THE MAST CELL DISEASE SOCIETY, INC.

FDA Patient Listening Session on Cutaneous and Systemic Mastocytosis

Session Date: 09/28/2021

Objective of session

Mastocytosis is a rare clonal disease that includes benign cutaneous variants, indolent systemic forms, smoldering systemic mastocytosis which shows signs of progression, and advanced, malignant forms including aggressive systemic mastocytosis, systemic mastocytosis with an associated hematologic neoplasm, and mast cell leukemia.[1, 2] The Mast Cell Disease Society (TMS) is dedicated to providing multi-faceted support to patients, families, and medical professionals in our community and to leading the advancement of knowledge and research in mast cell diseases through education, advocacy and collaboration. On Tuesday September 28, 2021, TMS representatives along with members of the mastocytosis community, participated in a 90-minute listening session where the impact of living with mastocytosis was discussed with representatives from the U.S. Food and Drug Administration.

The objectives of this session were to familiarize the FDA with:

1. The serious impact that mastocytosis has on quality of life
2. Difficulty in obtaining an accurate diagnosis and appropriate care
3. Burden of managing multiple medications with high costs and insurance hurdles
4. The intrusive and relentless symptoms for which there is very little relief from medications
5. The unpredictability of the onset of severely disabling symptoms which further significantly reduce of quality of life
6. The depression, anxiety, and social isolation which accompany chronic disease
7. The need for novel and effective therapies for all variants of mastocytosis to be developed and approved is urgent, and especially for patients affected by variants with a shortened life expectancy.

TMS representatives:

The session was moderated by Valerie M. Slee, RN, BSN, Chair, The Mast Cell Disease Society (TMS)

Additional presenters included Susan Jennings, PhD and Celeste Finnerty, PhD, Co-chairs, TMS Research Committee. Other guests included: Lauren Denton, TMS Executive Director; Jess Blomberg, TMS Research Committee; Andrew Slee, PhD, TMS Research Committee; and Ivy Lopez, TMS Director, Patient Programs.

Patient/family participants:

Pediatric Cutaneous Mastocytosis (CM):

- A mother, who is a patient herself and a caregiver of a school-aged child with CM and hereditary alpha tryptasemia (HαT)

Indolent Systemic Mastocytosis (ISM):

- An adult female patient who was diagnosed with CM in childhood and progressed to ISM
- A female patient diagnosed in adulthood with ISM and frequent anaphylaxis
- A male patient diagnosed in adulthood with ISM and associated chronic anemia

Smoldering Systemic Mastocytosis (SSM):

- An adult female patient

Systemic Mastocytosis - Associated Hematological Malignancy (SM-AHN):

- An adult female patient undergoing stem cell transplantation (the AHN is myelodysplastic syndrome)

Aggressive Systemic Mastocytosis (ASM):

- An adult female patient on a clinical trial

Mast Cell Leukemia (MCL):

- A mother of a young adult who passed away from MCL

Three guests related to the patient participants attended as well.

FDA Representation:

Advisors from the FDA to TMS: Susan Chittoran, Shawn Shermer, and Alec Halsne.

Office of the Commissioner (OC)

- OC/OCPP/OPA- Office of Clinical Policy and Programs/Office of Patient Affairs *(organizer)*
- OC/OCPP – Office of Clinical Policy and Programs
- OC/OCPP/OOPD - Office of Clinical Policy and Programs/Office of Orphan Products Development
- OC/OEA/SES – Office of External Affairs/Stakeholder Engagement Staff

Center for Biologics Evaluation & Research (CBER)

- CBER/OCD - Office of the Center Director
- CBER/OTAT/DCEPT – Office of Tissues and Advanced Therapies/Division of Clinical Evaluation and Pharm/Tox

Center for Devices and Radiological Health

- CDRH/OSPTI – Office of Strategic Partnerships and Technology Innovation
- CDRH/OSPTI/DAHRSSP - Office of Strategic Partnerships and Technology Innovation/Division of All Hazards Response Science and Strategic Partnerships

Center for Drug Evaluation and Research (CDER)

