

Treatment Strategies in Mastocytosis

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KEYWORDS

• Mastocytosis • Antimediator therapy • Mediator-related symptoms • Antihistamine
• Platelet-activating factor • Anti-IgE

KEY POINTS

- Most patients with mastocytosis suffer from the indolent form.
- Mediator-related symptoms and comorbidities significantly affect the quality of life.
- Available treatment options include antihistamines and other drugs directed against the effects of mast cells and their mediators.
- All of these drugs are off label.
- The recommendation to use these drugs is almost exclusively based on expert opinion; controlled clinical trials need to be performed.
- A better understanding of mechanisms in mastocytosis will allow for the identification of future targets for effective treatments.

INTRODUCTION

Mastocytosis is a heterogeneous group of diseases with an increased number of mast cells (MCs) in 1 or multiple organs, ranging from indolent to very rare aggressive forms with fatal outcome.¹ The current World Health Organization classification differentiates between 7 mastocytosis subtypes (**Table 1**), dividing cutaneous from systemic

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Table 1 World Health Organization classification of mastocytosis			
Category	Frequency (%)	Prognosis	Therapeutic Options
CM ISM	>80	Good	Antimediator therapy, ultraviolet or topical treatments, emergency medication, osteoporosis treatment
SM-AHNMD	10	Variable	Plus treatment of AHNMD
ASM	5	Poor	Plus cytoreductive therapy
MCL MSC	<5	Poor	Plus cytoreductive therapy, bone marrow transplantation (MCL)
ECM	<1	Good	Plus surgical excision (if applicable)

Abbreviations: ASM, aggressive systemic mastocytosis; CM, cutaneous mastocytosis; ECM, extracutaneous mastocytoma; ISM, indolent systemic mastocytosis; MCL, MC leukemia; MSC, MC sarcoma; SM-AHNMD, systemic mastocytosis with associated hematologic non-MC disease.

Data from Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res* 2001;25(7):603–25; and Cardet JC, Akin C, Lee MJ. Mastocytosis: update on pharmacotherapy and future directions. *Expert Opin Pharmacother* 2013;14(15):2033–45.

forms.^{2,3} Patients with systemic mastocytosis frequently also exhibit cutaneous lesions which is specified as mastocytosis in the skin (MIS), whereas cutaneous mastocytosis (CM) excludes systemic involvement. Mastocytosis is classified as a rare disease with an estimated prevalence of around 1 per 10.000⁴; however, epidemiologic studies are lacking, and the disease is probably underdiagnosed. Pathogenic mechanisms involve the presence of somatic, activating c-kit-mutations, most commonly the Kit D816V point mutation, which is present in more than 95% of adults and 40% of children with mastocytosis.⁵

The signs and symptoms in mastocytosis result either from effects of MC mediators or from organ impairment caused by MC infiltration. Of these signs and symptoms, mediator-related symptoms are prevalent and occur in all types of mastocytosis, whereas problems caused by infiltrating MCs are seen only in the rare, aggressive forms of mastocytosis.⁶

Mediator-related signs and symptoms are diverse. They may be acute, related to a sudden MC degranulation, or chronic and involve the skin (pruritus, flushing, and cosmetic complaints), the gastrointestinal tract (reflux, ulcers, cramping, and diarrhea), and the central nervous system (depression, moods, and cognitive symptoms) and musculoskeletal pain. Anaphylactic episodes occur in around 30% to 40% of patients and may be unpredictable, recurring, and non-IgE mediated.^{7–10} In addition, disease-associated comorbidities like osteoporosis or associated hematologic disorders are seen.

No curative therapy for mastocytosis exists, and the most important overall aim of treatment is the control of symptoms. Patients with cutaneous mastocytosis (CM) and indolent systemic mastocytosis (ISM) (ie, most patients with mastocytosis) have a normal, or near normal, life expectancy compared with the general population,¹¹ which underlines that the focus of disease management should be on symptom control.

Treatment recommendations for mastocytosis are based mostly on expert opinion rather than evidence obtained from controlled clinical trials. In this article, current treatment options available in mastocytosis are presented, with a focus on the control of mediator-related symptoms in patients with indolent disease.

