7.1)
No response, N (%)	12 (21.8)	7 (17.1)	6 (20.7)	1 (9.1)	0	5 (35.7)
Response at last follow up						
Persistent ORR, N (%)	**32 (58.2)**	**25 (61)**	**17 (58.6)**	**7 (63.6)**	**1 (100)**	**7 (50)**
CR, N (%)	1 (1.8)	1 (2.4)	1 (3.4)	0	0	0
MR, N (%)	23 (41.8)	17 (41.5)	12 (41.4)	4 (36.3)	1	6 (42.9)
PR, N (%)	8 (14.5)	7 (17.1)	4 (13.8)	3 (27.3)	0	1 (7.1)
No persistent response, N (%)	23 (41.8)	16 (39)	12 (41.4)	4 (36.3)	0	7 (50)
No response, N (%)	12 (21.8)	7 (17.1)	6 (20.7)	1 (9.1)	0	5 (35.7)
Loss of response, N (%)	4 (7.3)	3 (7.3)	2 (6.9)	1 (9.1)	0	1 (7.1)
Intolerance, N (%)	3 (5.4)	3 (7.3)	1 (3.4)	2 (18.2)	0	0
Lost from follow-up, N (%)	4 (7.3)	3 (7.3)	3 (10.3)	0	0	1 (7.1)

ORR: overall response rate, CR: complete response, MR: major response, PR: partial response

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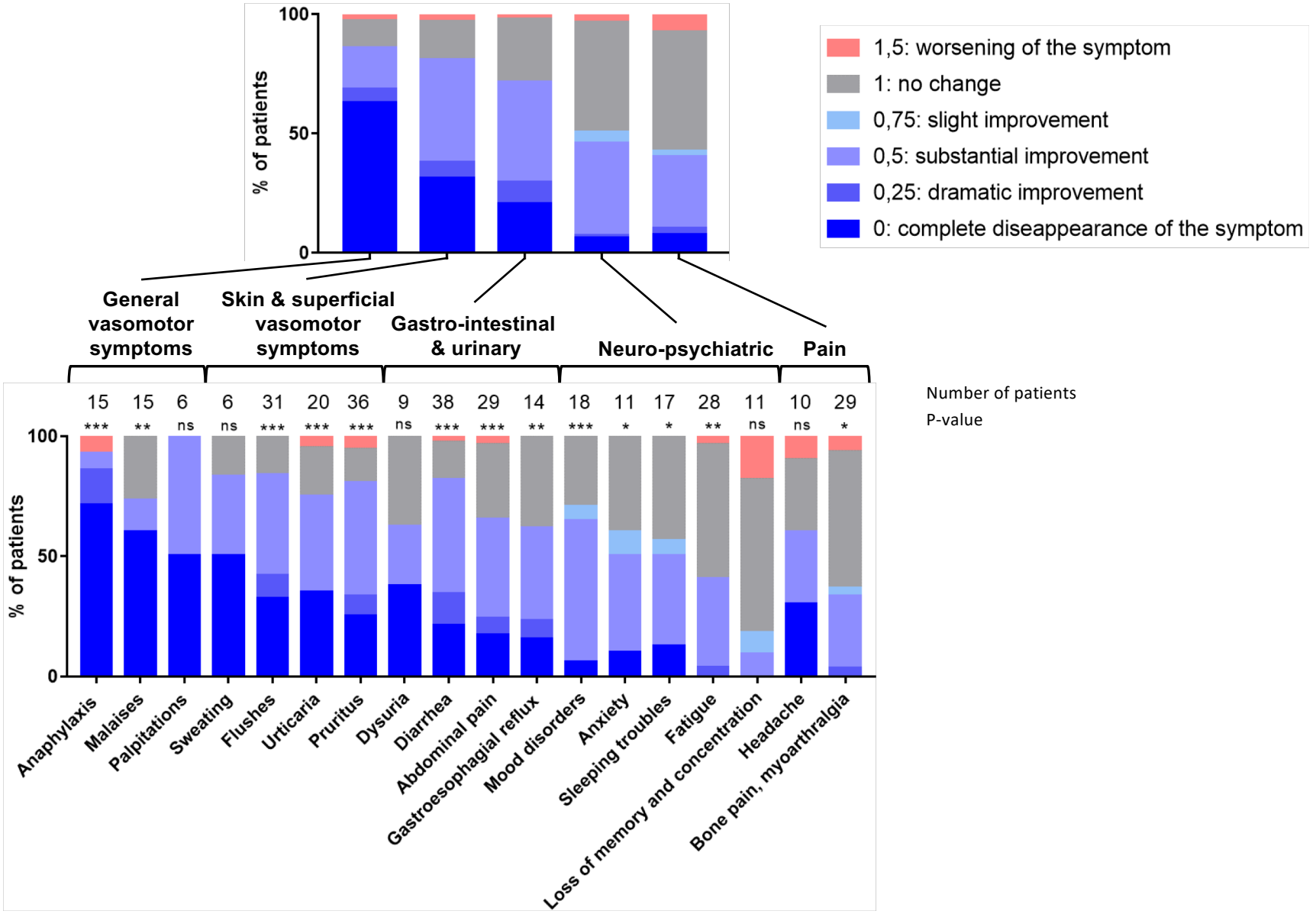
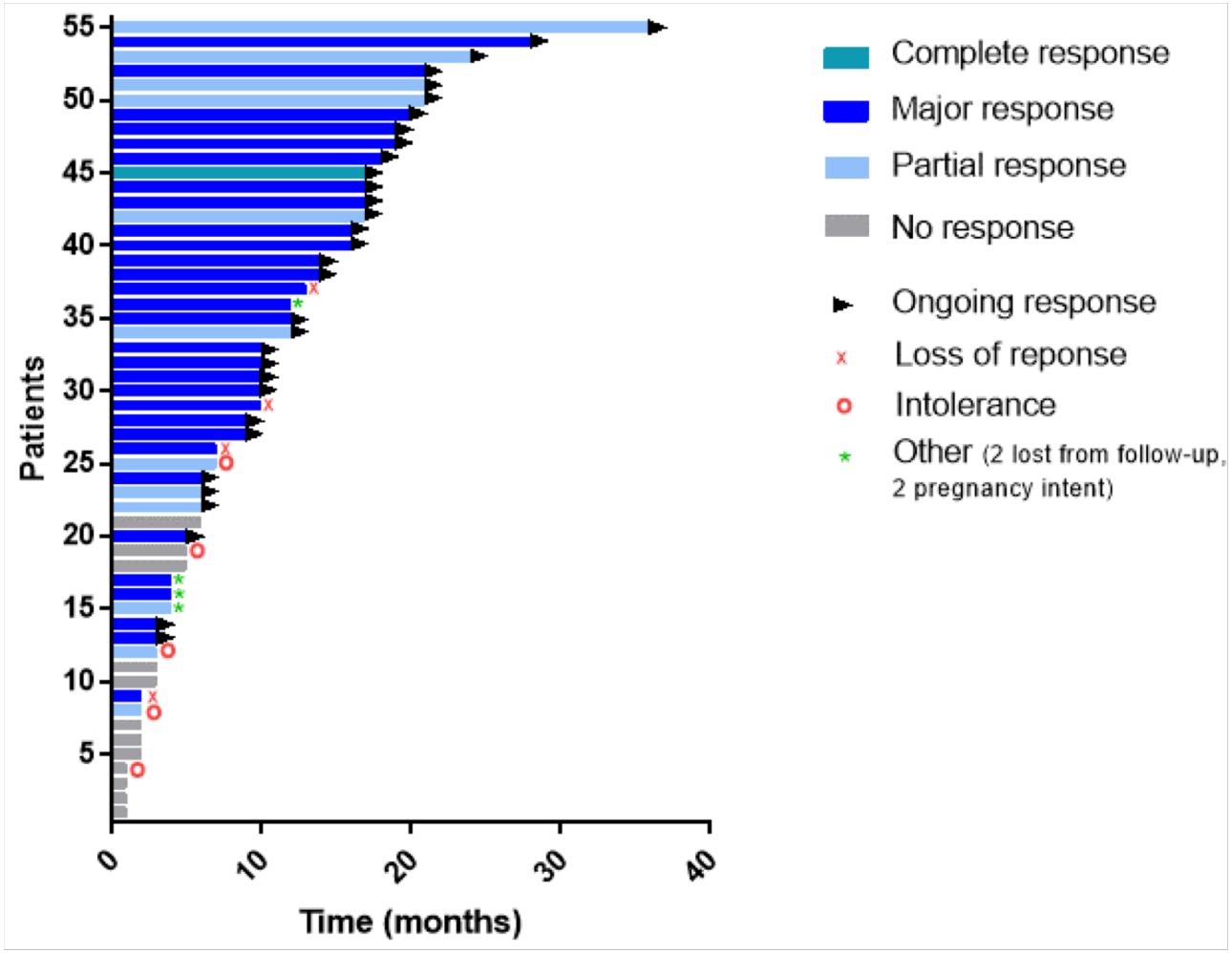
Figure legends