- CDER/OCD – Office of the Center Director
- CDER/OCD/PASES - Office of the Center Director/Professional Affairs and Stakeholder Engagement Staff
- CDER/OCD/PFDD – Office of the Center Director/Patient Focused Drug Development
- CDER/OND/OCHEN/DNH – Office of New Drugs/Office of Cardiology, Hematology, Endocrinology and Nephrology/Division of Non-Malignant Hematology
- CDER/OND/OII/DPACC – Office of New Drugs/Office of Immunology and Inflammation/Division of Pulmonology, Allergy and Critical Care
- CDER/OTS/OB/DBIX – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics IX
- CDER/OTS/OB/DBVI – Office of Translational Sciences/Office of Biostatistics/Division of Biometrics VI

Summary of topics discussed

Please note that the following abbreviated terms have been used in various quotations from the session: “masto” for mastocytosis, and “epi” to describe injectable epinephrine, also referred to as an Epi-Pen.

The path to a correct diagnosis of any form of mastocytosis is often long:

The participating patients reported an average of 8.8 years between the time of the first symptoms and diagnosis. During this time, they saw many doctors and received multiple interim diagnoses, some of which were incorrect. They reported receiving medications to treat the misdiagnosed disease, but did not receive the standard of care for mastocytosis. Some medications and treatments had serious side-effects.

- "It took a very long time to find a doctor who knew what mastocytosis even was, let alone how to treat it."
- "We saw around 12 doctors in the first four years of his life." "When he was three, I was reading medical journal articles about mast cell activation syndrome (MCAS)." The mother first asked their physician to pursue testing, and as a result, the child was first diagnosed (incorrectly) with MCAS. However, this first mast cell disease diagnosis ultimately led physicians to correctly diagnose the child with CM and HαT.

Early recognition of the disease could save lives:

Early recognition of mast cell diseases would allow for treatment that would stabilize the patient, help prevent the cascade of mast cell activation symptoms, and potentially prevent organ damage that occurs with disease progression, for example, in bone.

- "Currently my quality of life is just fair, limited most by my spinal damage and bone pain. I wake up every morning in acute pain and until my pain meds kick in, I am unable to function."
- "If only one of the doctors who had treated my daughter had recognized what her rash represented and diagnosed her earlier, she could have been treated and had a *chance* to live."

Symptoms can be unpredictable, relentless, and/or life-threatening:

One of the most challenging aspects impacting quality of life for patients with mastocytosis is ***the unpredictable onset of very disabling and sometimes life-threatening symptoms, including life-threatening anaphylaxis, sometimes with an atypical presentation***. Signs and symptoms of mastocytosis may have long-term impact on overall health.

- "Living with mast cell disease is very unpredictable… One of the most challenging things... is the lack of safe foods and traumatic life-threatening reactions. [My son] was living with these daily symptoms of severe GI pain, vomiting, choking on food to the point we had to pull him from his high chair to do Heimlich maneuver on him at almost every meal. He was having throat swelling and wheezing with many foods, which... was likely anaphylaxis."
- "I had rare bouts of abdominal cramping so severe I could only lie on the bathroom floor and not speak...I developed night sweats, severe diarrhea and projectile vomiting. The diarrhea was so explosive that it was like a colonoscopy prep and required cleaning of the toilet and me. The vomiting at times was projectile, and also required a cleanup of the room and me."
- "My symptoms are unpredictable… My anaphylaxis is atypical; I don't get hives; my blood pressure goes up and this just adds to the confusion. If you don't have 'textbook' anaphylaxis, it can be difficult to be taken seriously. ER physician education about mastocytosis and atypical anaphylaxis is desperately needed."

Triggers [3]

Triggers for mast cell activation can vary, and may include heat, cold, change in temperature, insect/other venom stings, odors, fatigue, exercise, friction/vibration, foods, medications, alcohol, infections, and stress - physical, environmental, and/or emotional. Triggers may change over time, and differ from one person to another.

- "I realized that emotionally based stress was my most significant trigger"
- "Pollen, heat and stress are my big triggers."

- “She became allergic to alcohol and cigarette smoke, when previously she had only reacted to a bee sting and shellfish”.

Disease management:

The huge burden of having mastocytosis can be draining. This may include ordering and taking multiple medications, oral and injectable, fighting insurance companies with prior authorizations, booking appointments, and maintaining communications with multiple specialists (5-12 for some patients) and trying to be the agent of care coordination for oneself.

