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## **Omalizumab Therapy for Mast Cell-Mediator Symptoms in Patients with ISM, CM, MMAS, and MCAS**

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

3  
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42  
43 **Running title:** Omalizumab in systemic mastocytosis

44 **Abstract:** 249 words – **Manuscript:** 3662 words – **Figures:** 2 – **Supplemental Figures:** 5 – **Tables:** 2  
45 – **References:** 33

47 **Abbreviations**

48 CEREMAST: French National Reference Center for Mastocytosis

49 CM: cutaneous mastocytosis

50 CR: complete response

51 IgE: immunoglobulin E

52 ISM: indolent systemic mastocytosis

53 MCA: mast cell activation

54 MCAS: Mast Cell Activation Syndrome

55 MMAS: Monoclonal MCAS

56 MR: major response

57 PR: partial response

58 SM: systemic mastocytosis

59 SM-AHN: systemic mastocytosis with associated hematologic neoplasm

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

61

62

63 **Highlights boxes**

64 1. What is already known about this topic?

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

68

69 2. What does this article add to our knowledge?

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

73

74 3. How does this study impact current management guidelines?

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

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84

85 **Abstract**

86  
87 **Background.** Patients with mast cell diseases may suffer from various distressing symptoms, which  
88 can be insufficiently controlled with available therapies, severely affecting their quality of life. There is  
89 a need for new and safe treatment options for these patients.

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

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

96 **Results.** A complete response was achieved for 1 patient (1.8%), a major response for 30 patients  
97 (54.5%) and a partial response for 12 patients (21.8%), resulting in an overall best response rate of  
98 78.2% (43/55 patients). The response was persistent at least 3 months in 33/43 (76.7%) responding  
99 patients. At last follow-up, the final overall response rate was 58.2% (32/55 patients). Median time to  
100 first response was 2 months and median time to best response was 6 months. Omalizumab was  
101 dramatically effective on all superficial and general vasomotor symptoms and on most gastrointestinal  
102 or urinary symptoms, and partially effective on most neuropsychiatric symptoms. Safety profile was  
103 acceptable, except for one severe adverse event (edema of the larynx and dyspnea after the first  
104 injection of omalizumab). Side effects were reported in 16 patients (28.6%), mainly of low to mild  
105 intensity, yet causing interruption of treatment in 6 patients (10.7%).

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

108

109 **Introduction**

110 Mast cells are effector cells involved in allergic and inflammatory reactions (1-3). They derive from  
111 myeloid stem cells, then migrate in tissues and organs (1). Mast cells are a well-known source for  
112 many proinflammatory mediators (such as histamine, tryptase, prostaglandin D<sub>2</sub>, platelet-activating  
113 factor, leukotrienes, various cytokines and chemokines) and express the high-affinity IgE receptor  
114 FcεRI (1-3). Once activated by an allergen that aggregates IgE and FcεRI complexes, or by non-IgE  
115 related stimuli, mast cells self-activate and release their mediators, which can cause many local and  
116 systemic symptoms.

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

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

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

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

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

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

154

## 155 **Methods**

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

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

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

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

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

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

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

- 202 • 1.5: Worsening of the symptom.
- 203 • 1: No change.
- 204 • 0.75: Slight improvement.
- 205 • 0.5: Substantial improvement.
- 206 • 0.25: Dramatic improvement.
- 207 • 0: Complete disappearance of the symptom.

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

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

214 50% of preexisting symptoms, according to symptom score. Absence of response was defined as a  
215 decrease of less than 10% of preexisting symptoms, according to symptom score, or worsening of  
216 preexisting symptoms or apparition of new symptoms.

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

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

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

227

## 228 **Results**

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

232 The diagnoses were: indolent systemic mastocytosis (ISM; 29 patients, 52.7%), mast cell activation  
233 syndrome (MCAS; 15 patients, 27.3%) and cutaneous mastocytosis (CM; 11 patients, 20%). Forty-  
234 nine patients/55 were evaluated for *KIT* mutation; *KIT* D816V mutation was found in 27/49 patients  
235 (55.1%): 23/28 (82.1%) patients with ISM, 3/9 (33.3%) patients with CM and 1/12(8.3%) patient with  
236 MCAS.

237 A large majority of these patients already received all classical therapies against symptoms related to  
238 mast cell activation, including antihistamines, cromolyn sodium or leukotriene inhibitors. 45/55 patients  
239 (82%) continued at least one of the classical therapies that they were receiving before initiation of  
240 omalizumab. Some patients already received multiple tyrosine kinase inhibitors, immunomodulatory or  
241 cytoreductive treatments. Patients' characteristics at inclusion, including previous treatments, are  
242 detailed in Table 1.

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

246 The overall response rate was 82.9% among the 41 patients with primary MCAS, and 68.7 among the  
247 14 patients with idiopathic MCAS. Detailed response rates are presented in Table 2.

248 **Time to first response and duration of response.**



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

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

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

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

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

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

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

271 **Dose modifications.** In 15/55 patients (27.3%), a dose escalation was prescribed in order to try to  
272 improve symptom control with omalizumab, according to CEREMAST initial recommendations (up to  
273 300 mg every 15 days for 14 patients, and up to 600 mg every 15 days for 1 patient, which was not a  
274 recommended schedule and without objective measures to substantiate efficacy). Among these 15  
275 patients, 14 patients (93%) improved their response, with 6 patients (40%) reaching a MR and 8  
276 patients (53.3%) improving their PR.

