

Mast Cell Activation Syndrome and Mastocytosis: Initial Treatment Options and Long-Term Management



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Learning objectives:

1. To be familiar with the enzymes responsible for metabolism of histamine.
2. To understand the required increase in the serum tryptase level above baseline for diagnosing a mast cell activation syndrome (MCAS) event.
3. To identify mast cell products for which there is insufficient evidence for their contribution to symptoms or in the diagnosis of systemic mastocytosis (SM) or MCAS.
4. To identify symptoms of SM, cutaneous mastocytosis (CM) and MCAS that improve with omalizumab treatment.

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Patients with clonal mast cell activation syndromes (MCAS) including cutaneous and systemic mastocytosis (SM) may

present with symptoms of mast cell activation, but in addition can have organ damage from the local effects of tissue infiltration by clonal mast cells. Patients with nonclonal MCAS may have chronic or episodic mast cell activation symptoms with an increase in serum tryptase and/or urinary metabolites of histamine, prostaglandin D₂, and leukotrienes. Symptoms of MCAS and SM can be managed by blockade of mediator receptors (H1 and H2 antihistamines, leukotriene receptor blockade), inhibition of mediator synthesis (aspirin, zileuton), mediator release (sodium cromoglycate), anti-IgE therapy, or a combination of these approaches. Acute episodes of mast cell activation require epinephrine, and prolonged episodes may be addressed with corticosteroids. Patients with clonal mast cell syndromes may need a reduction in the number of mast cells to prevent severe symptoms including anaphylaxis and/or progression to aggressive diseases. © 2019 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:1097-1106)

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Abbreviations used

2-CdA- 2-Chlorodeoxyadenosine
 AERD- Aspirin exacerbated respiratory disease
 BMD- Bone mineral density
 CM- Cutaneous mastocytosis
 CysLT- Cysteinyl leukotriene
 FDA- Food and Drug Administration
 LT- Leukotriene
 MCAS- Mast cell activation syndrome
 MC- Mast cell
 MU- Million units
 N-MH- N-Methylhistamine
 NSAID- Nonsteroidal anti-inflammatory drug
 PGD2- Prostaglandin D2
 SM- Systemic mastocytosis
 TKI- Tyrosine kinase inhibitor
 VIT- Venom immunotherapy

MAST CELL DISORDERS: DEFINITION AND HETEROGENEITY

Mast cell (MC) activation disorders include mastocytosis, a spectrum of rare and well-defined diseases associated with the clonal expansion of MCs in the skin and/or other tissues and organs, and mast cell activation syndrome (MCAS), a rare condition defined by acute and/or chronic symptoms of MC activation with elevation of MC mediators at baseline or during acute episode, without MC hyperplasia.¹ Primary MC activation disorders are due to intrinsic MC proliferation or clonal expansion and typically associated with KIT mutations such as mastocytosis and monoclonal MCAS.² Secondary MC disorders are those associated with allergic and other inflammatory or autoimmune disorders. Idiopathic MC activation syndrome or MCAS lacks evidence for clonal expansion or proliferation, but the symptoms are compatible with MC activation.³ Clonal MCs typically expand in the skin and/or other tissues, most commonly the bone marrow, gastrointestinal tract, lymph nodes, liver, and spleen and carry somatic activating mutations in the KIT proto-oncogene that drives the expansion and activation, with the aspartic acid 816 Valine (D816V) mutation being the most common.⁴ Cutaneous MC expansion can occur in children and adults and has been generally considered a benign condition due to the favorable outcomes in a majority of children.^{5,6} Maculopapular monomorphic cutaneous mastocytosis (CM), known as urticaria pigmentosa, is the typical presentation in adulthood and is associated in over 90% of the cases with systemic involvement.⁵ Although the polymorphic maculopapular variants are mostly seen in children and are not associated with other organ involvement, systemic symptoms of MC activation are common, including gastrointestinal, bone, and central nervous system (CNS) symptoms.⁷ Patients with low MC burden or absence of tryptase alpha genes can present normal tryptase with bone marrow MC aggregates, CD25 expression, and KIT D816V mutation, qualifying for World Health Organization criteria for systemic mastocytosis (SM).⁸ New forms of mastocytosis include patients without skin lesions and presenting with hymenoptera anaphylaxis⁹ and well-differentiated SM presenting as childhood papular lesions progressing to adult systemic involvement without KITD816V mutation in patients sensitive