GENERAL CONSIDERATIONS

In general, mastocytosis is best handled by a coordinated, multidisciplinary approach by centers with experience in managing the disease. The focus should be on individualized, tailored treatment and follow-up depending on symptoms and disease manifestations.

Overall, treatment strategies are divided into antimediator therapy aimed at MC mediators and cytoreductive therapies aiming at reduction of neoplastic MC burden. The latter should be reserved for patients with aggressive disease or severely affected patients with ISM because of potential side effects.

All patients benefit from thorough information and counseling tailored to the individual, bearing in mind that many patients go on the Internet for information, which may vary greatly in quality and relevance given the rarity and heterogeneity of the disease and thus may result in misinformation and unnecessary concerns.

Further, it is important to clarify relevant triggers for MC degranulation in order to avoid these. Even although some MC triggers are common (heat, alcohol, insect stings, spicy foods, certain drugs), general advice to avoid a long list of potential triggers is not helpful, but must be individualized and relevant to the patient's experiences. Information must be given on potential risk situations (eg, general anesthesia, contrast media), and it is advisable to provide written information on the disease to the patient and relevant health care professionals (eg a disease passport).

In general, most mastocytosis centers equip all adult patients with mastocytosis with an adrenaline autoinjector for use in case of anaphylaxis (Fig. 1). In children with mastocytosis, the risk of anaphylaxis is lower than in adults, and there is no consensus whether to prescribe an adrenaline autoinjector for all children or only in children with severe disease/bullous skin lesions/basal tryptase levels higher than 100 µg/L or a previous anaphylactic episode.^{7,9,12}

CM IN CHILDREN

The skin lesions in mastocytosis differ depending on the age of disease onset.¹³ In children, mastocytosis is mainly limited to skin; the most common type is the solitary mastocytoma. Other childhood-onset forms include maculopapular, nodular, xanthelasmoid, or pachydermatous lesions, as well as diffuse CM with the involvement of the entire integument.¹⁴ Up to the age of 3 years, some children suffer from blistering in affected areas, mostly as a result of mechanical irritation. Childhood-onset CM has a high chance of spontaneous remission, and treatment should be

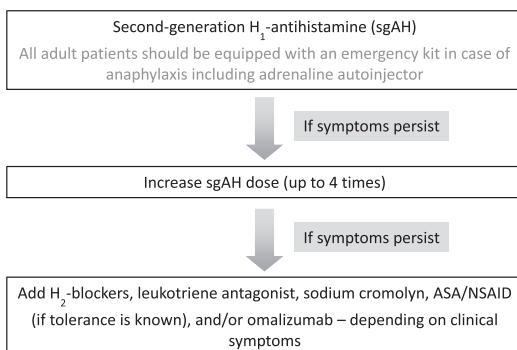


Fig. 1. Proposed therapeutic algorithm for antimediator treatment in mastocytosis.

based on symptoms. Clinically symptomatic mastocytomas may be treated with short-term high-potency topical corticosteroids or injected with crystalline steroid solutions. In single cases, the use of topical pimecrolimus has been reported to result in the remission of lesions.¹⁵ Mastocytomas accompanied by systemic symptoms (ie, recurrent anaphylaxis) may warrant surgical excision, depending on the location of the tumor.¹⁶

SKIN LESIONS IN ADULTS

In 80% to 90% of patients with adult-onset ISM, the skin is affected. The cutaneous manifestation typically presents with maculopapular skin lesions (historically called urticaria pigmentosa) with a positive Darier sign (whealing and flushing on mechanical irritation). The clinical picture ranges from only a few lesions, which are easy to miss in a routine diagnostic workup, to widespread lesions that cover up to 80% of the skin compartment. About 60% of patients complain about recurrent pruritic episodes or whealing, especially when exposed to triggers of MC activation, whereas some patients do not have any subjective symptoms at the skin. The number and distribution of the cutaneous lesions show individual variations but are of a chronic-stable nature. A major issue in many patients is cosmetic complaints, especially in youth. The challenge here is that the skin lesions are caused by MC infiltration, so an effective treatment demands reduction of this infiltration. The disappearance of cutaneous lesions in mastocytosis has been reported with the use of cytoreductive drugs, like tyrosine kinase inhibitors (TKIs) and cladribine in patients with advanced cases of systemic mastocytosis (SM)^{17,18}; however, the use of these potentially toxic drugs is obsolete in purely cutaneous or indolent forms of mastocytosis. So, therapeutic options to interfere with the clinical appearance of the skin lesions are virtually absent and limited to phototherapy, including UVA₁, narrow-band UVB, and UVA plus psoralen. There is well-reported efficacy of phototherapy in CM and MIS in regard to the mediator-related skin symptoms, including pruritus; however, complete or permanent disappearance of the lesions is not reported, and the overall period of symptom reduction is short.¹⁹ The immediate response may be improved by combining phototherapy with short-term high-potent topical steroids under occlusion; however, this does not influence the long-term efficacy outcome of the treatment. Thus, given the potential side effects of recurrent ultraviolet phototherapy, a calculated use of this treatment modality should be considered. Single case studies report about the successful use of neodymium-doped yttrium aluminum garnet laser therapy, which is certainly not an option for all patients, because of the different intensity and distribution of lesions, but is potentially useful for some patients (eg, with skin lesions in the face).^{20,21}

