



Letter to the Editor

Timing of response and long term efficacy of Omalizumab in non-clonal Mast Cell Activation Syndrome: A case series

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Mastocytosis is a clonal mast cell (MC) disorder including cutaneous Mastocytosis (CM), systemic Mastocytosis (SM) and MC sarcoma [1].

Signs and symptoms of the disease as anaphylaxis, flushing, abdominal cramping, diarrhea, breathing difficulties, pruritus, fatigue, depend on the release of preformed and new synthesized mediators [2].

Many patients, although presenting signs and symptoms related to the MC activation, do not meet the diagnostic criteria for Mastocytosis or monoclonal MC activation syndromes (MMAS), conditions defined by the presence of clonal MC in bone marrow (BM) but without sufficient criteria for SM and typical skin lesions. In those cases, Mast Cell Activation Syndrome (MCAS) can be suspected; this rare condition, as defined by the existing Consensus Criteria of the European Competence Network of Mastocytosis (ECNM) [3], is characterized by mediator-related symptoms associated with activation of mast cells (MC), multifunctional effector cells involved in innate and acquired immunity and inflammatory reactions. The terms MCAS applies when (1) typical signs of severe recurrent acute systemic MCA are present (involving at least 2 organ system), (2) the involvement of MCs can be demonstrated by biochemical analysis (preferably through an event-related increase of the serum tryptase level by 20% over the individual baseline plus 2 ng/mL, within 4 h windows after the reaction) and (3) the symptoms respond to treatment with MC-stabilizing agents or drugs targeted against MC mediator production, secretion or receptor binding. All the criteria must be fulfilled to establish the diagnosis of MCAS [4]. In most of patients with suddenly occurring MCAS symptoms, a previously determined tryptase baseline level is not available. Therefore, it is important to replace it by dosing blood tryptase at least 24 h after the resolution of all systemic symptoms and to compare the post-event tryptase level with the acute phase one [3].

On the basis of underlying conditions, patients can be further classified into (1) those with primary MCAS, where c-Kit mutated, clonal (CD25+) MCs are detectable as in Mastocytosis and in MMAS; (2) those

with secondary MCAS, where an underlying IgE-dependent allergy or other hypersensitivity reaction is detected, and (3) those with idiopathic MCAS, where no c-Kit mutated MCs and no overt inflammatory disorders are detected, and no triggers for hypersensitivity reaction are found [4].

The last two variants not showing BM clonal mast cells are defined non-clonal Mast Cell Activation Syndrome (nc-MCAS) [2].

We report on the use of Omalizumab at the dose of 300 mg every four weeks in five patients (Table 1), three with indolent SM (ISM) variant without skin lesions (Bone Marrow Mastocytosis – BMM) and two with nc-MCAS.

Diagnosis of ISM and nc-MCAS were performed respectively according to WHO criteria for SM and proposed criteria for MCAS [5]. BM evaluation included biopsy and smear, mast cells flow-cytometry and D816V c-Kit mutation molecular study. The two cases of nc-MCAS didn't fulfill any WHO criteria for Systemic Mastocytosis, excluding tryptase Level > 20 mcg/L (Table 1).

All 5 patients presented very severe mediator-related symptoms, in some cases life-threatening not sufficiently responsive to a combined anti-mediators therapy (antihistamines, leukotriene antagonist, cromoglycate, systemic gluco-corticosteroids).

Treatment was started after obtaining Informed consent.

Case 1 (nc-MCAS): presented 2–3 anaphylactic events per month, requiring also the use of adrenaline. An optimal disease control was obtained immediately after initiation of Omalizumab treatment, administered for 12 months, and currently maintained 6 months after Omalizumab discontinuation.

Anti H1 and H2, were suspended 6 months after the biologic treatment start.

Case 2 (nc-MCAS) experienced severe flushing with hypotension on a weekly base following exposure to heat. His symptoms resolved 3 months after Omalizumab initiation, when the anti H1 agent could also be suspended. Biologic treatment was administered for 6 months. He

Table 1
Characteristics of the patients with MCAS of the present report.