to imatinib.^{10,11} It is now possible to query KIT mutations in peripheral blood leukocytes with improved sensitivity and specificity, helping improve the evaluation of mastocytosis in patients with episodes of hypotension and/or anaphylaxis.¹² In the last 10 years, an increasing number of patients presenting with symptoms of MC activation without bone marrow MC aggregates and no evidence of MC expansion¹³ have been evaluated for MC activation disorders.¹ These patients present baseline and/or acute elevations of MC mediators including tryptase, urinary histamine, and/or prostaglandins and respond to treatment with MC mediator controller medications, improving their quality of life, but the molecular targets and mechanisms of MC activation are lagging.¹⁴ Recently, elevated tryptase levels in several family members with atypical symptoms of MC activation have been shown to relate to the duplication or triplication of tryptase alpha and beta genes,¹⁵ and it is estimated that 4% to 6% of the general population have increased tryptase gene copy numbers with unclear clinical significance.¹⁵ MC heterogeneity has been described with 3 types of human MCs in tissues: mucosal MCs containing tryptase only as seen in gastrointestinal mucosa and alveoli; connective tissue MCs containing tryptase, chymase, and carboxypeptidase as seen in skin, peritoneum, and submucosa, and responding to sodium cromolyn¹⁶; and chymase-only MCs in the gastrointestinal submucosa.¹⁷ New complexity to this understanding has been provided by the recent description of the MC transcriptome, which provided unique surface membrane receptors and granular components for MCs at each tissue, apart from basophils, eosinophils, dendritic, B cells, T cells, and other cells.¹⁸ Novel G protein coupled receptors such as MRGPRX2 that can activate MCs through non-IgE mechanisms appear to be abundant, and their role in MCAS needs to be defined. This indicates an unappreciated complexity for MC heterogeneity, which could contribute to explaining nonclonal MCAS, with local activation triggered by tissue-specific interactions.

MAST CELL ACTIVATION SYMPTOMS IN MASTOCYTOSIS AND MCAS

MC activation symptoms relate to the tissue response to the release of mediators such as tryptase, histamine, prostaglandins, leukotrienes (LTs), and cytokines among others and to the local MC burden in patients with mastocytosis.¹⁹ The symptoms can be infrequent and acute and associated with anaphylaxis, or chronic and persistent with subacute presentations.²⁰ Most patients with mastocytosis have an indolent disease with good prognosis. Patients with nonclonal MCAS can present with pruritus, flushing, syncope, gastric distress, nausea and vomiting, diarrhea, bone pain, and neuropsychiatric symptoms that may be controlled by targeted medications.^{5,19}

Mast cell mediators, background, measurement, and significance

Improvements in our abilities to diagnose and treat the symptoms resulting from SM and MCAS rely, in part, on accurately quantitating levels of secreted MC mediators in blood and urine, then blocking their synthesis, secretion, and/or receptors.

Mediators for which there is substantial evidence of clinical relevance in diagnosing and/or treating mast cell disorders

Histamine. Histamine, 2-[4-imidazolyl]-ethylamine, is a biogenic amine produced by the action of histidine

decarboxylase on the essential amino acid histidine. Its physiologic actions, first characterized over a century ago by Dale and Laidlaw,²¹ include vasodilation, contraction of uterine, airway and intestinal smooth muscle, stimulation of heart rate and contractility, a shock-like syndrome when injected into animals,²² and stimulation of gastric acid secretion.²³

Patients with SM have elevated plasma histamine levels, and these levels exhibit a diurnal variation with the highest plasma histamine level present in the early morning; however, plasma histamine is not a useful screening test for SM.²⁴ Rather, quantitation of urinary histamine metabolites is more sensitive and specific²⁵; 70% to 80% of released histamine is rapidly metabolized by histamine N-methyltransferase to N-methyl-histamine (N-MH) that is subsequently transformed by monoamine oxidase to N-methylimidazole acetic acid. Diamine oxidase present in the colon and kidney oxidatively deaminates the remaining 20% to 30% of histamine yielding imidazole acetaldehyde that is converted to imidazole acetic acid and conjugated with ribose phosphate.^{26,27} Urinary N-MH is currently measured by liquid chromatography/tandem mass spectroscopy and is expressed as "mcg/gm creatinine (Cr)." Normal values decrease with advancing age with normal levels of 120 to 150 (0-5 years), 70 to 330 (6-16 years), and 30 to 200 (above 16 years). Urinary N-MH levels greater than 400 mg/g Cr correspond to a high degree with bone marrow biopsies positive for atypical MCs, the presence of MC aggregates, and the presence of the *c-kit* Asp816Val mutation.²⁸ In contrast, only 2 of 25 patients with symptoms of MCAS had increased baseline excretion of N-MH, whereas 17 of 25 had baseline elevation of urinary 11 β -PGF2 α .²⁹

Tryptase. Essentially absent from basophils, the serine protease tryptase resides in MC secretory granules where mature tetrameric tryptase is complexed to heparin proteoglycan.^{30,31} Immature α - and β -tryptase monomers are continuously secreted and α -pro-tryptase is the chief form of tryptase present in the circulation in patients with SM and normal subjects. The appropriate time to measure released tryptase during MC activation events such as anaphylaxis (30-120 minutes after the development of symptoms) differs from that for measuring released histamine that peaks after 5 to 10 minutes.³²

