

Omalizumab in the treatment of adult patients with mastocytosis: A systematic review

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Abstract

Background: Mastocytosis is associated with mast cell (MC) mediator-related symptoms for which limited therapies are available.

Objective: Our aim was to assess the efficacy and safety of omalizumab in the treatment of MC mediator-related symptoms in adult patients with mastocytosis.

Results: We identified one multi-centre retrospective cohort study (39 patients), one retrospective cohort study (13 patients), 4 case series and 10 case reports. No published controlled randomized study was identified. We included 69 patients (13 patients with cutaneous mastocytosis and 56 with systemic mastocytosis). The mean age was 48 years. Omalizumab maintenance dose was 300 mg for the majority of patients. The mean duration of treatment was 17 months. Treatment led to a tolerability of venom immunotherapy and to a complete resolution of severe reactions in all patients with post-honeybee sting anaphylaxis. Complete resolution of idiopathic anaphylaxis episodes was noted in 84% of the patients. Complete resolution of palpitations, gastrointestinal, cutaneous, neuropsychiatric, respiratory and musculoskeletal symptoms was observed at a rate of 43%, 29%, 27%, 11%, 9% and 0%, respectively. Efficacy was maintained for the entire duration of the treatment in all but four responders. Adverse events were reported for 13 patients.

Conclusions and Clinical Relevance: Omalizumab appears to prevent some life-threatening reactions associated with mastocytosis and may be a good option to treat the associated symptoms. However, the evidence relied upon is observational, uncontrolled and from a small number of patients. A randomized controlled trial is needed to better understand the place of omalizumab in mastocytosis treatment.

KEYWORDS

anaphylaxis, cutaneous mastocytosis, mast cells, Omalizumab, systemic mastocytosis, venom and insect allergy

1 | INTRODUCTION

Mastocytosis is characterized by clonal proliferation and/or the accumulation of abnormal mast cells in tissues. It includes cutaneous

mastocytosis (CM) and systemic mastocytosis (SM).¹

Common symptoms in mastocytosis are caused by the release of mediators from mast cells (MCs). These mediators may be associated with signs and symptoms affecting the following organs: the skin

(pruritus, flushing and hives), the gastrointestinal tract (nausea, vomiting, diarrhoea, cramping, ulcers and reflux), the respiratory system (shortness of breath, chest tightness and cough), the cardiovascular system (palpitations and severe anaphylaxis), the central nervous system (depression, migraine, fatigue and cognitive symptoms) and the musculoskeletal system (pain).¹ Anaphylactic reaction to hymenoptera stings and intolerance to venom immunotherapy (VIT) as well as idiopathic anaphylaxis would appear to be more likely to develop in patients with mastocytosis than in the general population.²⁻⁴ Such symptoms can dramatically affect the patient's quality of life and, under certain circumstances, can become life-threatening.^{5,6}

There is no curative therapy for mastocytosis. Conventional treatments include drugs that target MC mediator-related symptoms (such as histamine receptor antagonists and *montelukast*), MC activation (such as *Ketotifen*) or drugs that interfere with MC activation, proliferation and survival (such as tyrosine kinase inhibitor).¹ All these therapies are used "off label" for mastocytosis and are, in some cases, insufficient to control symptoms.

Mast cells are well known for their activation via the cross-linking of the IgE bound to the high-affinity Fc epsilon receptor 1 (FcεRI) at the cell surface.^{7,8} An anti-IgE monoclonal antibody, *omalizumab*, which is approved for the treatment of asthma and chronic spontaneous urticaria,⁹ may interfere with MC activation and control MC mediator-related symptoms.

We performed a systematic review of the efficacy and safety of *omalizumab* in the treatment of MC mediator-related symptoms in adult patients with mastocytosis in the literature up to April 2019.

2 | METHODS

Our systematic review protocol is registered in PROSPERO (International Prospective Register of Systematic Reviews) (Registration number: CRD42020151313) and reported in line with the recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA).¹⁰

2.1 | Search method

We searched the following international electronic database up to April 2019: MEDLINE, EMBASE, Web of Science, The Cochrane Central Register of Controlled Trials and The Cochrane Database of Systematic Reviews. The grey literature was reviewed post hoc (opengrey.eu), but no references related to the subject were found.

