Year: 2020

Efficacy of omalizumab in mastocytosis: allusive indication obtained from a prospective, double-blind, multicenter study (XOLMA Study)

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Abstract: **BACKGROUND:** Patients with mastocytosis often suffer from a variety of symptoms caused by mast cell mediators where treatments remain difficult, showing various success rates. Omalizumab, a monoclonal anti-IgE antibody, has been postulated to have a positive impact on mastocytosis-associated symptoms such as flush, vertigo, gastrointestinal problems, or anaphylaxis. **OBJECTIVE:** To investigate the efficacy and safety of omalizumab in systemic mastocytosis. **METHODS:** Patients with histologically proven mastocytosis were investigated in a multicenter prospective double-blind placebo-controlled trial to receive either omalizumab or placebo, dosed according to IgE and body weight. The primary endpoint was change in the AFIRMM activity score after 6 months of treatment. Different laboratory parameters were analyzed. **RESULTS:** Sixteen patients were analyzed: 7 to omalizumab and 9 to placebo (mean age 47.7 ± 13.8 vs. 45.4 ± 8.8 years; 66.6 vs. 85.7% were female; mean disease duration 10.0 ± 5.1 vs. 4.5 ± 2.9 years, respectively). After 6 months the median AFIRMM score decreased 50% from 52.0 to 26.0 in the omalizumab group versus 104.0-102.0 in the placebo group ($p = 0.286$); however, the difference was not significant ($p = 0.941$). Secondary endpoints, including the number of allergic reactions, changes in major complaints, wheal-and-flare reaction due to mechanical irritation (Darier's sign), and frequency of the use of mastocytosis-specific drugs improved in the omalizumab group, but not significantly. Adverse events like urticaria, bronchospasm, and anaphylactic shock showed no significant difference between the groups. No severe adverse events occurred. Fc RI (Fc-epsilon receptor) expression on basophils decreased after receiving omalizumab versus placebo. **CONCLUSION:** Omalizumab was safe and showed a tendency to improve mastocytosis-related symptoms, in particular diarrhea, dizziness, flush, and anaphylactic reactions, including the AFIRMM score and secondary endpoints; however, the difference was not significant. Due to the small study size and difference at baseline between the study groups, further studies are required to confirm our findings.

DOI: <https://doi.org/10.1159/000504842>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://www.zora.uzh.ch/184368>

Journal Article

Published Version

Originally published at:

Distler, Meike; Maul, Julia-Tatjana; Steiner, Urs C; Jandus, Peter; Kolios, Antonios G A; Murer, Carla; Graf, Nicole; Seebach, Jörg D; Pichler, Werner J; Navarini, Alexander A; French, Lars E; Helbling, Arthur;

Schmid-Grendelmeier, Peter (2020). Efficacy of omalizumab in mastocytosis: allusive indication obtained from a prospective, double-blind, multicenter study (XOLMA Study). *Dermatology*, 236(6):529-539.
DOI: <https://doi.org/10.1159/000504842>

Efficacy of Omalizumab in Mastocytosis: Allusive Indication Obtained from a Prospective, Double-Blind, Multicenter Study (XOLMA Study)

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Keywords

Mastocytosis · Omalizumab · Therapy · Clinical trial

Abstract

Background: Patients with mastocytosis often suffer from a variety of symptoms caused by mast cell mediators where treatments remain difficult, showing various success rates. Omalizumab, a monoclonal anti-IgE antibody, has been postulated to have a positive impact on mastocytosis-associated symptoms such as flush, vertigo, gastrointestinal problems, or anaphylaxis. **Objective:** To investigate the efficacy and safety of omalizumab in systemic mastocytosis. **Methods:** Patients with histologically proven mastocytosis were investigated in a multicenter prospective double-blind placebo-controlled trial to receive either omalizumab or placebo, dosed according to IgE and body weight. The primary endpoint was change in the AFIRMM activity score after 6