The degree of symptom-associated tryptase increase required for diagnosing MCAS is an increase above baseline of 20% plus 2 ng/mL.³³ The normal range of tryptase levels in adults is 1 to 15 ng/mL, average 5 ng/mL, and levels greater than 11.5 ng/mL, the 95th percentile are considered to be elevated.³⁴ For children, the median value is 3.3 ng/mL, interquartile range 2.38 to 4.36.³⁵ In one series, infants less than 3 months of age displayed the highest levels of serum tryptase (6.12 $\pm$ 3.47 ng/mL). By 9 to 12 months of age, the levels gradually decreased to those described in adults and older children (4.12 $\pm$ 3/38 ng/mL).³⁶

The importance of finding an elevated basal level of serum tryptase is manifold. As noted elsewhere, a level greater than 20 ng/mL is one of the minor criteria for diagnosing SM, except in patients with systemic mastocytosis with an associated hematological neoplasm (SM-ANH). Moreover, an elevated basal tryptase level signals a patient at increased risk for a variety of untoward reactions such as anaphylaxis to vespid stings, for urticaria and angioedema, or for medication or radiocontrast media

reactions, with severe reactions occurring more often in subjects having baseline tryptase values >20 ng/mL.^{37,38}

Four members of a family with familial hypertryptasemia have had clinical symptoms consistent with MCAS that were controlled with oral cromolyn plus H1 and H2 antihistamines.³⁹ In more recent studies, elevated serum basal tryptase has been found in cohorts with increased *TPSAB1* copy number and associated with multisystem complaints. In the families reported, a gene-dose effect was observed, with patients having alleles encoding 3 copies of alpha tryptase having higher basal serum levels of tryptase and more symptoms than those with alleles encoding 2 copies.⁴⁰

Prostaglandin D2 (PGD2). Elevations of PGD2 and its metabolites have been reported in the urine and/or the circulation in various disorders for nearly 40 years. The biologic effects of PGD2 (vasodilation, flushing, tachycardia, nasal congestion, bronchoconstriction, platelet aggregation) are well known. What is not commonly appreciated is that the initial F-ring metabolite of PGD2, 11 β PGF2 α , is also biologically active (uterine smooth muscle contraction, hypertension, agonist for the PGD2 chemotactant receptor CRTH2).⁴¹

In early reports, substantial increases in the PGD2 metabolite 9 α ,11 β -dihydroxy-15-oxo-2,3,18,19-tetranorprost-5-ene-1,20-dioic acid could be measured in the baseline state and/or associated with acute symptoms in patients with mastocytosis many of whom had not responded to H1 and H2 receptor blockade, but who responded to aspirin.⁴²⁻⁴⁵ Previously, in the clinical laboratory measurement of the F-ring metabolite of PGD2, 11 β -PGF2 α was expressed as nanograms excreted in a 24-hour urine sample. More recently, levels of 2,3-dinor-11 β -PGF2 α , a downstream metabolite of 11 β -PGF2 α , are measured by LC-MS/MS and normalized to urine creatinine levels with normal values <5205 pg/mg Cr.

The importance of measuring PGD2 metabolites in the diagnosis and treatment of MC disorders has been confirmed in several reports.^{29,46,47} For patients with SM, urinary excretion of 11 β PGF2 α above 3500 ng/24 hours (reference range <1000 ng/24 hours) corresponded to a high degree with bone marrow biopsies positive for atypical MCs, the presence of MC aggregates, and *c-kit* mutation.²⁸ Desensitization to aspirin is possible in those patients with SM who have previously responded adversely to nonsteroidal anti-inflammatory drugs (NSAIDs).⁴⁸

Cysteinyl leukotrienes (LTE4). Measurement of urinary levels of excreted LTE4, the stable cysteinyl leukotriene (CysLT) derivative of LTC4, can be used to quantitate whole body production of CysLT, reflecting short-term changes in secretion.^{49,50} Most recently, urinary LTE4 has been measured by LC-MS/MS with levels expressed as picograms of LTE4 per milligram of creatinine with a reference range among normal volunteers <104 pg/mg Cr.⁵¹ MCs, basophils, and eosinophils synthesize LTs that can also be produced in platelets and endothelial cells by transcellular biosynthesis.⁵² Increased urinary levels of LTE4 have been reported in several conditions, such as aspirin exacerbated respiratory disease (AERD), in which MC activation occurs. A 5.5- to 52-fold increase in urinary CysLT has been reported during anaphylactic reactions.⁵³ Several studies have now confirmed significant elevations in urinary LTE4 among patients with SM when compared with nonmastocytosis populations including