- “I am currently on 17 different prescriptions, taking 38 pills... on a bad day.”
- “I am so complex that I have a team of doctors. Coordinating this team is my full-time job. Prior authorizations became an often-fought battle. I’ve often been afraid that I would be unable to get medicines in time to stay alive.”

Challenge of being taken seriously in the emergency room (ER):

Patients reported being challenged by poor care in the ER, and having to convince physicians that atypical anaphylaxis is real, having to teach staff what mastocytosis is even while critically ill. Some physicians will read and utilize an emergency protocol from a mast cell disease physician; others will not even look at it. Getting appropriate treatment for anaphylaxis or any emergency while ill with mastocytosis is a pressing need.

- “Sometimes in the ER, I am greeted with “you are having a panic attack” because the Epi has already worked and the symptoms of anaphylaxis are resolving. This is totally humiliating for patients as sick as we are not to have ER staff understand our disease and how sick we are”
- “Interacting with ER providers is frustrating. Most have never heard of SM; some are willing to reference and use my ER care plan, which is a sigh of relief, but others are offended and refuse to use it. I’ve been called a liar, a faker and drug seeker. My anaphylaxis is atypical; I don’t get hives; my blood pressure goes up and this just adds to the confusion. If you don’t have “textbook” anaphylaxis, it can be difficult to be taken seriously.”

Impact of side effects of treatment:

Patients vary in their response to treatment. Some qualify for clinical trials or chemotherapy but find the treatment worse than the disease. Others have very disabling symptoms but do not qualify for a therapy which has the potential to alleviate them.

- “Rydapt. Initially it reduced my symptoms and tryptase, but for me, the side effects were worse than my symptoms of masto with violent, projectile vomiting and/or severe nausea every day. No anti-nausea drug helped.“
- ”As with the first stem cell transplant, I am finding the second transplant much easier to tolerate than mastocytosis. The transplant has a schedule of events [and treatments] and my recovery is following that expected plan.”

Issues related to progression:

Patients with advanced variants frequently are given life expectancies based on what little data is available, adding additional emotional stress to their lives.

- “Past studies indicate the median survival rate after ASM diagnosis is 41 months. It’s been 37 months since my formal ASM diagnosis.”

Costs of treatment of mastocytosis:

Patients are challenged by the costs associated with managing multiple medications, including compounded medications and specialty formulas - none of which are covered by insurance. One mother reported that her son required a special formula costing $36/day, paid out-of-pocket for several years. Chemotherapy can be extremely expensive with out-of-pocket costs as much as $70,000 / year *after* insurance and drug company assistance. Patients may avoid using Epi-Pens due to the cost, and many insurance plans limit the number of auto-injectable epinephrine devices that a patient may have in a given period of time, regardless of their documented history of anaphylaxis.

- "At one point I was using more than 10 epi auto-injectors each month and my insurance would only allow 2. My family had to learn to manually draw up syringes of epi when anaphylaxis hit as we couldn't afford to pay out of pocket for autoinjectors. Imagine my 10-year-old son being called to break ampules of epi, use filtering needles to draw up the appropriate dose then switching to the injection needle before using it on me while I struggled to breathe."
- "I am in the ER for anaphylaxis at least 6 times per year. One problem I have is that I cannot get enough injectable Epi-Pens. Each time I go into anaphylaxis, I need to give two doses. Because I am on Medicare, I am not eligible to use the coupons for free or reduced cost Epi. This is so unfair. We are the patients who require this life-saving drug, we are on disability because we are sick, but that disqualifies us from getting the drug that saves us during anaphylaxis! Epi-Pens cost me $590.00 for a pair! If I am in the ER in anaphylaxis, they make me use my own Epi-Pens! Epi-Pens are a life-saving drug and should be provided free of charge in any quantity that is required by patients who go into anaphylaxis."