Medical Subject Headings (MeSH) terms related to mastocytosis and *omalizumab* were identified.

Details on the MEDLINE search strategy are presented below:

- MeSH terms
 1. Mastocytosis
 2. Cutaneous mastocytosis OR Urticaria pigmentosa

3. Systemic mastocytosis

4. *Omalizumab*

- Search strategy:

1. 1 AND 4

2. 2 AND 4

3. 3 AND 4

Only articles in French or in English were selected. Congress abstracts were not included. Reference lists were also searched manually to retrieve potential relevant articles.

2.2 | Criteria for considering studies for this review

Three reviewers (FJ, CP and CBL) reviewed the title and abstract of each reference and identified potentially relevant references. Disagreements between reviewers were resolved by consensus.

Considering the full texts, papers were selected using the following inclusion criteria:

- Randomized controlled trials (RCTs), cohort studies, case series and case reports reporting the efficacy and safety of *Omalizumab* in mastocytosis.
- Adult patients diagnosed with cutaneous mastocytosis and systemic mastocytosis according to the WHO criteria were included.¹¹

Paediatric patients, patients whose mastocytosis was not diagnosed according to the WHO criteria or patients who received concomitant cytoreductive therapy were excluded. Data retrieved from congress abstracts (non-published articles) were excluded from analysis.

2.3 | Type of outcome measures

We stipulated the following outcome measures:

1. Clinical improvement: prevention or resolution of MC mediator-related symptoms. Patients were divided into 5 groups:
 - Patients with complete resolution of symptoms (100%).
 - Patients with major improvement of symptoms (≥50%).
 - Patients with partial response (<50%).
 - Patients with no clinical response (0%).
 - Patients with a worsening of symptoms (<0%).
2. The quality of life assessed by visual analog scale (VAS) (0-10) and/or AFIRMM score (calculated according to the patient's perception of the severity of their symptoms and their impact on the quality of life).
3. The biological effect of *omalizumab*: serum tryptase, total IgE level, specific IgE level (in case of VIT intolerance), peripheral blood KIT D816V allele and basophil activation status (evaluated by flow cytometric measurement of CD63 surface expression).

2.4 | Data extraction and quality assessment

Data were extracted by one reviewer (FJ) using a data extraction form which was tested for accuracy on ten references and refined accordingly.

Two authors (CP and CBL) checked the extracted data. Disagreements were resolved by discussion between the three review authors.

Extracted data included: type of manuscript, gender and age of patients, mastocytosis form, duration of the disease, previous treatment, *omalizumab* initial dose, *omalizumab* maintenance dose, injections frequency, outcome measures, time to first response to treatment, maintenance efficacy period, treatment period, drug tolerability and the adverse effects. We also contacted two authors for further information. One responded and provided the raw database of the CEREMAST (the French References Center of Mastocytosis) retrospective cohort study published by Lemal *et al*.¹² The efficacy of *omalizumab* on each symptom was extracted individually for all patients from the latter database. The methodological quality of studies was assessed independently by two reviewers (FJ and CBL) using the Newcastle-Ottawa Scale for cohort studies and Cochrane risk-of-bias tool for randomized trials when available. The disagreements about methodological assessments were resolved by consensus.

3 | RESULTS

Of the 35 potentially relevant papers screened, 16 articles—two retrospective cohort studies, four case series and ten case reports—were included (Figure 1). Risk of bias within the two included cohort studies was considered as low.^{12,13}

Seven congress abstracts without published articles—one RCT, three case series and three case reports—were not included in the systemic review. References, type of MC mediator-related symptoms and treatment outcomes in these studies are given separately for information in Table 1.¹⁴⁻²⁰

Of the 69 patients enrolled, 25 were male and 44 were female. The mean age was 48 years [range: 21-77].