months of treatment. Different laboratory parameters were analyzed. **Results:** Sixteen patients were analyzed: 7 to omalizumab and 9 to placebo (mean age 47.7 ± 13.8 vs. 45.4 ± 8.8 years; 66.6 vs. 85.7% were female; mean disease duration 10.0 ± 5.1 vs. 4.5 ± 2.9 years, respectively). After 6 months the median AFIRMM score decreased 50% from 52.0 to 26.0 in the omalizumab group versus 104.0–102.0 in the placebo group ($p = 0.286$); however, the difference was not significant ($p = 0.941$). Secondary endpoints, including the number of allergic reactions, changes in major complaints, wheal-and-flare reaction due to mechanical irritation (Darier's sign), and frequency of the use of mastocytosis-specific drugs improved in the omalizumab group, but not significantly. Adverse events like urticaria, bronchospasm, and anaphylactic shock showed no significant difference between the groups.

M.D. and J.-T.M. co-shared first authorship.

No severe adverse events occurred. FcεRI (Fc-epsilon receptor) expression on basophils decreased after receiving omalizumab versus placebo. **Conclusion:** Omalizumab was safe and showed a tendency to improve mastocytosis-related symptoms, in particular diarrhea, dizziness, flush, and anaphylactic reactions, including the AFIRMM score and secondary endpoints; however, the difference was not significant. Due to the small study size and difference at baseline between the study groups, further studies are required to confirm our findings.

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Introduction

Mastocytosis is a rare disease with a prevalence of 1/10,000 and often associated with symptoms that severely impair the quality of life of affected patients [1]. In addition, potentially life-threatening anaphylaxis occurs in as many as 30–49% of patients with mastocytosis representing an approximately 1,000-fold increase compared with the general population [2]. The disease is characterized by an accumulation of mastocytes in various organs, most commonly in the skin, bone marrow, and gastrointestinal tract [3–5]. Several forms can be distinguished, mainly cutaneous mastocytosis, where mast cell proliferation is limited to the skin, and systemic forms with involvement of the bone marrow and other organs.

Disease symptoms are caused by the release of mast cell mediators leading to nausea, fatigue, wheals, abdominal cramps, diarrhea, or hypotension. These patients also have an increased frequency of anaphylactic/anaphylactoid reactions due to allergens such as Hymenoptera or nonspecific stimuli such as contrast media, local anesthetics, or analgesics which may be life-threatening [2, 6].

The trigger for mast cell activation may be allergic and therefore IgE dependent (food, medication, Hymenoptera venom, or aeroallergens). Mast cell activation can also be induced by IgE-independent drug reactions, alcohol, physical factors (trauma, friction, or extreme temperatures), stress, venom, and acute or chronic infections. The discovery of the MRGPRX2 receptor on mast cells has shown that mast cells are capable of IgE-independent pathways of activation by different substances [7].

Symptoms of mastocytosis respond to treatment with antihistamines, glucocorticoids, or mast cell stabilizers, but often this treatment is insufficient or cannot be given permanently because of side effects. In patients with rapidly progressive systemic mastocytosis, aggressive mastocytosis, and mast cell leukemia, tyrosine kinase inhibitors

are a therapeutic alternative and there are ongoing clinical studies addressing the subject. But these therapies reveal a lot of side effects and are in general not a treatment option for patients with indolent systemic or cutaneous mastocytosis [8–10].

Several case reports and small observational studies suggest that omalizumab might decrease symptoms including mastocytosis-associated anaphylaxis. Omalizumab has already been used successfully in long-term therapy of mastocytosis-associated anaphylaxis [11–17].

Omalizumab is a therapeutic monoclonal anti-IgE antibody, approved for treatment of allergic asthma and chronic spontaneous urticaria. In asthma the onset of clinical efficacy of omalizumab is considered to take place about 4 months after the start of treatment. The suggested onset of action of omalizumab in other conditions such as urticaria has been described as within 8 weeks or 1–2 weeks, respectively [18].