	Case #1 F 54 y	Case #2 M 28 y	Case #3 M 60 y	Case #4 M 59 y	Case #5 F 69 y
Diagnosis	nc-MCAS negative	nc-MCAS negative	BMM positive	BMM positive	BMM positive
Bone Marrow evaluation	2	49.5	6.3	79.9	44.2
Trypsin before Omalizumab(mcg/L)	Anaphylaxis: 3–4 a months (adrenaline)	Flushing and hives weekly in summer months	Anaphylaxis every 2 months (adrenaline) and flushing	Flushing, pruritus and tachycardia 2–3 a week	Anaphylaxis once a week + flushing
Clinical manifestation	Unknown	Heat	Drug, Unknown	Unknown	Unknown
Trigger	Grasses allergy	Olive tree allergy	/	GERD	Allergic rhino conjunctivitis, Shellfish allergy
Other Diseases					
Evidence based therapy before omalizumab	Anti-H1, anti-H2, sodium chromoglycate	Anti-H1, anti-H2, anti-LT	Anti-H1, anti-H2, sodium chromoglycate	Anti-H1, anti-H2, sodium chromoglycate, anti-LT	Anti-H1, anti-H2, anti-LT
Omalizumab start date N of administered injections	3/2017 6 no	05/2018 6 no	04/2017 12 yes	10/2018 5 yes	10/2018 6 yes
Ongoing treatment	0	Pruritus	0	Flushing	0
Relapses	1.8	29.8	7.7	158	n.a.
Trypsin after Omalizumab (mcg/L)	Anti-H1 and anti-H2	Anti-H1, anti-H2, anti-LT	Anti-H1, anti-LT	Anti-H1, anti-H2, sodium chromoglycate, anti-LT	Anti-H1, anti-H2, anti-LT
Evidence based therapy after omalizumab					

BMM: Bone Marrow Mastocytosis nc-MCAS; non-clonal Mast Cell Activation Syndrome n.a.: not available.

kept assuming anti H1, anti H2 and Montelukast.

Case 1 (BMM): experienced anaphylactic reactions every two months and mediators-related symptoms 2–3 times per week, without any triggering factor. Since the first Omalizumab injection no more anaphylaxis occurred, whilst flushing resolved 2 months after biologic treatment start. He kept assuming anti-mediators therapy; omalizumab treatment is ongoing.

Case 4 (BMM): presented flushing, pruritus and tachycardia 2–3 times a week, during physical exercise, including sexual intercourse, requiring ER admission for intravenous steroid and antiH1 administration; 3 months after Omalizumab treatment start, he reported symptoms improvement in terms of frequency and intensity. Also, the prompt self-administration of oral anti H1 and steroid were able to block the manifestation with no need for ER admission. Biologic treatment is still ongoing. He keeps assuming anti H1, anti H2 and Montelukast.

Case 5 (BMM): experienced anaphylaxis and mediators-related symptoms up to once a week with a great negative impact on her quality of life. Since the first Omalizumab injection no more anaphylaxis occurred, whilst flushing resolved 3 months after biologic treatment start. Omalizumab therapy is still ongoing, together with anti-mediators treatment.

In all patients, no adverse reactions of any grade were detected during the treatment course.

The present data support Omalizumab safety and efficacy as a treatment option in Clonal Systemic Mastocytosis resistant to the traditional therapy, as shown by previous findings in literature. Furthermore our findings suggest the relevance of anti - IgE therapy (Omalizumab) in treating patients affected by Non-Clonal Mast Cell Activation Syndrome and in improving their quality of life. Of note, similarly to what has been described in patients with SM, Omalizumab treatment is effective in preventing anaphylaxis since the first injection also in subjects suffering from nc-MCAS, whilst mediators-related symptoms resolve 2–3 months after the treatment start. Taking into consideration both the clinical ground and sustainability, recurrent anaphylaxis, in particular when refractory to anti-mediators medications, could represent a major indication for the biological treatment in patients with SM and nc-MCAS. Interestingly, in patients with nc-MCAS the absence of anaphylaxis relapse could be observed even after omalizumab treatment stop. The longest available follow-up is 12 months. To the best of our knowledge, no other studies have so far addressed the long-term benefits of omalizumab after treatment stop in nc-MCAS patients and no recommendations are currently available concerning that issue. As reported by other studies, tryptase does not seem to parallel clinical response, although omalizumab reduces the potential reactivity of mast cells and resulting in down-regulation of FcεRI expression and in an increase in the threshold above which degranulation is triggered [6,7]. Thus tryptase cannot be considered a good biomarker in managing omalizumab treatment. Further studies are needed to confirm the reported findings, especially when considering nc-MCAS patients.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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Marco Caminati^{a,b,*}, Elisa Olivieri^b, Francesca Nalin^c, Roberta Zanotti^d,
Gianenrico Senna^b, Michele Schiappoli^b, Annarita Dama^b,
Patrizia Bonadonna^b

^a *Department of Medicine, University of Verona, Verona, Italy*

^b *Asthma Center and Allergy Unit, Verona University Hospital, Verona, Italy*

^c *Department of Medicine, Specialization Course in Allergy and Clinical Immunology, University of Verona, Verona, Italy*

^d *Department of Medicine, Haematology Unit, Verona University Hospital, Verona, Italy*

E-mail address: ma.caminati@gmail.com (M. Caminati).

* Corresponding author at Asthma Center and Allergy Unit and Department of Medicine, University of Verona, Verona University Hospital, Piazzale Scuro 10, 37134 Verona, Italy.