Cutaneous mastocytosis was noted in 13 patients and SM in 56 patients: 54 indolent SM (ISM), one smouldering SM (SSM) and one aggressive SM (ASM). Symptoms for which treatment with *omalizumab* was required included: severe idiopathic anaphylaxis (33 patients), post-honeybee sting anaphylaxis (5), VIT intolerance (3) and diverse mast cell activation symptoms. These symptoms were cutaneous (53), gastrointestinal (50), respiratory (18), musculoskeletal (37), neuropsychiatric (48) and palpitations (22).

Before initiation of *omalizumab* therapy, patients had received multiple treatment regimens. Those included mainly antihistamines (64), *montelukast* (49), *sodium cromoglycate* (14), *hydroxychloroquine* (1), *acetylsalicylic acid* (3), inhalant *salbutamol* (2), inhalant corticosteroid (1), phototherapy (2), *hydroxyurea* (1), *imatinib* (6), *masitinib* (8), *rapamycin* (3), *interferon* (2) or *cladribine* (8). Frequent use of oral corticosteroids and *epinephrine* was reported, respectively, in five

and two patients. The treatment prescribed prior to the initiation of *omalizumab* therapy was not detailed for two patients.

Omalizumab was initially given subcutaneously in various doses: 300 mg for 35 patients, 150 mg for 32 patients and 75 mg and 375 mg each for one patient. Maintenance doses were 300 mg (48 patients), 150 mg (18), 375 mg and 600 mg each for one patient. Initial injection frequency was every 4 weeks for 31 patients, every 2 weeks for 33 patients and every week for five patients. The mean duration of treatment was 17 months [1-144]. The mean time for the first response (mentioned for 40 patients) was 2.3 months [1-6 months].

The efficacy of treatment with *Omalizumab* on different symptoms is summarized in Figure 2 and Table 2.^{12,13,21-34}

Of the five patients who experienced hymenoptera sting anaphylaxis and who were treated with *omalizumab*, three did not tolerate the desensitization therapy. Two patients received *omalizumab* before the onset of the desensitization therapy to prevent anaphylactic reactions. *Omalizumab* treatment led to tolerability of the VIT and to a complete resolution of severe anaphylaxis in all patients. In two patients who experienced VIT anaphylaxis, tolerability of the desensitization therapy was sustained after discontinuation of *omalizumab* therapy.^{30,32} A bee sting challenge was performed and was well tolerated in three patients.^{29,32} Two patients showed a decrease in honeybee venom-specific IgE titres.^{32,33}

Of the 33 patients who experienced multiple episodes of severe idiopathic anaphylaxis, 28 showed complete resolutions of symptoms (84%).

Regarding the effect of *omalizumab* on MC mediator-related symptoms, complete resolution of symptoms was noted in patients with palpitations, gastrointestinal and cutaneous symptoms at a respective rate of 43%, 29% and 27%. The efficacy on respiratory, musculoskeletal and neuropsychiatric symptoms was milder. In fact, a complete response was reported for only 11% of the patients with neuropsychiatric symptoms, 9% for patients with respiratory symptoms and none for patients with musculoskeletal symptoms.

In addition, conventional treatment could be discontinued or the dose reduced for 5 patients on *omalizumab*.^{22,24,27,28,31}

For patients who responded to therapy, efficacy was maintained for the entire duration of the treatment for all patients, except for four patients whose response was lost 2 to 13 months after treatment.¹² Efficacy was sustained after the discontinuation of treatment with *omalizumab* for two patients with a mean follow-up period of 13 months.^{30,32}

The biological impact of *omalizumab* was also assessed. The effect on serum tryptase under treatment was assessed for 34 patients. Only five patients out of 34 (14.7%) showed a decrease in serum tryptase level after treatment.^{12,22,25,28,29} Total IgE level was assessed for 15 patients and found to be increased in 11 patients, while stable in the four remaining patients. Peripheral blood KIT D816V allele burden was assessed for 11 patients, and the level remained stable in all cases.¹³ The basophil activation status was assessed for two patients, and a decrease was shown in the IgE load on basophils.^{25,32} In one patient, mast cell infiltrate was found to be