The aim of this study was to investigate in a prospective double-blind, randomized placebo-controlled multicenter trial whether patients suffering from mastocytosis benefit from a 6-month course of omalizumab regarding symptoms and quality of life.

Methods

For further details, see the online supplementary Material (see www.karger.com/doi/10.1159/000504842 for all online suppl. material,) [19, 20] (Fig. 1).

Results

Study Population

A total of 63 patients were pre-screened for this trial. Of these, 17 patients fulfilled the inclusion criteria and were enrolled at the 3 study centers: Zurich (ZH) ($n = 9$), Geneva (GE) ($n = 4$), and Berne (BE) ($n = 4$). Major reasons for the rejection to participate were fear of getting placebo and difficulties in attending the visits. Eleven patients suffered from indolent systemic mastocytosis, confirmed by bone marrow biopsy – 3 patients from cutaneous mastocytosis without sign of bone marrow involvement in the bone marrow biopsy. In 3 patients only a skin biopsy was done to confirm the diagnosis of cutaneous mastocytosis and a systemic mastocytosis was not excluded. Two patients suffered from gastrointestinal mastocytosis with corresponding histology (in some cases multiple instances) (Table 1).

The age distribution was the same in both groups (mean age 47.7 ± 13.8 years in the verum group vs. $45.4 \pm$

Fig. 1. Flowchart of Methods: study enrolment. Patient inclusion and exclusion flow diagram of the XOLMA trial. Analyzing placebo versus verum (omalizumab) in patients with mastocytosis.

8.8 years in the placebo group; 66.6 vs. 85.7% were female, respectively). Similarly, a slight but not significant difference in the duration of the disease was seen in both groups (verum 10.0 ± 5.1 years vs. placebo 4.5 ± 2.9 years). There was no difference between the groups regarding disease manifestation (systemic vs. cutaneous mastocytosis) and tryptase level (Table 1).

Randomization was based on study site and blog vise after the sequence of inclusion into the study. Unfortunately, due to withdrawal of some patients after the randomization an imbalance in the groups appeared.

Of the 17 patients included, 1 patient discontinued the study after the screening visit without stating reasons. Two other patients discontinued the study after random-

ization, but prior to any study medication, one because he did not want to risk placebo therapy because of his symptoms, and the other gave no reasons for discontinuation. After the start of the therapy, 2 other patients discontinued the study without giving reasons. Twelve patients completed the study (Fig. 1).

Of the 14 patients receiving medication, 12 patients received 150 mg of the study medication (5 verum, 7 placebo) every 4 weeks and 2 patients received 300 mg (1 verum, 1 placebo) every 4 weeks.

Clinical Efficacy

The primary endpoint of the study was the change in the AFIRMM score between baseline at randomization

Fig. 2. Change of mastocytosis symptoms. **a** AFIRMM score measured at all visits (V1 to V11) for the placebo group ($n = 8$) and the omalizumab group ($n = 6$) in the XOLMA trial. **b** Change of asthenia from visit 1 to 8. **c** Change of diarrhea from visit 1 to 8. **d** Change of gastrointestinal track complaints from visit 1 to 8. **e** Change of allergy/flush/shock from visit 1 to 8. **f** Change of pruritus using the VAS from visit 1 to 8. Numerically, a difference was seen in mastocytosis symptoms; however, no significant difference was shown between omalizumab and placebo.

(Figure continued on next page.)

(visit 1 [V1], month 0) and the end of treatment (visit 8 [V8], month 6), to assess the efficacy of omalizumab in mastocytosis (Fig. 2a).

Because of the low number of patients and the difference in the initial AFIRMM score between the placebo and verum groups, the relative difference with respect to

V1 was also investigated in addition to the absolute difference in the AFIRMM score at V8.