Diminished quality of life:

Adults and children affected by all variants of mastocytosis report poorer physical and mental health than do volunteers from the general population. Patients report a surprisingly high number of days per month when they do not feel well. (TMS presented unpublished data on quality of life; we will add the link to the publication when it is available)

- "My quality of life is ***UNfair***! Regardless of the effects of any past treatments, let me be clear in saying that I never have a good day."
- "I am now homebound, some days bed bound. I leave the house for doctor appointments and the very rare family function. All household chores must be done by my husband, as I am too weak. I have symptoms every day. I've missed family vacations... weddings, holidays and get-togethers. I cannot spend any time outside because of the pollen, pollution, and wildfire smoke."
- "I've yet to find a treatment that has made any significant change in my quality of life."
- "The No list is very long. There are many foods that he can't eat, places he can't go, he can't go outside too long or he will swell up with hives from heat or cold... I had to quit my job and career as an oceanographer because it was not conducive to having a child with mastocytosis."
- "Our life expectancy may not be cut short due to mastocytosis, but the life we are left with is undesirable & miserable."
- "During severe mast cell flares, you have both--periods of chronic illness that are interrupted by sudden critical illness that eventually slides back into periods of chronic illness."

Impact of mastocytosis on family and social relationships:

Social isolation becomes a significant issue as patients and families sacrifice interactions, activities, and comfortable relationships while trying to

establish new and safer ways to connect. Family dynamics frequently change with necessary adjustments made to manage the disease.

- "I know it is disturbing for my family members to see my physical limitations and disabilities."
- "I literally have no good friends except for the other masto sufferers I've met through on-line support groups. My husband is wonderful and does all the daily chores, but our personal relationship is tough... We both grieve and long for "what was" and have gone kicking and screaming into "what is"... My adult daughters were 13 when I was diagnosed...Sadly, they don't recall the mom who worked full-time, took them to and from school, attended all the sports events, band concerts, etc."
- "After [my daughter] passed away I was traumatized. I lost my house, I got divorced, I drank heavily and took [medications] to just numb my pain.... I became very isolated. I continue to be on psychiatric medicine and continue with prolonged grief."

Comorbid conditions:

In addition to the burden of disease itself, mastocytosis patients may also suffer from comorbidities such as connective tissue disorders, autonomic dysfunction, and primary immunodeficiencies.[4] These comorbidities complicate elucidating symptom etiology and management. HαT may also be a disease modifier for mastocytosis; the exact role that it plays is currently the topic of much discussion and research.

Hope for the Future - the ideal medication:

Any medication that can benefit a patient with one type of mast cell disease, like mastocytosis, can have the potential to help patients with other mast cell diseases (e.g., MCAS, HαT), who may share both the normal and abnormal functions of the mast cell. Collectively the patients expressed a desire for an ideal treatment for mastocytosis that would be affordable and readily available for all who need it with minimum side effects. Taken early in the disease course, it could potentially prevent progression to more advanced stages and would also minimize symptoms of mast cell activation. It would improve quality of life for patients and their families, and restore independence. Additionally, patients asked for other ways to deliver epinephrine aside from injections, and for medications that target other histamine receptors beyond the H1 and H2 receptors. Patients with mastocytosis requested better medication to control pain that would not trigger, activate, or degranulate mast cells. Finally, participants asked for epinephrine autoinjectors to be free for any patient with recurrent anaphylaxis, or at least to be covered by insurance in unlimited quantities.

- "When I asked [*my son*] what he wants me to ask you [*the FDA*] for, he said please ask them to find a cure! He said he wants to be able to do activities more like a normal kid."

Closing:

The Mast Cell Disease Society, Inc. would like to thank the FDA for this valuable opportunity to speak about mastocytosis, and the patients and families who participated, for their time, courage and advocacy.

Disclaimer:

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects The Mast Cell Disease Society's account of the perspectives of patients and caregivers who participated in the FDA Patient Listening Session on Mastocytosis with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of mastocytosis, health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire

mastocytosis patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report

References:

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3. Jennings SV, Slee VM, Finnerty CC, Hempstead JB, Bowman AS. Symptoms of mast cell activation: The patient perspective. *Ann Allergy Asthma Immunol*. Oct 2021;127(4):407-409. doi:10.1016/j.anai.2021.07.004
4. Gotlib J, George TI, Carter MC, et al. Proceedings from the Inaugural American Initiative in Mast Cell Diseases (AIM) Investigator Conference. *J Allergy Clin Immunol*. Jun 2021;147(6):2043-2052. doi:10.1016/j.jaci.2021.03.008