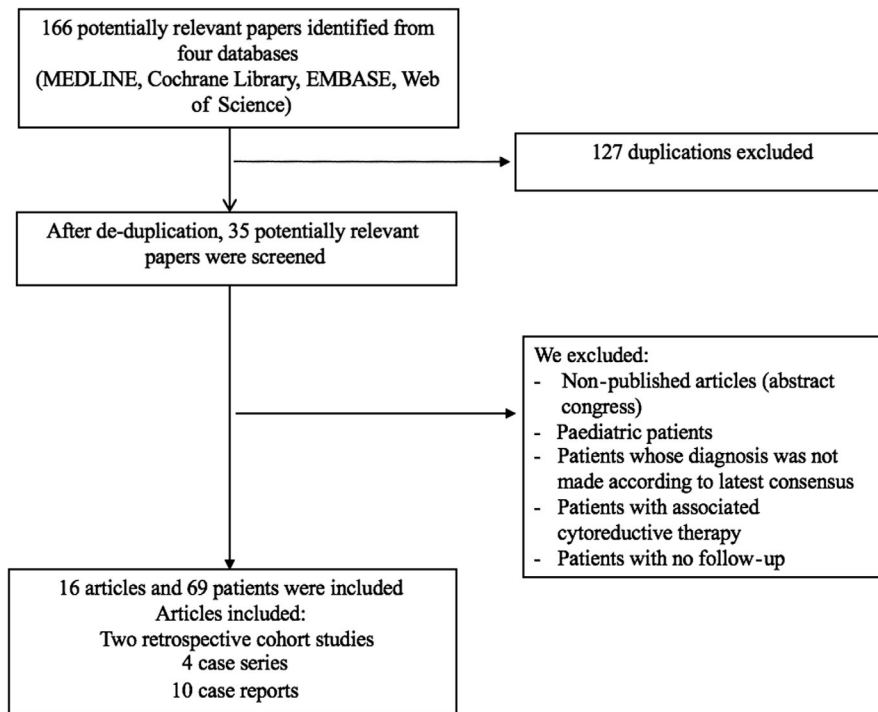


FIGURE 1 Flow diagram of the systematic review

TABLE 1 Data retrieved from congress abstracts (non-published articles)

Reference	Design and population	Symptoms	Treatment outcome
Distler et al ¹⁴	Randomized controlled study Seven patients under omalizumab	Idiopathic anaphylaxis, diffuse MC mediator-related symptoms: cutaneous, GI and neuropsychiatric symptoms	Reduction of AFIRMM score from 52 to 26 in <i>omalizumab</i> group VS 104 to 102 in placebo group Improvement in the number of allergic reactions, cutaneous symptoms and the frequency of the use of conventional therapies compared to the placebo group, but the difference was not statistically significant
Filis et al ¹⁵	Case series (Three patients)	Venom-induced anaphylaxis (3), VIT intolerance (2), unprovoked anaphylaxis (1)	Resolution of spontaneous, venom- and VIT-induced anaphylaxis
Fok ¹⁶	Case series Three patients	Hymenoptera venom anaphylaxis and VIT intolerance	VIT tolerance
Demirturk ¹⁷	Case report	Hymenoptera venom anaphylaxis and VIT intolerance	Only half of the immunotherapy maintenance dose reached due to systemic reaction
da Silva et al ¹⁸	Case series One patient with ISM	Hymenoptera sting anaphylaxis	Resolution of anaphylaxis episodes and VIT tolerance
Mikos ¹⁹	Case report	Hymenoptera sting anaphylaxis and VIT intolerance	VIT tolerance and negative test challenge with natural bee sting
Zubrinich ²⁰	Case report	Hymenoptera venom anaphylaxis and VIT intolerance	VIT tolerance even after omalizumab discontinuation

diminished on a second skin biopsy performed 10 months after the initiation of *omalizumab* compared to the initial biopsy.³¹

Patients' quality of life was evaluated by the VAS in 13 patients on *omalizumab*, and a significant decrease from 8 to 2 was shown in all patients at the last follow-up.¹³

Regarding the safety profile, tolerability was good in 56 patients while 13 patients showed various adverse effects including a severe reaction with oedema of the larynx and dyspnoea (1), migraine (1), fatigue (3), dizziness (1), local injection reactions (3), sweating (1),

palpitations (1), nausea (3), abdominal pain (2), bleeding (2), pruritus (1), paraesthesia (1) and fungal infections (1).^{14,15,21,28} Treatment was stopped for six patients due to adverse effects.^{12,13}