TABLE I. Substances with no current role in diagnosis or treatment of SM and MCAS

Mediator	Comment: clinical effect	Comment: <i>in vitro</i> effect	Reference(s)
IL-8	Levels significantly different in ASM and SM-AHN vs ISM	Release from mast cell lines demonstrated	58-61
Heparin	Anticoagulant	—	62-66
Chondroitin sulfate	—	Inhibits IL-8 and TNF release from LAD2 cells	67
Serotonin	No correlation with serum tryptase of urinary mediators	—	68,69
Chromogranin A	PPI-induced increase only; scant staining of bone marrow mast cell lesions	—	70
Neuropeptides	No significant differences among symptomatic patients with SM or MCAD	—	71
Corticotropin-releasing hormone (CRH)	One ISM case with CRH elevation and bone marrow staining	CRH synthesized and secreted by human mast cells	72,73
Platelet activating factor (PAF)	Detected in blister fluid of bullous mastocytosis	Causes degranulation of mast cells	74-77
Chymase	Present in skin and bone marrow lesions in ISM	Conversion of angiotensin I to II; cleaves stem cell factor	78-80
Stem cell factor (SCF)	—	Differentiation, maturation, chemotaxis, activation of mast cells	81
Nerve growth factor (NGF)	Increased serum levels of NGF and neurotrophins in SM	Promotes proliferation, chemotaxis, survival of mast cells	82,83
Vascular endothelial cell growth factor (VEGF)	—	Produced by many cell types including mast cells	—

AHN, Associated hematological neoplasm; ASM, aggressive systemic mastocytosis; ISM, indolent systemic mastocytosis; MCAD, mast cell activation syndrome; PPI, proton pump inhibitor; SM, systemic mastocytosis.

patients having symptoms that could be ascribed to excessive MC mediator release (chronic urticaria, idiopathic angioedema, drug allergy, food intolerance, and others).⁵⁴

IL-6

Plasma levels of IL-6 in patients with SM correlate with disease severity and progression, serum tryptase levels, symptom severity, hematologic abnormalities, presence of osteoporosis, and others.^{55,56} Levels of IL-6 greater than 2.5 pg/mL indicated patients with severe disease. Moreover, patients with indolent systemic mastocytosis (ISM) who subsequently progressed already had increased IL-6 at the time of diagnosis.⁵⁷

Mast cell products for which there currently is insufficient clinical evidence for their contribution to symptoms or utility in the diagnosis of SM or MCAS. Table I lists mediators secreted by MCs and/or by other inflammatory cells. Some of these products have effects on MCs *in vitro*, whereas increased levels of others have been documented in clinical settings in which MCs participate. To date none of these mediators have been of proven value either in the diagnosis of SM or MCAS or in designing of clinical treatments.

Initial steps in the treatment of symptoms from MCAS and SM

Exclude confounding disorders. The first step in the approach to management of patients with MCAS or SM is to exclude common confounding disorders that can mimic MCAS or SM (Table II). These may include endocrine causes (pheochromocytoma, thyrotoxicosis, medullary carcinoma of the thyroid, insulinoma, carcinoid syndrome); cardiovascular disorders (labile hypertension, deconditioning, orthostatic hypotension, paroxysmal arrhythmias, baroreflex dysfunction); psychologic diseases (anxiety and panic attacks, somatization disorder, hyperventilation); pharmacologic changes (withdrawal of adrenergic inhibitor, mono amino oxidase [MAO] treatment + tyramine, sympathomimetic ingestion, illegal drug ingestion, chlorpropamide-alcohol flush, vancomycin-red-man syndrome); and neurologic reasons (postural orthostatic tachycardia syndrome, autonomic neuropathy, migraine headache, seizure disorders, stroke, cerebrovascular insufficiency) (Table III).

Avoid known and specific triggers. Patients must recognize and avoid general and specific individual factors that trigger symptoms. These can commonly include physical factors such as heat, changes in temperature, pressure, cold, or rubbing; some forms of exercise, emotions, stress, sleep deprivation; diagnostic and therapeutic agents such as opiates, NSAIDs, succinylcholine, and agents with tetrahydroisoquinoline (THIQ) motifs such as atracurium, rocuronium, quinolones that may activate MCs through non-IgE MRGPRX2 receptors⁸⁴; foods including those containing or releasing histamine, alcohol; hymenoptera venoms; and many others that can be unique for the individual patient such as latex and seminal plasma. Particular attention needs to be paid at times of surgery, invasive procedures, radiological use of contrast media, vaccinations, and dental procedures. Premedication regimes have been used with a combination of anti-H1 and anti-H2 histamine receptor medications, an LT receptor blocker and 0.5 mg/kg of prednisone for major procedures and anti-H1

and anti-H2 histamine receptor medications for minor procedures; although consensus recommendations have not been formulated or universally accepted. Diagnostic procedures such as skin testing and challenges are indicated for foods and medications to rule out IgE-mediated allergy, which occurs in patients with MCAS in a similar frequency as in the general population. Intolerance to NSAIDs is present in approximately 25% to 30% of patients and needs to be established through controlled challenge, because general deprivation of NSAIDs is not indicated and can be detrimental at the time of need to address pain and inflammation. Environmental skin testing is also indicated to address the symptoms of rhinitis, conjunctivitis, and asthma.