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

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

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

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

293 **Safety.** Overall, safety profile was acceptable. Sixteen patients (29%) presented side effects, among  
294 whom 6 patients interrupted omalizumab therapy because of these side effects. One patient (1.8%)  
295 developed a severe adverse event with edema of the larynx and dyspnea 30 minutes after the first  
296 injection of omalizumab. Symptoms were controlled after corticosteroids, antihistamine and  $\beta$ 2  
297 mimetics therapy, but persisted moderately around 3 weeks according to the patient. Three patients  
298 (5.5%) presented a significant “flare” effect with accentuation of their symptoms on therapy, requiring  
299 omalizumab discontinuation. Other side effects included: fatigue (3 patients), fever (3 patients),  
300 headache (2 patients), malaise (2 patients), nausea (2 patients), abdominal pain (2 patients), bleeding  
301 (increased menstruations and epistaxis for 1 patient, ecchymosis for 1 patient) pruritus (1 patient),  
302 local rash (1 patient), sweating (1 patient).

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

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

309 We observed an increase in total IgE levels on therapy, with a mean value of 235.1 UI/mL [3.5 – 1616]  
310 before omalizumab and 772.8 UI/mL [6.6 – 4356] on therapy. Among the 15 tested patients, 11  
311 (73,3%) presented an increase of total IgE level while the 4 remaining patients (26,7%) presented  
312 stable total IgE levels. The evolution of total IgE levels was not correlated with treatment efficacy or  
313 tolerance in this small tested sub-group of patients.

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

315

## 316 **Discussion**

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

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

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

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

333 In our study, omalizumab's efficacy was rapidly observed with a median time to first response of 2  
334 months and a median time to best response of 6 months. Time to response nevertheless ranged from  
335 1 to 10 months, depending on the patient and on the symptom considered. Consistently with available  
336 data, the most rapid effect of omalizumab was observed on general vasomotor symptoms, including  
337 anaphylaxis. We also observed persistent responses, with an ongoing maximum duration of 36  
338 months at last follow-up. Only 4 patients lost their response, after 2 to 13 months of treatment.

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

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

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

357 not cytoreductive. We observed an increase in total IgE levels in 11 patients among the 15 tested  
358 patients. This effect might be due to stabilization of total IgE (which includes free and omalizumab-  
359 bound fractions), as previously reported in allergy patients (25) and in chronic spontaneous urticaria  
360 (26). Total IgE levels did not seem to correlate to clinical efficacy nor tolerance in our series. In allergic  
361 diseases already routinely treated with omalizumab, a reduction of inflammatory mediator release by  
362 omalizumab requires a 95% reduction in serum free IgE levels to modify allergen responses via  
363 receptor downregulation (25, 27, 28). Therefore, in allergic asthma, doses of omalizumab are adapted  
364 to serum total free IgE level and body weight to achieve this reduction in free IgE (29, 30). In  
365 symptomatic chronic idiopathic/spontaneous urticaria, which is not a classic allergen-driven disease,  
366 dose of omalizumab is fixed and measurement of total or free IgE level under therapy is not necessary  
367 (9, 24, 31, 32). Omalizumab's mechanism of action in symptomatic chronic idiopathic/spontaneous  
368 urticaria is however not entirely understood (26, 33). Further studies remain necessary to better  
369 understand how omalizumab therapy results in improvement of mast cell disorders symptoms, and  
370 whether and how free or total IgE levels are correlated with clinical efficacy.

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

385

#### 386 **Author contributions**

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

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

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

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

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

392

**Table 1. Patients' characteristics.**

		<b>N = 55</b>
<b>General characteristics</b>		
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
<b>Disease classification in the whole cohort</b>		
<b>Primary MCAS (N=41)</b>	<b>Indolent Systemic Mastocytosis (ISM), N (%)</b>	29 (52.7)
	- <i>KIT</i> D816V mutation positive, N	23
	- <i>KIT</i> D816V mutation negative, N	5
	- <i>KIT</i> D816V mutation not evaluated	1
	<b>Cutaneous Mastocytosis (CM), N (%)</b>	11 (20)
	- <i>KIT</i> D816V mutation positive, N	3
- <i>KIT</i> D816V mutation negative, N	6	
- <i>KIT</i> D816V mutation not evaluated	2	
<b>Idiopathic MCAS (N=14)</b>	<b>Mast Cell Activation Syndrome (MCAS), N (%)</b>	15 (27.3)
	- <i>KIT</i> D816V mutation positive (=MMAS), N	1
	- <i>KIT</i> D816V mutation negative, N	11
	- <i>KIT</i> D816V mutation not evaluated	3
<b>WHO 2016 criteria</b>		
Multifocal dense infiltrates of MCs ( $\geq 15$ 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%)
<i>KIT</i> 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%)
<b>Disease presentation</b>		
Involved skin, N (%)		35 (63.6)
	Maculopapular cutaneous mastocytosis, N (%)	31 (56.4)
	Histological criteria, N (%)	28 (50.9)
	<i>KIT</i> 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)
<b>Tryptase and total IgE levels at diagnosis (N=15)</b>	
Tryptase (ng/mL), mean (range)	30.1 (2.5 – 145)
Total IgE (UI/mL), mean (range)	151.2 (2 – 1616)
<b>Previous lines of therapy</b>	
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						
<b>ORR, N (%)</b>	<b>43 (78.2)</b>	<b>34 (82.9)</b>	<b>23 (79.3)</b>	<b>10 (90.9)</b>	<b>1 (100)</b>	<b>9 (64.3)</b>
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						
<b>Persistent ORR, N (%)</b>	<b>32 (58.2)</b>	<b>25 (61)</b>	<b>17 (58.6)</b>	<b>7 (63.6)</b>	<b>1 (100)</b>	<b>7 (50)</b>
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).**