4 | DISCUSSION

Our review suggests that *omalizumab* has a positive effect and a good safety profile in the prevention of clinical manifestations such

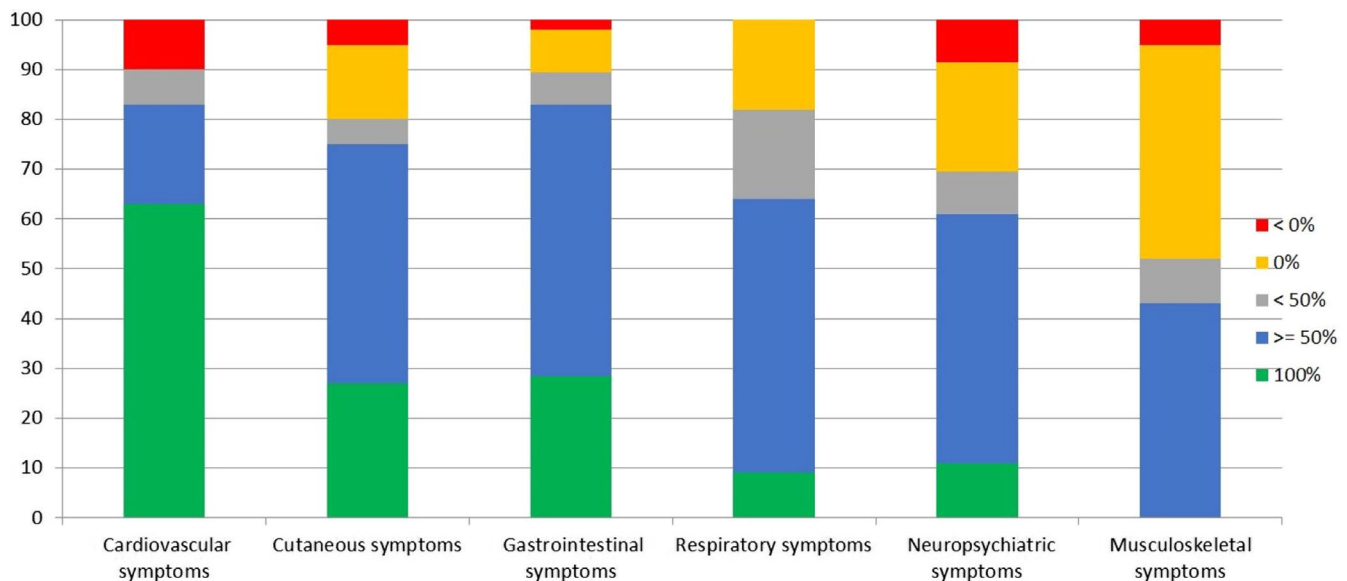


FIGURE 2 Effect of *omalizumab* on diverse mast cell mediator-related symptoms

as cardiovascular, cutaneous and gastrointestinal symptoms associated with severe mast cell activation.

The efficacy of *omalizumab* appears to be limited for respiratory, musculoskeletal and neuropsychiatric symptoms. This discrepancy in the therapeutic effect observed might be explained, at least in part, by the different mast cell activation profiles in response to various stimulatory signals associated with MC mediator-related symptoms.³⁵

A literature review of the use of *omalizumab* in patients with mastocytosis was published in 2014.³³ In this article, only the effect of *omalizumab* on VIT intolerance in patients with mastocytosis was assessed.

We questioned the effect of *omalizumab* on idiopathic anaphylaxis, hymenoptera venom anaphylaxis, VIT intolerance and various mast cell mediator-related symptoms in adult patients with mastocytosis diagnosed according to the latest consensus.

This leads us to consider the possible mechanism of action of *omalizumab* in patients with mastocytosis.