Primary Endpoint

For the intention-to-treat analysis, 16 patients were included. The median AFIRMM score at V1 (month 0, run-

2

in period) was 104.0 and 52.0 for the placebo ($n = 9$) and omalizumab groups ($n = 7$), respectively. Thus, the AFIRMM score was different between the placebo and omalizumab groups already at V1, though not significantly ($p = 0.077$). At V8, the median AFIRMM score was 102.0 and 26.0 for the placebo and omalizumab groups, respectively ($p = 0.286$). The AFIRMM score was thus reduced in both treatment groups, that is, by a median of 8 score points in the placebo group and 6 score points in the omalizumab group (Table 2).

The reduction was not statistically significantly different in the treatment groups ($p = 0.941$). For the per protocol analysis, 12 patients were included (Table 3). The median AFIRMM score at V1 was 102.0 ($n = 7$) and 32.0 ($n = 5$) for the placebo and omalizumab groups, respectively. Thus, the AFIRMM score was significantly different between the placebo and omalizumab groups already at V1 ($p = 0.035$). At V8, the median AFIRMM score was 84.0 and 22.0 for the placebo ($n = 7$) and omalizumab groups ($n = 5$), respectively ($p = 0.048$). The AFIRMM

Table 1. Demographics of the XOLMA trial

Patient	Age at baseline, years	Gender	Disease duration until start of study, years	Year of initial diagnosis	Disease manifestation	Tryptase at baseline, µg/L	IgE at baseline, kU/L
ZH-1	45	Male	10	2006	ISM	37.6	4
ZH-2	49	Male	6	2006	MIS	14.8	5
ZH-3	67	Female	4	2007	ISM	20.8	5
ZH-4	30	Female	3	2010	ISM	52.7	10
ZH-5	38	Male	2	2012	CM	23.7	24
ZH-6	53	Female	13	2006	CM	9.11	21
ZH-7	28	Female	8	2004	MIS	24.2	3
ZH-8	47	Female	18	2010	ISM	3.9	7
ZH-9	47	Female	7	2007	MIS	15.2	10
BE-1	36	Female	10	2003	ISM	n.a.	102
BE-2	48	Female	NA	2005	ISM	70.4	17
BE-3	57	Female	2	2012	ISM	32.2	NA
BE-4	52	Female	9	2014	ISM	30.4	5
GE-1	24	Female	1	2012	ISM	18.5	2
GE-2	63	Female	10	2003	CM	26.8	16
GE-3	36	Female	3	2010	ISM	n.a.	5
GE-4	48	Male	NA	2013	ISM	54.4	36

ISM, indolent systemic mastocytosis; CM, cutaneous mastocytosis (systemic mastocytosis excluded by bone marrow investigation); MIS, mastocytosis in the skin (cutaneous mastocytosis without bone marrow investigation).

Table 2. Primary endpoint: difference in AFIRMM score between visit 1 and 8 in the clinical trial population (placebo vs. omalizumab)

Group	N	AFIRMM V1, median	AFIRMM V8, median	Reduction AFIRMM, median	<i>p</i> value
Placebo	9	104.0	102.0	−8.0	
Omalizumab	7	52.0	26.0	−6.0	
All	16				0.941

Intention-to-treat analysis. V1, visit 1; V8, visit 8.

score was thus reduced in both treatment groups, that is, by a median of 18 score points in the placebo group and 12 score points in the omalizumab group. The amount of absolute reduction was not significantly different between the treatment groups ($p = 0.912$). The amount of relative reduction was also not significantly different between the treatment groups ($p = 0.432$); however, it was twice as large in the omalizumab as in the placebo group (Table 4).

Secondary Endpoints

Secondary endpoints were the changes in the AFIRMM score at the end of the study, the number of allergic/anaphylactic reactions, changes in visual analog scale (VAS)

for major complaints and itching, changes in wheal-and-flare reaction, and the use of mastocytosis-specific drugs such as antihistamines or cromoglycates. Adverse events were also documented as safety endpoints, especially allergic events such as urticaria, bronchospasm, anaphylactic shock, and local reactions.

