

Mastocytosis, Quinolones, MRGPRX2, and Anaphylaxis



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Patients with systemic mastocytosis have a higher burden of mast cells and are at a high risk of severe anaphylactic reactions.¹ In this issue of the journal, Giavina-Bianchi et al² describe a patient with systemic mastocytosis who developed 5 episodes of life-threatening anaphylaxis. Three of those episodes were secondary to hymenoptera stings and 2 to a quinolone antibiotic (ciprofloxacin).² Specific IgE serologies, allergy skin testing results, and component-resolved testing results to venom allergens were negative. Skin test result to ciprofloxacin was negative; however, there is currently no reliable testing to evaluate quinolone allergy.³ The authors hypothesize that the mechanism involved in the patient's life-threatening reactions is mediated via direct activation of the Mas-related G protein-coupled receptor (MRGPR) MRGPRX2.² Quinolones⁴ and mastoparan⁵ (a component of hymenoptera venom) are known to activate MRGPRX2. A succinct review of the literature regarding MRGPR and its subtypes is presented in the article. Different agents that can activate mast cell MRGPRX2 receptors, which include quinolones and neuromuscular blockers, are also discussed. The authors recommend caution in prescribing quinolones to patients with mastocytosis.

Activation of mast cells via Fcε receptor-1 is the hallmark of classical Gell and Coombs type I hypersensitivity reactions.⁶ Acute hypersensitivity reactions to drugs and other agents that are not IgE-mediated have been referred to as pseudoallergic and/or anaphylactoid.^{4,7} There is mounting evidence, from *in vitro* studies and rodent models, that some non-IgE-mediated anaphylactic reactions are a result of stimulation of mast cell MRGPR receptors.^{4,8} This class of G protein-coupled receptors consists of about 40 members classified into 9 separate families, A-H and X.⁹ MRGPRX1 and MRGPRX2 are expressed in primates, on neurons and mast cells, respectively.⁹ MRGPRX2 appears to play a role in human non-IgE-mediated acute drug hypersensitivity reactions.¹⁰

MRGPRX2 is activated by multiple classes of agents,^{2,4} with some neuromuscular blockers¹¹ and antimicrobials¹² representing 2 of those classes. Neuromuscular blockers that activate MRGPRX2 are implicated in anaphylactic/anaphylactoid reactions in patients with mastocytosis. Avoidance of these neuromuscular blockers is the current standard of care for

patients with mastocytosis.¹³ To date, there are no published studies of allergy to quinolones in patients with mastocytosis.

It is of critical importance to understand the mechanisms of non-IgE-mediated acute life-threatening reactions. Identification of the factors that activate mast cells via non-Fcε receptors such as MRGPRX2 is clinically relevant. Such understanding will further our ability to prevent those reactions and identify MRGPRX2 antagonists that could result in new therapeutic strategies. Mention should be made of naturally occurring missense variants of MRGPR that are inactive.¹⁴ How these inactive variants of MRGPR will affect our future practice of medicine and personalized medicine remains to be understood. It is clear that further clinical and epidemiologic studies are needed to evaluate drug allergy profiles in patients with mastocytosis. Comparative studies contrasting the reactions of patients with mastocytosis to the general population are needed. Finally, this non-IgE-mediated, pseudoallergic/anaphylactoid-MRGPRX2-mediated pathway requires further research in humans. Its relevance to patient care will continue to unfold.

The MRGPRX2 pathway heralds a new field in our understanding of acute type hypersensitivity reactions. Type I hypersensitivity reactions, which are classically IgE-mediated, could benefit from reclassification. The classification of type IV hypersensitivity reactions has been enhanced by their subclassification into types IV.a., IV.b., IV.c., and IV.d. based on their pathophysiologic mechanisms.¹⁵ Along the same lines, the clarity of type I hypersensitivity reactions could be enhanced by subclassification based on pathophysiology. Type I reactions can plausibly be divided into type I.a. (IgE-mediated), type I.b. (MRGPRX2-mediated), and type I.c. (other mechanism(s)). This in turn should standardize the current clinical nomenclature of anaphylaxis using the terms anaphylaxis I.a. to denote IgE-induced anaphylaxis, anaphylaxis I.b. to denote MRGPRX2-induced anaphylaxis, and anaphylaxis I.c. to denote currently unknown mechanisms of anaphylaxis.

Finally, we agree with authors' recommendation of caution when prescribing quinolones to patients with mastocytosis. Further research is needed in studying MRGPRX2 and its variants, activators, and inhibitors because they relate to human anaphylaxis. Rodent experimental research and *in vitro* studies of human mast cell and mast cell lines is the first step, but it is not sufficient for generalization until further evidence becomes available.

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Conflicts of interest: The author declares no relevant conflicts of interest.

Received for publication February 11, 2019; accepted for publication February 11, 2019.

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J Allergy Clin Immunol Pract 2019;7:2091-2.
2213-2198

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<https://doi.org/10.1016/j.jaip.2019.02.015>

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