SKIN SYMPTOMS

Recurring episodes of pruritus, whealing, and flushing can be controlled by first-generation and second-generation H₁ antihistamines (sgAH).²² However, many patients may need increased doses of antihistamines to completely control symptoms.^{23,24} During the last 2 decades, only 1 single controlled clinical trial showing efficacy of sgAH in the treatment of mastocytosis has been performed.²² In this trial, the sgAH rupatadine has been shown to significantly reduce mediator-related symptoms and improve patients' quality of life. Despite missing further evidence for mastocytosis, treatment regimens and guidelines for other MC-driven diseases (ie, chronic spontaneous urticaria), it can be considered to increase the dose up to 4-fold the usual daily dose.²⁵ In most countries, antihistamines are not licensed to be used in patients younger than 2 years. However, the pharmacologic profile of most sgAH may allow for

their use during pregnancy and infancy. Sodium cromolyn has been reported to be effective in both children and adults to relieve cutaneous symptoms, used topically as well as perorally.^{26,27} The mechanism of action is not clear, because enteric absorption of sodium cromolyn is minimal²⁸ and its effects on human MCs unclear.²⁹ The use of topical steroids may be valuable to reduce skin symptoms as short-term use; however, long-term use must be avoided because of side effects, taking into account the chronicity of the disease. In addition, other substances, including polidocanol and topical antihistamines, have been reported to support relief of pruritus in CM. Further treatment considerations for skin symptoms besides sgAH include efforts to block additional mediators that are involved in symptom formation (ie, leukotrienes, platelet-activating factor, or prostaglandins).^{22,30–33}

GASTROINTESTINAL SYMPTOMS

Gastrointestinal manifestations in patients with mastocytosis are highly prevalent and may be severe.^{34,35} About 30% of patients with mastocytosis have gastrointestinal symptoms, including bloating, abdominal pain, nausea, and diarrhea. Patients with mastocytosis also show a significantly higher incidence of duodenal ulcers. The gastrointestinal symptoms of mastocytosis are not disease specific, and differential diagnoses must be considered and ruled out (ie, *Helicobacter pylori*-associated ulcers, celiac disease, inflammatory bowel disease, irritable bowel syndrome, or malignant disease). Patients with moderate or severe symptoms should be referred to a gastroenterologist. Histologic analyses of duodenal biopsies may show increased numbers of neoplastic MCs, but this does not correlate clearly with the clinical symptoms. Moreover, histologic findings are nonspecific and may lead to misinterpretation in the absence of other clinical signs for mastocytosis.³⁵ Treatment options for gastrointestinal symptoms include continued use of sgAH up to 4-fold of daily recommended dose, H₂-blockers, proton pump inhibitors, and oral sodium cromolyn, which has been shown to be effective in the control of diarrhea in many patients. Further, triggers that may provoke gastrointestinal symptoms in the individual patient must be identified and avoided, including the subgroup of patients with IgE-mediated food allergy. In the rare aggressive forms of mastocytosis, malabsorption caused by profound MC infiltration of the gastrointestinal tract may be seen, and warrant further aggressive therapies or glucocorticoid use.^{36,37}