AFIRMM Score at Follow-Up

The absolute difference of the AFIRMM score between V1 (month 0, run-in period) and V9/V11 (month 7/12) was also computed and compared between the treatment groups. At V9, the median difference with respect to V1 was increased by 16 score points for the placebo group, but decreased by 10 score points for the omalizumab

Table 3. Primary endpoint: absolute difference in AFIRMM score between visit 1 and 8 in the XOLMA population

Group	N	AFIRMM V1, median	AFIRMM V8, median	Absolute reduction AFIRMM, median	p value
Placebo	7	102.0	84.0	–18.0	
Omalizumab	5	32.0	22.0	–12.0	
All	12				0.912
Per protocol analysis.					

Table 4. Primary endpoint: relative difference in percent AFIRMM score between visit 1 and 8 in the XOLMA population

Group	N	AFIRMM V1, median	AFIRMM V8, median	Relative reduction AFIRMM, median	p value
Placebo	7	102.0	84.0	–17.6	
Omalizumab	5	32.0	22.0	–37.5	
All	12				0.432
V1, visit 1; V8, visit 8.					

group ($p = 0.322$). At V11, the median difference with respect to V1 was decreased by 15 score points for both the placebo and the omalizumab group ($p = 0.610$).

Hermine et al. [20] assumed the mean AFIRMM score to be 117 in mastocytosis patients. This assumption was clearly not met, especially within the omalizumab group. As patients from the placebo and the omalizumab group were already different at V1, it cannot be ruled out that patients in the omalizumab group did not show a greater decrease in the affirm score because they started at a lower level.

Changes in VAS for Single Main Complaints

Three patients in the omalizumab group and 5 patients in the placebo group indicated asthenia as the main complaint. The course of the daily VAS score for asthenia, which has been summarized per month, is shown in Figure 2b. Three patients in the omalizumab group and 4 patients in the placebo group indicated diarrhea as the main complaint. The course of the daily VAS score, which has been summarized per month, is shown in Figure 2c.

Four patients in the omalizumab group and 6 patients in the placebo group had a total of 6 and 7 complaints, respectively, from the gastrointestinal tract complaints of the AFIRMM score (aerophagia, nausea, epigastric pain, diarrhea, pseudo-occlusive syndrome) as main complaints. The course of the daily VAS score, which has been summarized per month, is shown in Figure 2d.

Three patients in the omalizumab group and 3 patients in the placebo group had a total of 5 and 3 complaints, respectively, from the allergy/flush complaints of the AFIRMM score (food allergy, drug allergy, olfactory intolerance, anaphylaxis, flush) as main complaints. The course of the daily VAS score, which has been summated per month, is shown in Figure 2e.

The changes for pruritus between V1 and V8 are shown in Figure 2f. The median slope was 3.6 in the placebo group and –3.1 in the omalizumab group. This difference was not statistically significant ($p = 0.317$).

Mast Cell-Specific Drugs

Since only 1 patient from the omalizumab group and 4 patients from the placebo group used mast cell-specific drugs, a more detailed analysis was not possible due to the low number of patients.

Laboratory Markers

Of the IgE values determined at the beginning of the study, only in 1 patient was the total IgE >100 kU/L. The tryptase values were between 3.94 and 70.4 µg/L. Tryptase values remained unaltered for all patients for whom values were present, even after therapy with omalizumab.

FcεRI (Fc-epsilon receptor) expression showed a clear reduction in patients with omalizumab but was unchanged in patients with placebo (Fig. 3).

Fig. 3. **a** FcεRI expression (mean receptor density per cell) in patients treated with omalizumab measured at visits 1, 3, 7, and 9 during the clinical trial. **b** FcεRI expression (mean receptor density per cell) in patients treated with placebo measured at visits 1, 3, 7, and 9 during the clinical trial.