Treat persistent and/or episodic symptoms. The subsequent steps focus on treating specific organ-related symptoms (gastrointestinal, dermatologic, orthopedic, cardiovascular, respiratory, neuromuscular, and psychiatric) with appropriate medications. In addition, treatment can be based on targeting elevated urinary MC mediator levels (LTE4, 2,3-dinor-11 β -PGF2 α LTE4, N-MH) as well as monitoring serum tryptase levels obtained at baseline and during symptoms. Generally, symptoms of MCAS and of SM can be managed by blockade of mediator receptors (H1 and H2 antihistamines, LT blockade), inhibition of mediator synthesis (aspirin, zileuton), mediator release (sodium cromolyn), anti-IgE therapy, or a combination of these approaches. Importantly, there are neuropsychiatric symptoms associated with the presence of elevated mediators (mixed organic brain syndrome, which has been associated with elevated PGD2 metabolites) that can include anxiety, depression, inability to concentrate, brain fog, and short memory span that have been addressed with antidepressants and anxiolytic medications either chronically or during acute episodes. Therapy and psychiatric consultation are strongly recommended as MC activation disorders are chronic diseases that can be debilitating and have an impact in the quality of life. Patients' perception of their disease is an important factor in the treatment, and improvement of the quality of life is a major goal.⁸⁵ For some patients with clonal MC syndromes, the reduction in the number of MCs is necessary (see the "Medications useful for resistant symptoms" section).

Blockade of mediator receptors. H1 antihistamines are the cornerstone of the treatment with a combination of non-sedating (Table II) (cetirizine, fexofenadine, loratadine, desloratadine, levocetirizine) and sedating (diphenhydramine, hydroxyzine, cyproheptadine, doxepin, ketotifen) at Food and Drug Administration (FDA)-approved dosages, which have been escalated as indicated up to 4 times their recommended dose, without anecdotal evidence of severe side effects except for sedation and mucosal dryness. H2 antihistamines and proton pump inhibitors can address gastrointestinal symptoms such as ranitidine, cimetidine, and famotidine. A combination of baseline anti-H1 nonsedating with the addition of sedating medications mostly used for breakthrough symptoms or at bed time and an H2 blocker are recommended. LT receptor blockade such as montelukast or zafirlukast at FDA-recommended doses can add protection. Nasal antihistamines and corticosteroids are recommended for nasal congestion, sneezing, and postnasal drip. Environmental allergy testing is

TABLE II. Approach to mast cell mediator-induced symptoms in mastocytosis and MCAS.

A. Avoidance of triggers: patient specific	
Specific foods, medications (NSAIDs, vancomycin, quinolones), environmental allergens, and general triggers (stress, lack of sleep, emotions)	
Physical triggers (exercise, rubbing, pressure)	
Changes in temperature (heat, cold)	
Extreme temperatures	
Dryness of skin	
B. Premedications recommended for surgery, invasive procedures (endoscopy, colonoscopy, others), radiological procedures with contrast dyes, dental procedures, and vaccinations: 12 and 1 h	
• Antihistamine receptors H1 and H2	
• Leukotriene blocker	
• Steroid (0.5-1 mg/kg)	
C. Management of cutaneous mastocytosis:	
Local care of skin	
Skin moisturizer	
Water-soluble sodium cromolyn cream/ointment (1% to 4%)	
Avoid friction, pressure, and temperature changes	
Consider surgical excision for mastocytomas (flexures, soles, palms, scalp)	
Steroid creams	
PUVA (psoralens)	

MCAS, Mast cell activation syndrome; NSAID, nonsteroidal anti-inflammatory drug; PUVA, phototherapy and photochemotherapy.

recommended for all patients with naso-ocular symptoms because sensitization to environmental allergens occurs in over 25% of MC activation patients, as in the general population.⁸⁶

Inhibition of mediator release: sodium cromolyn.

Sodium cromolyn has shown to provide improvement of skin, gastrointestinal, and neuropsychiatric symptoms⁸⁷ and the recommendation is to start patients at 100 mg daily and escalate in 8 weeks to 800 mg divided in 200 mg 4 times daily, on an empty stomach before meals and at bed time. Severe gastrointestinal symptoms may require further escalation to 1000 to 1200 mg daily. Side effects are rare and include headache and constipation.