OTHER MC MEDIATOR-RELATED SYMPTOMS

Neuropsychiatric symptoms, which include headache, loss of concentration/memory problems, fatigue and depressive symptoms, are prevalent and seen in approximately one-third of adults with mastocytosis.^{8,38–40} In about 10% of patients, symptoms are severe and have tremendous impact on daily life. The pathogenesis and mechanisms involved are not clear but probably involve MC mediator effects in the central nervous system. Hormonal factors in women may also be involved. Further, secondary causes may play an important role, bearing in mind that mastocytosis is a chronic disease, with heterogeneous, often severe symptoms, which in many cases are not easy to cope with. Management should include a thorough workup for differential diagnoses depending on symptoms and severity involving psychiatric or neurologic workup. Treatment options include sgAH (often up dosed), leukotriene antagonists, antidepressants, and psychological support. Sodium cromolyn reportedly also may have a slow-onset beneficial effect on this type of symptoms⁴¹; however, the mechanism of action is not clear, especially because of the aforementioned lack of absorption of the drug

from the gastrointestinal tract, and other studies have not been able to document a similar effect.^{42,43}

Poorly localized pain from soft tissue and bone is a frequent finding in mastocytosis⁴⁴ and may be related to MC prostaglandin synthesis, but mechanisms are poorly understood. Differential diagnoses, mainly rheumatic, must be considered. Treatment options include nonsteroidal antiinflammatory drugs (NSAIDs)/aspirin if tolerated, sgAH, leukotriene antagonist, and sodium cromolyn, in addition to low-potency analgesics and nonpharmacologic measurements recommending exercise and physiotherapy.^{42,45–47} Bisphosphonates have been reported to relieve bone pain, in patients with mastocytosis treated for osteoporosis.⁴⁸ Symptoms may sometimes be severe and influence daily functions; however, opioids should be generally avoided in most of these cases because of side effects and chronicity of symptoms, and further because they are a frequent trigger of MC degranulation. If these symptoms, associated with mastocytosis, are provoked by MC mediator release (possible because of unidentified or multiple factors), more general approaches of inhibiting MC functions may result in better symptom control. Such approaches are either missing or infrequently used because of lacking evidence. Recent reports have promised potential beneficial effects using omalizumab, a humanized anti-IgE antibody, in the treatment of mastocytosis.^{49–51} Omalizumab is labeled for the therapy for severe allergic asthma and has been recently shown to be effective in symptom control of a variety of MC-mediated diseases, including urticaria, mastocytosis, and idiopathic anaphylaxis.^{49–53} A controlled clinical trial to investigate the efficacy of omalizumab in the treatment of mastocytosis is ongoing.

BONE DISEASE AND OSTEOPOROSIS

Bone manifestations are a frequent finding in adult patients with mastocytosis, most commonly osteoporosis or osteopenia and more rarely, osteolytic lesions or osteosclerosis.^{54–56} Around half of adults with SM have osteopenia or osteoporosis, which may go undetected because of lack of symptoms. It is in general advisable to screen all adult patients by dual-energy X-ray absorptiometry (DXA) as well as checking vitamin D levels and supplement if low, including sufficient daily calcium intake.

Further workup and radiologic examinations depend on clinical presentation, including presence of focal skeletal symptoms or bone pain.

The pathogenic mechanisms involved in the bone manifestations of mastocytosis are not clear but may involve an effect of MC mediators such as histamine, heparin, and interleukin 6 or MC-derived cytokines such as Receptor Activator of NF- κ B Ligand (RANKL), which influence balance of bone formation and resorption.^{57,58}

Controlled clinical trials investigating effect of specific treatments in mastocytosis-associated osteoporosis are lacking, and it is advisable to follow general guidelines for osteoporosis concerning treatment and follow-up in these patients, including treatment with bisphosphonates and vitamin D plus calcium supplements. Patients with severe osteoporosis and osteoporotic fractures and young individuals should be evaluated by specialists in osteoporosis.

The lack of knowledge regarding the pathologic mechanisms involved limit present disease-specific treatments. It may be speculated that an effective antimediator or MC stabilizing treatment may prevent development of osteoporosis in mastocytosis, but data are lacking. Further, the effectiveness of newer drugs such as denosumab remains to be elucidated. MC burden itself does not seem to increase frequency of osteoporosis,^{8,59} and cytoreductive treatments are in general not warranted. As opposed to the rarely encountered large, osteolytic bone lesions, osteoporosis/osteoporotic fractures should not be considered a C-finding and sign of aggressive disease.