Adverse Events

Of a total of 100 occurring adverse events, 59 were found in the placebo group and 41 in the verum group. Ninety-one events were rated as mild and 9 as moderate (7 in the placebo group and 2 in the verum group). No severe adverse events occurred. An association with the study medication was considered as possible in a total of 9 patients (5 in the placebo group and 4 in the omalizumab group); all these events were classified as mild. All adverse events are listed in detail in the online supplementary Appendix.

There were 4 adverse events like urticaria, bronchospasm, anaphylactic shock, and local reactions which are known to be associated with the study drug; 3 patients from the placebo group reported flushing and dizziness or muscle pain in the shoulder, flatulence or stomach

cramps, and limb aches, respectively, after the injection of the study drug, and 1 patient in the omalizumab group reported headache and pain at the injection site after administration of the study drug. There was no difference between the 2 groups ($p = 0.702$).

Discussion

To our knowledge, this is the first randomized, placebo-controlled study of omalizumab in mastocytosis. To date, only small open studies and case reports reported an effect of omalizumab in mastocytosis, especially for anaphylaxis [11–14]. Unfortunately, we were able to include significantly fewer patients than originally planned; thus,

our study has more the ability to detect trends than to reach significant changes in the 2 groups due to the small sample size.

An improvement in the AFIRMM score between V1 and V8 was seen as the primary endpoint and target parameter for the efficacy of omalizumab. The AFIRMM score represents the only published score in the literature to assess the severity of the disease in mastocytosis at the time of the study start [19, 20]. However, this score is very comprehensive and time-consuming as it includes a total of 38 items of potential symptoms in mastocytosis. One can consider that in some patients the AFIRMM score was not sensitive enough to detect smaller changes in the complaints. To simplify assessments, Broesby-Olsen et al. [14] used a physician global assessment symptom score for their cohort of 14 patients that focused on 5 symptom categories [6], and Siebenhaar et al. [21] developed a mastocytosis activity score with only 3 domains (skin, gastrointestinal tract, and others). These simplified and alternative approaches could have enhanced differences between the study groups.

After 6 months of therapy with omalizumab, the per protocol analysis in the omalizumab group showed a twice as high reduction in the AFIRMM score than in the placebo group. However, the low number of patients included did not allow to reach differences that were at a significant level, even more so as it must be considered that the baseline values differed significantly in both groups.

Thus, a tendency to improve mastocytosis symptoms was observed in the omalizumab treatment group, which corresponds to the effect described in the literature. The effect did not reach statistical significance, but this is most probably mainly due to the very low number of patients in this study who also showed a low disease severity [14].

The effect of omalizumab at the secondary endpoints was similar. The comparison of AFIRMM scores from baseline to follow-up showed large variations in the placebo group. In contrast, in the omalizumab group both the early follow-up (1 month after administration of the last study drug) and the late follow-up (4 months after administration of the last study drug) values showed an improvement of the AFIRMM scores. Differences were again not statistically significant.

Observational studies and case reports report a positive effect of omalizumab on the incidence of anaphylaxis [11, 13, 20]. This effect was not confirmed in the present study because allergic or anaphylactic reactions occurred only twice in the small patient population, so that a more accurate analysis between the 2 treatment groups was not pos-

sible. The low number of anaphylactic reactions again indicates that less severely affected patients were included in this study than in comparable studies. To study this potential effect more closely, larger studies would be necessary.

Similarly, it was not possible to compare the use of mast cell-specific drugs in both groups, since only a few patients were using them – again confirming that the study included mainly less affected patients.

Looking at the course of the individual main complaints indicated by the patients by using an analog scale, there was a slightly different pattern for the main complaint “diarrhea” in 3 patients with omalizumab and 4 patients with placebo. While the symptoms decreased with omalizumab, one saw very strong fluctuations in the placebo group. However, the significance of these values is again only very limited since only a few patient data are available. This observation corresponds to reports in the literature, which also indicate an amelioration of gastrointestinal complaints [11, 13].