Inhibition of mediators synthesis: aspirin therapy and zileuton. There is no reason to avoid aspirin or other NSAIDs once a diagnosis of SM or MCAD has been made if the patient has tolerated these medications previously. Generally, 80% to 90% of patients will tolerate aspirin or other NSAIDs, and there have been no deaths reported from aspirin administration to patients with SM or MCAS.

To reduce an elevated level of PGD2 (as reflected by urinary excretion of 2,3-dinor-11 β -PGF2 α), a starting dose of 81 mg twice a day (BID) is frequently all that is required, but its effect at lowering PGD2 must be confirmed by a recheck of urinary metabolite excretion. The dose can be started with one-fourth of an 81 mg aspirin tablet (approximately 20 mg) and sequentially increased to one-half of an 81 mg tablet (approximately 40 mg) and after an additional 2 hours to 81 mg.

If necessary, as reflected by subsequent urinary tests of the PGD2 metabolite, the dose of aspirin can be progressively

TABLE III. Targeted approach for mast cell mediators–related symptoms in mastocytosis and MCAS

Systems and symptoms	Medications targeting mast cell mediators
Skin: pruritus, flushing, urticaria, angioedema, dermatographism	
1	H1-blockers and H2-blockers: Cetirizine 10 mg up to QID Loratadine 10 mg up to QID Fexofenadine 180 mg up to QID Hydroxyzine 10-25 mg QID Cyproheptadine 4 mg TID Doxepin 10-50 mg Ranitidine 150-300 mg BID Cimetidine 300 mg BID Pepcid 20-40 mg dq
2	Leukotriene receptor blockers/ antagonist Montelukast 10 mg Zileuton 650 mg BID
3	Aspirin 81-650 mg BID
4	Ketotifen 1-2 mg BID
5	4% sodium cromolyn cream/ ointment
Gastrointestinal: diarrhea, abdominal bloating, cramping/pain, nausea, vomiting, GER	
1	H2-blockers (as per above)
2	Cromolyn sodium 100-200 mg QID
3	Proton pump inhibitors (as per above)
4	Leukotriene receptor blockers/ antagonists (as per above)
5	Ketotifen 1-2 mg BID
Neuro/psychiatric: headache, poor concentration, short memory span, brain fog, anxiety, depression	
1	H1-blockers and H2-blockers (as per above)
2	Cromolyn sodium (as per above)
3	Ketotifen (as per above) Aspirin (as per above)
Cardiovascular: presyncope, syncope, tachycardia, hypotension, hypertension	
1	H1-blockers and H2-blockers
2	Corticosteroids 0.5-1 mg/kg
3	Epinephrine 0.3-0.5 mg
Pulmonary: wheezing, shortness of breath, throat swelling	
1	Bronchodilators Steroid/bronchodilator combination
2	H1-blockers and H2-blockers (as per above)
3	Corticosteroids 0.5-1 mg/kg
4	

(continued)

TABLE III. (Continued)

Systems and symptoms	Medications targeting mast cell mediators
Anaphylaxis	
Acute	Epinephrine IM 0.3-0.5 mg Corticosteroids (0.5-1 mg/kg) X1 dose IV fluids Antihistamine receptors H1 and H2
Prevention	H1-blockers and H2-blockers Leukotriene blockers Corticosteroids 0.5-1 mg/kg Omalizumab 300 mg every 28 days
Hymenoptera-induced	Venom immunotherapy Omalizumab 300 mg every 28 days
Naso-ocular: nasal stuffiness, nasal pruritus, conjunctival injection	H1-blockers (as per above)
	Inhaled corticosteroids Nasal cromolyn sodium
Bone: osteopenia, osteoporosis, bone fractures	Calcium, Vit D Biphosphonates Clodronate, pamidronate, alendronate, zoledronate Interferon alpha 2a

BID, Twice a day; *GER*, gastrointestinal reflux; *IV*, intravenous; *MCAS*, mast cell activation syndrome; *QID*, four times a day.

increased: 162 mg BID → 325 mg BID → 500 to 650 mg BID with guidance by the local care provider or allergist.

If there is a history of a mild prior reaction (flushing, hives, or rash without bronchospasm, hypotension, or angioedema), aspirin can be administered in an outpatient setting and given every 30 to 60 minutes beginning at 0.1 mg with subsequent doses of 0.3, 1.0, 3.0, 10, 20, 40, 81, 161, and 325 mg with subsequent administration twice daily.