Omalizumab is a recombinant DNA-derived humanized immunoglobulin monoclonal antibody that selectively binds to human IgE.³⁶ Therefore, by binding with high affinity to free IgE, it prevents IgE from attaching to FcεRI.³⁷ The decrease in free IgE levels results in a reduction in the number of FcεRI receptors on mast cells, basophils and other innate immune cells with antigen-presentation capabilities.³⁷⁻⁴⁰ This reduction occurs more slowly on mast cells than on basophils (70 vs 7 days) in skin biopsies from patients with allergic rhinitis.⁴¹ In addition, skin biopsies from patients with chronic spontaneous urticaria treated with *omalizumab* did not show a significant reduction in the number of IgE/FcεRI-positive cells until day 85, yet the symptoms were reduced by day 8.⁴² It is therefore tempting to speculate that other mechanisms might contribute to the early effects observed when chronic spontaneous urticaria and mastocytosis are treated with *omalizumab*.

It is known that antigens binding to their specific IgE can activate mast cells via the aggregation of FcεRI localized on the surface of mast cells and cause the release and/or production of a broad panel of pro-inflammatory mediators.^{43,44} Mast cell degranulation can be triggered by antibody-dependent signals (eg via FcR)⁴⁵ or by “innate” stimuli that function independently of antibodies and FcR.⁸ Moreover, it has been recently reported that mast cells could differentially regulate their degranulation dynamics and associated inflammatory reactions in response to activation via FcR (eg activation of FcεRI by IgE/antigens) or G protein-coupled receptors (eg activation of MRGPRX2 with substance P).⁸ However, mast cell activation by IgE may also occur in the absence of the specific antigen, which raises the question of potential endogenous factors that might influence FcεRI aggregation.³⁵ The binding of IgE to mast cells is not merely a passive sensitization step, as previously believed. On the contrary, IgE actively plays an important role in promoting the survival of mast cells. It has been reported that monomeric IgE could render mast cell resistant to apoptosis and induce the release of cytokines.³⁵

It is important to notice that our review points out some limitations in our understanding of *omalizumab* treatment in mastocytosis patients. The efficacy on symptoms and the treatment dose and frequency were heterogeneous, which made an overall assessment difficult. The majority of articles were case reports or case series which represents a high risk of positive publication bias. The only RCT performed was published as an abstract congress and then was not included in the systemic review. Moreover, the short mean duration of follow-up studies did not allow a robust assessment of the long-term efficacy and safety of *omalizumab* in patients with mastocytosis.