For the main complaint asthenia, which was also often mentioned by our patients, the picture between the verum and the placebo group is more heterogeneous, but here also only a few patients could be included.

On the other hand, there was no effect of omalizumab on the main complaint “pruritus,” which was recorded in all patients.

In order to make further statements about the main complaints, the gastrointestinal symptoms reported by the patients as single main complaints, as well as the complaints from the area of allergy/flush as mentioned above, were summarized according to the grouping in the AFIRMM score and compared between the omalizumab and the verum group.

For the summarized gastrointestinal complaints, a total of 6 complaints in the verum and 11 complaints from the placebo group were observed. A similar picture was found for diarrhea alone with a decrease in the verum group and a very heterogeneous picture in the placebo group, but again without a significant difference. A corresponding picture was obtained in the summarized complaints from the allergy/flush group. Although there is a tendency for omalizumab to be effective in these complaints, larger studies are necessary to allow more accurate conclusions.

In terms of laboratory results, no correlation between total IgE and response to omalizumab could be investigated. However, this may be due to the fact that only 1 patient had a highly positive IgE (102 kU/L), whereas it was not over 36 kU/L in the other patients. Tryptase values seemed to remain unchanged during the course.

There was a clear decrease in FcεRI expression after omalizumab treatment. However, a correlation with clinical response to omalizumab could not be proven with certainty due to the low number of cases and the limited meaningfulness of the AFIRMM score in this study.

There was no significant difference between the verum and placebo groups regarding adverse events. Adverse events were mostly classified as mild, rarely as moderate, and for the most part unrelated to study medication. Omalizumab was generally very well tolerated. Adverse events, which were considered to be associated with the administration of the study drug, were hypertension in a patient with known arterial hypertension and hypercholesterolemia, and injection site reactions and slight general symptoms in another patient. This study in mastocytosis thus confirms the good tolerability of omalizumab already described for use in allergic asthma.

Our study has several limitations. First, all results of this study can only be evaluated to a limited extent due to the low number of patients. The small number of patients (5 verum/7 placebo group) resulted from the recruitment, which was complicated by the fact that many of the 67 pre-screened mastocytosis patients had too few complaints to participate in the study, whereas patients with too severe symptoms rejected study participation because of their concerns of being assigned to the placebo group. To account for the latter, we suggest a cross-over design for a future protocol in order to provide all study patients with the verum. Frequent study visits and/or duration of the study were other reasons not to participate. Therefore, the value of the study results is only limited.

Omalizumab is meanwhile approved for the treatment of urticaria in a dosage of 300 mg every 28 days. Perhaps this dosage would have shown more pronounced effects in this study. However, at the time of the study design and start of study, the results of the studies on the therapy of urticaria with omalizumab were not yet available, so that the dosages were adjusted to the recommendations for the treatment of bronchial asthma.

In conclusion, according to the collected data, some of the investigated parameters showed a tendency to improve the mastocytosis complaints under omalizumab. This was particularly true for the main complaints individually indicated by the patients, especially gastrointestinal complaints and complaints like drug or food allergy or flush. A similar tendency was also shown for the summarized complaints in the relative AFIRMM score. These effects are in line with the effects of omalizumab in mastocytosis described in the literature and confirm the beneficial effect seen in other studies regarding the use of omalizumab in mastocytosis.

Unfortunately, the observed effects were not significant, which was mainly due to the low number of patients resulting from the difficult recruitment. However, the tendency for improvement, especially for gastrointestinal complaints, observed in this study indicates that the effect of omalizumab in mastocytosis is not only limited to diminishing allergic reactions. Therefore, further studies would be useful in order to verify these effects in a larger patient cohort.

