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Mast cell Pharmacological regulation - Alicia B Penissi - Institute of Histology and Embryology

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Abstract

Mast cell activation disease (MCAD) may be a term pertaining to a heterogeneous group of disorders characterized by aberrant release of variable subsets of mastocyte (MC) mediators along side accumulation of either morphologically altered and immunohistochemically identifiable mutated MCs thanks to MC proliferation (systemic masto cytosis [SM] and MC leukemia [MCL]) or morphologically ordinary MCs thanks to decreased apoptosis (MC activation syndrome [MCAS] and well-differentiated SM). Clinical signs and symptoms in MCAD vary counting on disease subtype and result from excessive mediator release by MCs and, in aggressive forms, from organ failure associated with MC infiltration. In most cases, treatment of MCAD is directed primarily at controlling the symptoms related to MC mediator release. In advanced forms, like aggressive SM and MCL, agents targeting MC proliferation like kinase inhibitors could also be provided. Targeted therapies aimed toward blocking mutant protein variants and/or downstream signaling pathways are currently being developed. Other targets, like specific surface antigens expressed on neoplastic MCs, could be considered for the event of future therapies. Since clinicians are often underprepared to guage, diagnose, and effectively treat this clinically heterogeneous disease, we seek to familiarize clinicians with MCAD and review current and future treatment approaches.

Treatment options

Due to its genetic roots, MCAD generally is considered incurable. Recent mutational studies revealed that each patient has an individual pattern of genetic and epigenetic alterations which may affect the intracellular signal transduction pathways and receptive sites involved in sensory perception. As a consequence, mediator formation and release as well as inhibition of apoptosis and/or increase in proliferation are determined by individual genetic and epigenetic conditions and represent potential targets for therapy. Hence, there's need of highly personalized therapy for the disease. Unfortunately (with regard to easy detection), most genetic alterations (with a few exceptions such as certain mutations in tyrosine kinase KIT, e.g., KITD816V) do not alter the morphology and immunohistochemistry of the surface of the affected MCs. Thus, in most cases except for patients with the reliably identifiable D816V mutation, it cannot be decided by simple tests whether MCs found in biopsies are genetically altered MCs or physiological MCs.

Acute and chronic immunosuppressive therapies

Though typically not first-line, acute and chronic immunosuppressive therapies can be considered and should be particularly appropriate for patients possibly manifesting an autoimmune component of the disease as could be suggested by the presence, for instance , of anti-IgE or anti-IgE-receptor antibodies. Glucocorticoids may exert beneficial effects in MCAD, including a decrease in production of somatic cell factor (SCF, and possibly other cytokines) and a decrease in MC activation, by various mechanisms which have been extensively reviewed by Oppong et al. 2013. Glucocorticoids at doses >20 mg prednisone equivalent per day are frequently needed to effectively control otherwise refractory acute (and chronic) symptoms.

A variety of medicine are shown to inhibit MC growth, to decrease MC mediator release, and/or to alleviate mediator-induced symptoms in in vitro and in vivo animal models Some of these drugs are

approved for certain indications (such as ambroxol, statins, mefloquine, and ruxolitinib) and, thus, may be used (if accessible given financial considerations for some agents) if MCAD patients suffer from both the disorder of indication (e.g., hypercholesterolemia—statins, mucous congestion—ambroxol, polycythemia vera—ruxolitinib) and MCAD. An important question is what the role of the other compounds without approved indications should be in clinical practice. There are several challenges that may hamper the clinical introduction of novel targeted therapies in general. Some of these challenges include inherent problems in the translation of preclinical findings to the clinic, the presence of multiple coactive deregulated pathways in the disease, and questions related to the optimal design of clinical trials (e.g., eligibility criteria and endpoints). In particular, the testing of novel targeted treatment in an isolated fashion may be problematic and may in fact underestimate the effectiveness of these novel compounds. It is reasonable to assume that combination therapy are going to be the key to focus on parallel critical pathways.

Taking into account that the identification of novel molecules for effective treatment of inflammatory and immune diseases is one of the main present medical needs, and one of the major goals of the pharmaceutical industry, the aim of our work is intended to provide new therapeutic strategies and a deeper understanding of the mechanism of action of new drugs related to such disorders. Our research team has shown that some natural and synthetic lactones developed by our laboratory, as well as phenols from virgin olive oil, inhibit mast cell activation induced by immune and non-immune pathways, thus acting as mast cell stabilizers. Recently, we have started to explore whether the application of these mast cell stabilizers will be useful for prevention and/or treatment of mast cell-mediated disorders.

Diseases investigated include: peptic ulcer, tumor development, multiple sclerosis and allergic asthma. Our laboratory investigates the role of mast cells in such pathologies and the pharmacological regulation of mast cell activation by conducting studies on animal and human mast cells, and by analyzing specimens derived from patients with mast cell disorders. Biochemical, chemical, cell biology, molecular biology, and a variety of microscopic techniques were used, as well as animal models for the investigated diseases in which mast cells are involved. These studies may lead to an increased understanding of these disorders and may contribute to new preventive measures, diagnosis and treatments.