For the rare patient with a history of bronchospasm, hypotension, or anaphylaxis after aspirin administration who requires aspirin to prevent symptoms, hospitalization in an intensive care unit setting is required. A similar slow up dosing schedule is used but the interval between doses is increased to 2 to 3 hours. It may be necessary to treat reactions and readminister the last tolerated dose of aspirin several times before the dose can be advanced. This process can take several days. This gradual up dosing schedule has been published as an approach to desensitize patients with aspirin-aggravated angioedema.⁸⁸ As in AERD, zileuton has been helpful to control asthmatic symptoms and also gastrointestinal symptoms at 1200 mg twice daily.

Acute mast cell activation episodes. Surgery, radiological procedures, infections, allergenic foods, or medications can trigger acute MC activation events that need to be treated with intramuscular epinephrine. Mastocytosis patients with elevated tryptase or with prior anaphylactic events need to carry at least 2 autoinjectable devices, which may need to be used. Patients with CM and with MCAS without anaphylactic episodes do not need to carry autoinjectable epinephrine. Massive

MC activation events require 2 doses of intramuscular epinephrine (0.3 mg for adults, 0.15 mg for children) that can be administered at 1- to 5-minute intervals. Intravenous epinephrine is not recommended due to the potential of TakoTsubo and Kounis syndromes and will only be required in cases of cardiovascular collapse. Antihistamines at twice the standard dose may be required for 24 to 48 hours and prednisone at 0.5 to 1 mg/kg for the next 48 to 72 hours. Hydration is also recommended during emergency department visits.

Monitoring of bone density. Bone involvement by SM can cause osteopenia, osteosclerosis, osteoporosis, as well as long bone or vertebral pathologic fractures. There are no studies of bone involvement in nonclonal MCAS or in monoclonal mast cell activation syndrome (MMAS). The frequency of bone mineral density (BMD) measurements can be individualized depending on the presence of skeletal-related symptoms, the presence of “C” symptoms indicating aggressive disease with organ involvement and compromised function, the rapidity of BMD decline, and the response to treatment. There are no firm guidelines, however.

Fractures are reported in 16% of patients with SM,⁸⁹ and certain groups have an increased frequency of fractures (young men and postmenopausal women with ISM), whereas premenopausal women do not have an increased risk. Also, the presence of urticaria pigmentosa has been reported to protect against fractures,⁹⁰ and elevated tryptase levels have been associated with greater bone density in patients with SM.⁹¹

One recommendation has been to perform BMD every 18 months in patients with osteoporosis and every third year in patients with osteopenia.⁹²

In one of the coauthor's (JB) practice, stable patients with ISM have BMD measurements every 24 months. The initial approach is to evaluate vitamin D and if deficient start additional supplementation of vitamin D and calcium. Bisphosphonates and Rank ligand inhibitors are recommended (Table II) for osteoporosis.

Medications useful for resistant symptoms

Interferon alpha-2b. Because the response to IFN- α does not depend on *c-kit* mutational status, it can be successfully used to treat SM in *c-kit* D816V positive patients resistant to imatinib mesylate.⁹³ In large reviews, IFN- α is listed as a first-line treatment for approximately 27% of patients.⁹⁴ Used alone in high doses (10 million units [MU] 3/week), IFN- α can markedly reduce bone marrow infiltration by MCs, cause fading of urticarial pigmentosa, and induce weight gain.⁹⁵ At lower doses (3-5 MU 3 $\times$ /week) in combination with prednisolone, IFN- α can result in complete or partial resolution of C-findings or can stabilize disease.⁹⁶ An increase in bone density has resulted from the combined use of low-dose IFN- α (1.5 MU 3 $\times$ /week) plus pamidronate.⁹⁷

Omalizumab. Omalizumab, a humanized murine mAb, binds to free IgE in the serum, thereby preventing binding to the high-affinity FC ϵ RI present on MCs and basophils subsequently reducing involvement of these cells in allergic reactions. Omalizumab has been beneficial in the management of clinical problems in adults and children with various forms of mastocytosis as well as MCAS.

Toddlers with severe diffuse CM as well as adults with urticarial pigmentosa have shown marked improvement.^{68,98,99} Also,

among the pediatric population, omalizumab has been effective in controlling idiopathic anaphylaxis, and as a component in the treatment of Kounis syndrome. Teenage girls with MCAS including idiopathic anaphylaxis respond to omalizumab. Among adult patients with SM, omalizumab has been successful in the management MC mediator symptoms, including anaphylaxis with complete control in nearly 40% of patients in one series.¹⁰⁰ Gastrointestinal and cutaneous symptoms in ISM have also responded.¹⁰¹

Omalizumab has been effective in preventing acute reactions to venom immunotherapy (VIT), thereby allowing completion and continuance of injections.^{102,103} Premedication with omalizumab has also allowed advancement of VIT to a dose of 200 μ g. Low-dose (150 mg SC monthly) omalizumab has successfully controlled VIT-induced anaphylaxis in idiopathic, nonclonal MCAS.