Presumably due to the low number of participants, and possibly due to the fact that less severely affected patients were included, the effect of omalizumab on anaphylaxis in mastocytosis patients described in the literature could unfortunately not be further explored in this study. Again, larger studies would be necessary to investigate this effect.

Conclusion

Treatment of mastocytosis involves control of symptoms by blocking the action of mast cell mediators. Although several new therapeutic strategies seem promising, including tyrosine kinase inhibitors for more severe forms of disease by targeting mast cell growth and its development, therapy remains difficult, especially for patients with mainly allergic symptoms. In view of the heterogeneous nature of disease manifestations, the therapy should be individually adapted to each patient's clinical presentation and prognosis. The role of omalizumab in an individualized treatment approach has yet to be determined, but seems to be beneficial from the results of our trial and also those of other small studies. Our results showed an improvement in mainly allergic symptoms, which should be confirmed by further studies with larger patient collectives.

Key Message

Omalizumab seems to have positive effects on mastocytosis symptoms in this clinical trial.

Acknowledgments

We thank all the patients who contributed to the clinical trial, without whom this research would not have been possible. We especially acknowledge the substantial contribution of the coordinating team and finally the enthusiastic collaboration of all the dermatologists and specialist nurses.

Statement of Ethics

This study was approved by the local Ethic Committee (Kantonale Ethikkommission Zurich, No. 829) and was conducted according to the Declaration of Helsinki. Patients who were enrolled in this study signed a consent form containing all explanations regarding participation in this study.

Disclosure Statement

M.D., U.C.S., C.M., N.G., and A.H. report no conflicts of interests. J.-T.M. is an employee of USZ and holds a “Filling the GAP” scholarship. P.J. received honoraria for consulting and advisory board attendance from Astra-Zeneca, GlaxoSmithKline, Biotest, and Shire, and received research support from CSL-Behring and Shire. A.G.A.K. has served as an investigator, speaker, and/or advisor for AbbVie, Abbott, Janssen, Eli Lilly, MSD, Pfizer, Celgene, Novartis, Actelion, Leo, Amgen, and Alk-Abello and does not hold any shares or other financial interest in any related pharmaceutical company. J.D.S. received an unconditional research grant from CSL Behring. W.J.P. is employed by ADR-AC GmbH and has received consultancy fees from ViiV/gsk, Hoffmann-La Roche, Galapagos, Teleflex, and Alnylam. A.A.N. is funded by the Promedica and Bruno-Bloch Foundation, as well as Hochspezialisierte Medizin 2 of the Kanton Zürich, Switzerland. He is also on the advisory board of AbbVie, Pfizer, Novartis, Celgene, MSD, Galderma. L.E.F. has received honoraria for consult-

ing and advisory board attendance from AbbVie, Amgen, Celgene, Eli Lilly, Galderma, Janssen, Leo, Novartis, and Pfizer. P.S.-G. has received honoraria for consulting and advisory board attendance from AbbVie, Abionics, Allergopharma, ALK-Abello, AstraZeneca, Bemcard, CSL Shering, GSK, Lilly, Menarini, Novartis, Nestlé, Leo, Roche-Posay, Sanofi, Shire, Stallergenes, and Thermo Fisher.

Funding Sources

This independent clinical trial was funded by Novartis Switzerland with no veto rights of Novartis Switzerland or rights to access the manuscript before submission.

Author Contributions

M.D.: study design, patient interviews, physical examination, data collection, and writing of the manuscript. J.-T.M.: data collection, patient interviews, physical examination, and writing of the manuscript. U.C.S., P.J., and A.G.A.K.: patient interviews, physical examination, data collection, and revising of the manuscript. C.M.: patient interviews. N.G.: statistical analysis and revising of the manuscript. J.D.S., W.P., A.A.N., L.E.F., and A.H.: study design and revising of the manuscript. P.S.: study design and writing of the manuscript.

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