Figure 1. Symptoms improvement in the whole cohort (N=55).

*Comparison of the symptom score before and under omalizumab therapy: p-value: ns: > 0.05; *: p < 0.05; **:p < 0.01; ***:p < 0.001*

Figure 2. Follow-up of responses in the whole cohort (N=55).


100
50
0
% of patients
1,5: worsening of the symptom
1: no change
0,75: slight improvement
0,5: substantial improvement
0,25: dramatic improvement
0: complete diseappearance of the symptom
General vasomotor symptoms
Skin & superficial vasomotor symptoms
Gastro-intestinal & urinary
Neuro-psychiatric
Pain
Number of patients
P-value
15 15 6 6 31 20 36 9 38 29 14 18 11 17 28 11 10 29
*** ** ns ns *** *** *** ns *** *** ** *** * * ** ns ns *
Anaphylaxis
Malaises
Palpitations
Sweating
Flushes
Urticaria
Pruritus
Dysuria
Diarrhea
Abdominal pain
Gastroesophagial reflux
Mood disorders
Anxiety
Sleeping troubles
Fatigue
Loss of memory and concentration
Headache
Bone pain, myoarthralgia


Patients
55
50
45
40
35
30
25
20
15
10
5
0
10
20
30
40
Time (months)
Complete response
Major response
Partial response
No response
Ongoing response
Loss of reponse
Intolerance
Other (2 lost from follow-up, 2 pregnancy intent)