ANAPHYLAXIS

Anaphylaxis is defined as an acute, suddenly occurring, severe systemic hypersensitivity reaction in at least 2 organ systems, often including skin symptoms, consisting of wheal-and-flare-type reactions, pruritus and flushing, respiratory compromise, or cardiovascular responses, including decreased blood pressure with or without the loss of consciousness.^{60,61}

Epidemiologic data on the incidence of anaphylaxis in the normal population vary because of diversity in study designs and definitions of anaphylaxis from 8 to 50 per 100,000 person years.^{62–66} The lifetime prevalence of anaphylaxis has been calculated to be approximately 0.05% to 2.0%.⁶⁷ The results of previous studies and clinical observations indicate an increased risk of anaphylaxis in mastocytosis with a reported prevalence of about 35% to 50% in adult patients with various subtypes of mastocytosis.^{7,68,69} The most prominent cause of anaphylaxis in mastocytosis is Hymenoptera sting in up to 50% of cases.⁷⁰ Drugs, including antibiotics, opioids, NSAIDs, radio contrast media, and muscle relaxants are also common reported causes of anaphylaxis in mastocytosis, whereas more infrequent triggers include IgE-mediated food allergy. The incidence of IgE-mediated food allergy in mastocytosis is not known to be greater than that of the general population, but the symptoms of food allergy may be more severe if the patient has both conditions. Isolated exposure to more general triggers like heat, cold, physical stress, exercise, alcohol, and spicy foods is rarely related to severe anaphylactic reactions, but may act combined. Despite described elicitation factors, the rate of anaphylaxis of unknown cause (ie, idiopathic anaphylaxis) is reported to be very high in mastocytosis and to occur in about 35% of cases.⁷⁰ Although the overall rate of type I IgE-mediated sensitizations in mastocytosis and the prevalence of atopy are suggested to not differ from the general population, patients with mastocytosis may be more prone to react to unusual triggers (eg, Diptera bites).^{10,71} It has been reported that the risk for severe anaphylactic reactions in mastocytosis is not correlated with the MC burden,⁸ or may even be inversely correlated,⁷² and patients without skin lesions tend to show more frequent anaphylactic reactions with unique features.^{9,70,73} Therefore, anaphylactic episodes are frequently the first sign that lead to further investigation and result in the diagnosis of a previous undetected SM in patients with anaphylaxis. No predicting factors are available allowing for the exact risk estimation of anaphylaxis in mastocytosis.⁷⁴ Therefore, the meticulous management of patients with mastocytosis to prevent unpredictable and potentially life-threatening anaphylactic episodes is of major importance. Equipment with emergency medication and treatment strategies targeting the elicitation factor should also be considered in patients with mastocytosis. Patients with Hymenoptera allergy are eligible for specific immunotherapy (SIT) to bee or wasp venom or both and should be given lifelong treatment.⁷⁵ In cases of severe bee sting anaphylaxis, a dose adjustment should be considered to better protect the patient from recurrent anaphylactic episodes.⁷⁶ However, patients with mastocytosis are also at higher risk of experiencing severe side effects to venom injections, and thus, SIT is not tolerated by all patients. Because SIT in Hymenoptera anaphylaxis is the only available treatment option that reduces the risk of life-threatening anaphylactic episodes, strategies to improve the tolerability of SIT in patients with mastocytosis are of great value. In recent years, numerous case studies have reported major success in simultaneously treating patients with omalizumab. It has been reported in many patients that the treatment of omalizumab resulted in increased tolerability of SIT and mediated solid protection from anaphylactic episodes in patients with mastocytosis.^{77–81}