Similar to its beneficial effects in patients with SM, omalizumab increasingly is finding use in the treatment of MCAS and idiopathic anaphylaxis resistant to conventional therapy.¹⁰⁴ Patients having monoclonal MC activation disorder with refractory and recurrent anaphylaxis also respond well to omalizumab.¹⁰⁵

Other medication

Cladribine (2-chlorodeoxyadenosine [2-CdA]). 2-CdA is a purine analog with activity against both resting and actively dividing cells. In 2001, the first successful use of 2-CdA in SM was reported in a 57-year-old man who had not derived benefit from prolonged treatment with interferon alpha. After 6 cycles of 2-CdA, he experienced resolution of urticarial pigmentosa lesions and a marked reduction in MC bone marrow infiltration.¹⁰⁶ Cladribine is administered by intravenous infusion (0.13-0.17 mg/kg/day) over 2 hours for 1 to 5 consecutive days and repeated every 4 to 12 weeks for up to 9 courses.

In a large series of patients with SM, overall response rates of 50% to 82% for patients with advanced SM and 60% in patients with bone marrow mastocytosis and ISM have been reported¹⁰⁷ with significant improvement as a single agent for multiple symptoms in aggressive systemic mastocytosis (ASM).¹⁰⁸ One patient having SM-associated hematological neoplasm (AHN) resistant to treatment with dasatinib showed a good response to 2-CdA (lessened itching, reduced need for paracentesis of ascites).

Partial, temporary responses are often reported.¹⁰⁹ Side effects including anemia, myelosuppression, and prolonged suppression of the CD4+ T cells may lead to susceptibility to viral infections such as progressive multifocal leukoencephalopathy.¹¹⁰

Hydroxyurea. Hydroxyurea has mainly been used in the treatment of SM-AHN. In the largest series of 30 patients (1 ASM, 28 SM-ANH, 1 mast cell leukemia [MCL]), given doses of 500 mg every other day to 2000 mg/day with evaluation possible in 26 patients, an overall response rate of 19% (control of thrombocytosis, leukocytosis, and/or splenomegaly) was observed, and the median duration of response was 31.5 months.¹⁰⁷

Tyrosine kinase inhibitors (TKIs)

Imatinib mesylate. Several TKIs have now been employed to manage SM, but there is no study of their use in MCAS. In the minority of patients with SM with wild-type *KIT*, imatinib therapy is highly successful in controlling symptoms, and the

control can be prolonged.¹¹¹ Although symptomatic improvement has been reported with imatinib use in patients harboring the *c-kit* D816V mutation,^{111,112} imatinib is generally ineffective therapy for patients with SM with this mutation.^{113,114}

Midostaurin (PKC412). Midostaurin, a multikinase inhibitor, has generally been used for the treatment of advanced SM (ASM, SM-AHN and MCL). In a phase 2 trial, midostaurin was well tolerated affording durable, clinically meaningful responses including the reduction of marrow MC burden, disappearance of splenomegaly, decrease in serum tryptase, transfusion independence, and normalization of marked eosinophilia in 3 patients with SM-chronic myelomonocytic leukemia (CMML).¹¹⁵ A subsequent trial in 38 patients with advanced SM showed an overall response rate of 60%, a response shown to be dependent on the presence or absence of additional non-KIT mutations.¹¹⁶

Dasatinib. The clinical results with dasatinib in SM have been disappointing in patients harboring the *KIT* D816 mutation, with an overall response rate of 33% and temporary symptomatic responses lasting 3 to 18+ months.¹¹⁷ Generally well tolerated, dasatinib does not prevent the development of AML in patients with SM and has not reduced the frequency of anaphylactic episodes in a symptomatic patient with ISM.¹¹⁸

Avapritinib (BLU-285). BLU-285, a potent, and highly specific oral inhibitor of *KIT* activation loop mutants including D816V, has shown encouraging results in a phase 1 study in patients with advanced SM, including those who have failed midostaurin and other cytotoxic therapies. Improvements have included reduced MC burden and D816V mutant allele fraction. BLU-285 is well tolerated, and no patient discontinued treatment because of drug-related adverse reactions.¹¹⁹

CONCLUSIONS

Major advances have occurred in the last 5 years regarding the diagnosis, prognosis, and treatment of mastocytosis including new TKIs with targeted precision for KIT and KIT mutations, but much research is needed for nonclonal MCAS. Mastocytosis and MCAS are rare diseases for which there is presently no cure, and windows of opportunity exist now for the study of genes and proteins that govern MC activation, which can translate into therapeutic interventions to alleviate the suffering of all patients with MCAS.

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