TABLE 2 Symptoms for which *omalizumab* was indicated and the effectiveness

Reference	Design and population	Symptoms	Treatment outcome
Lemal et al ¹²	Multi-centre retrospective cohort study 39 patients	Anaphylaxis Diffuse MC mediator-related symptoms	Overall response rate: 90.9% for CM and 79.3% for SM
Broesby-Olsen et al ¹³	Retrospective cohort study 13 patients	Cutaneous (2), gastrointestinal (2) and diffuse (5) symptoms Idiopathic anaphylaxis (5)	Complete clearance of anaphylaxis severity, reduction of 65.4% of cutaneous symptoms, 53.6% of GI symptoms, 50% of musculoskeletal and marginal effect on neuropsychiatric symptoms with 34.5% improvement Serum tryptase level and <i>KIT</i> D816V allele burden (% mutated alleles) remained stable for all patients
Lieberoth et al ²¹	Case series Two patients	Cutaneous and gastrointestinal symptoms for 2 patients, musculoskeletal symptoms and fatigue for one patient	Resolution of GI and cutaneous symptoms for two patients, musculoskeletal pain remained stable for one patient, effect on fatigue not mentioned
Molderings et al ²²	Case series Two patients	Diffuse MC mediator-related symptoms: fatigue, weight loss, GI, respiratory, cardiovascular, neuropsychiatric, musculoskeletal for two patients, cutaneous for one patient	Decreasing of symptoms intensity in the two patients, decreasing of serum tryptase level for one patient
Hinojosa et al ²³	Case series Two patients	Cutaneous mastocytosis (Two patients), various MC mediator-related symptoms: gastrointestinal (Two patients), cardiovascular (one patient), neuropsychiatric (one patient) and fatigue (one patient)	Reduction of 50% (one patient) and 90% (one patient) in skin involvement Mild and complete improvement of MC mediator-related symptoms for, respectively, one patient
Carter et al ²⁴	Case series 1 adult patient included (1 paediatric patient excluded)	Idiopathic anaphylaxis with GI, respiratory and cutaneous MC mediator-related symptoms	Complete resolution of symptoms except one mild episode of diarrhoea
Douglass et al ²⁵	Case report	Idiopathic anaphylaxis	Complete resolution of anaphylaxis episodes. Decrease of serum tryptase level, decrease of basophils sensitivity for activation (by basophil activation test) and persistence of abnormal CD25 and CD2 positive mast cells
Chen ²⁶	Case report	Cutaneous, gastrointestinal, respiratory and musculoskeletal MC mediator-related symptoms	Significant improvement of symptoms
Kibsgaard et al ²⁷	Case report	Idiopathic anaphylaxis and cutaneous symptoms	Complete resolution of anaphylaxis episodes and effect on skin flares not mentioned. Serum tryptase level was stable
Kontou-Fili et al ²⁸	Case report	Hymenoptera sting anaphylaxis, VIT intolerance, cutaneous symptoms	VIT and hymenoptera stings tolerance, resolution of cutaneous symptoms
Kontou-Fili et al ²⁹	Case report	Hymenoptera sting anaphylaxis	Complete resolution of anaphylaxis episodes, tolerance to VIT and bee sting challenge, decrease of serum tryptase level
Castells ³⁰	Case report	Hymenoptera sting anaphylaxis and VIT intolerance Diffuse MC mediator-related symptoms: cutaneous, cardiovascular, GI, musculoskeletal and neurological	Tolerance of the VIT even after discontinuation of <i>omalizumab</i> therapy (only one episode of mild flushing and dizziness responding to oral antihistamines) and resolution of anaphylactic episodes Effect on diffuse symptoms not mentioned

(Continues)

TABLE 2 (Continued)

Reference	Design and population	Symptoms	Treatment outcome
Paraskevopoulos et al ³¹	Case report	Idiopathic anaphylaxis	Resolution of the anaphylactic episodes
Gonzalez-de-Olana et al ³²	Case report	Hymenoptera venom anaphylaxis and VIT intolerance	VIT tolerance Decrease of specific IgE Negative basophil activation test and sting challenge test
Sokol et al ³³	Case report	Hymenoptera sting anaphylaxis, <i>omalizumab</i> was given 5 mo prior to the VIT	Tolerance of the desensitization therapy, improvement of skin lesions and decrease of specific honeybee venom IgE and tryptase level
Siebenhaar et al ³⁴	Case report	Cutaneous symptoms associated with Meniere disease symptoms (tinnitus, hearing loss and vertigo/nausea)	Complete disappearance of wheal formation and pruritus and complete resolution of vertigo and nausea of Meniere disease

5 | CONCLUSION

Overall, *omalizumab* appears to be a promising option in the treatment of adult patients with mastocytosis, especially in the prevention of life-threatening episodes of anaphylaxis. It also seems to improve MC mediator-related symptoms and consequently patients' quality of life. Further large-scale randomized controlled studies are needed to unambiguously explore the efficacy and safety of *omalizumab* treatment in mastocytosis patients more extensively.

CONFLICTS OF INTEREST

Fatma JENDOUBI, Mathilde NEGRETTO, Adeline GALLINI and Nicolas GAUDENZIO declare that they have no conflicts of interest. Cristina BULAI LIVIDEANU and Carle PAUL have been investigators and consultants for Novartis.

AUTHOR CONTRIBUTIONS

Fatma JENDOUBI, Carle PAUL and Cristina BULAI LIVIDEANU performed the literature search, selected the articles and extracted the data. Fatma JENDOUBI drafted the article. Mathilde NEGRETTO participated in the literature search. Adeline GALLINI critically revised the methodology. Nicolas GAUDENZIO, Carle PAUL and Cristina BULAI LIVIDEANU critically revised the work. All authors read and approved the final manuscript.

ETHICAL APPROVAL

Ethical approval is not applicable as this is a review article.

INFORMED CONSENT

Informed consent is not applicable as this is a review article.

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