KIT-TARGETING THERAPIES

Somatic Kit-mutations have been recognized as one of the major pathogenic factors in mastocytosis. KIT (CD117) is a transmembrane receptor tyrosine kinase that is involved in MC survival, differentiation, and activation under the control of its ligand stem cell factor (SCF).⁸² More than 95% of patients are detected to carry the D816V Kit-mutation, a point mutation with substitution of valine for aspartate in codon 816 of exon 17.⁵ This gain-of-function mutation leads to an autoactivation of the receptor kinase, resulting in SCF-independent signaling. Besides the occurrence of Kit-mutations, other incidences (eg, secondary mutations of TET2 or epigenetic factors) are suggested to be involved in the determination of the disease category and intensity of symptoms.^{83–86} However, during recent years, Kit-targeting agents have been in the research focus as a novel therapeutic strategy in mastocytosis. Imatinib is the only TKI that has received approval from the US Food and Drug Administration (FDA) for the treatment of aggressive SM. Patients carrying the D816V mutation are resistant to imatinib, and therefore, its use is restricted to non-D816V mutations, which excludes most patients with mastocytosis. However, imatinib has been reported to be effective in selected patient populations.⁸⁷ Second-generation TKIs, including dasatinib and nilotinib, so far have shown limited overall clinical efficacy. The protein kinase C inhibitor midostaurin is under investigation for efficacy in advanced types of mastocytosis. Preliminary data analyses show efficacy in terms of a reduced MC burden in a subset of patients.⁸⁸ The wild type Kit inhibitor masitinib was tested in patients with indolent mastocytosis and showed effects on symptom improvement in some patients but did not result in a significant reduction of the MC burden.⁸⁹ No Kit-targeting therapy has been approved for the use in D816V-positive patients with mastocytosis, and the use of TKIs is an option in selected cases of severely affected patients with advanced forms of mastocytosis. The results of ongoing and future studies will show their value for use in indolent types of mastocytosis.

FUTURE PERSPECTIVES

A true revival of MC research is under way. Because of the tremendous progress made during recent years, the field now has the tools to translate newly acquired knowledge of MC biology to novel therapies and measures of disease control.

Downregulation of MC function and survival is warranted in mastocytosis treatment. Human MCs have recently been reported to express receptors that could allow for the induction of apoptosis and inhibition of activation, like the Tumor Necrosis Factor Related Apoptosis Inducing Ligand receptor (TRAIL-R) and the inhibitory receptors CD300a and Siglec-8.^{90–92} TRAIL-R is the only death receptor known so far to be expressed on human MCs and, therefore, exhibit an interesting therapeutic target. The newly described inhibitory receptors, CD300a and Siglec-8, showed potential downregulatory properties on MC activation and survival *in vivo*.⁹³ A selective targeting of these receptors could lead to a potential innovative treatment strategy in mastocytosis.⁹⁰

MCs express a variety of other receptors allowing for the modulation of both activating or inhibiting pathways, which might serve as novel therapeutic targets in disease control. Although with some of those targets we are close to developing drugs, for others, further basic studies on their functions are required. For example, BH3-only proteins, a group of proapoptotic factors, have been described to modulate MC survival *in vitro* and *in vivo*.^{94–99} Agents, like calcineurin inhibitors or dimethylfumarate, have been reported to induce apoptosis in MCs and in disease models of mastocytosis.^{100–102} Other substances were tested for their efficacy in pilot clinical trials,

like the raft modulator miltefosine. Miltefosine has been shown to reduce the release of histamine, tumor necrosis factor, and prostaglandin D₂ from MCs on IgE-mediated and non-IgE-mediated activation. In addition, topical administration of miltefosine showed a reduction of histamine-induced wheal-and-flare-type skin reactions in vivo. In a randomized, placebo-controlled, double-blind clinical trial, topical miltefosine has been shown to inhibit MC activation in patients with CM.^{103–106}

The recent creation of mouse models carrying the Kit D816V mutation and its mouse homologue Kit D814V, respectively, will allow more insight in the pathologic features of disease development and the associated alteration in MC function.¹⁰⁷ Physiologically, skin MCs are found in close anatomic vicinity to blood vessels and sensory nerves, which has been shown to be relevant in various inflammatory conditions.^{108,109} In which sense such intense immunologic interactions are affected by mastocytosis to contribute to the elicitation of symptoms is unknown, but they may harbor additional targets for innovative treatment options.

Taken together, there is increasing evidence for MC mediators and receptors as well as other drugable targets to have a strong potential for therapeutic intervention. However, a more detailed understanding of their pathophysiologic functions is required to develop effective therapeutic strategies free from side effects in future. The first controlled clinical trials have already shown that cutaneous SM and ISM are diseases suitable for study of new drugs that can be tested for efficacy and safety.

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