

Empty mast cell syndrome: fallacy or fact?

Omar E Mohamed ¹, Richard L Baretto,¹ Ian Walker,² Cathryn Melchior,¹ Jane Heslegrave,¹ Ruth Mckenzie,² Chidanand Hullur,² Anjali Ekbote,¹ Mamidipudi Thirumala Krishna^{1,3}

¹Allergy and Immunology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

²Anaesthesia, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK

³Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK

Correspondence to

Dr Omar E Mohamed, University Hospitals Birmingham NHS Foundation Trust, Birmingham B9 5SS, UK; yaomar2000@gmail.com

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ABSTRACT

Post-anaphylaxis mast cell anergy (PAMA), commonly referred to as 'empty mast cell (MC) syndrome', is a state of temporary loss of cutaneous MC reactivity in the immediate aftermath of anaphylaxis. Data relating to this condition are sparse and the incidence rate is currently unknown. PAMA has been described only in a few published case reports in the context of hymenoptera venom allergy and perioperative anaphylaxis. Best practice guidelines regarding optimal timing for performing skin tests postanaphylaxis are largely based on expert opinion, and allergy work-up has been recommended after 4–6 weeks postanaphylaxis to avoid false-negative results.

This article provides a review of clinical literature surrounding PAMA, critically evaluates intracellular events in MCs from in vitro data and hypothesises regarding plausible immune mechanisms. There are no published data to directly explain molecular mechanisms underlying this phenomenon. Although not evidence based, PAMA has been attributed to depletion of MC granules following anaphylaxis. It is also plausible that exposure to high allergen concentrations in anaphylaxis can induce a temporary shift in MCs towards dominance of inhibitory signalling pathways, thus contributing to a state of transient hyporesponsiveness observed in some patients. Other potential contributory factors for reduced MC reactivity include downregulation of FcεRI expression, cross-linking of FcεRI to the inhibitory, low-affinity IgG receptors and administration of pharmacotherapeutic agents for anaphylaxis treatment. It is likely that this interesting phenomenon can be explained by a combination of these proposed mechanisms in addition to other genetic/host factors that have not yet been identified.

INTRODUCTION

Mast cells (MCs) are haemopoietically derived tissue resident cells that play a central role in the immunopathogenesis of immediate IgE-mediated hypersensitivity reactions (HSRs). On exposure to an allergen challenge in sensitised subjects, MCs release a spectrum of preformed vasoactive mediators (eg, histamine, proteoglycans and proteases) by degranulation, as well as by de novo synthesis of arachidonic acid metabolites, proinflammatory cytokines, chemokines and growth factors.¹ A skin test assesses an in vivo response of cutaneous MCs to the allergen in question and is considered to be the primary diagnostic modality of choice for evaluation of suspected IgE-mediated reactions.²

The concept of post-anaphylaxis mast cell anergy (PAMA), commonly referred to as 'empty MC

syndrome', is widely accepted among allergists. It can be defined as a state of temporary loss of cutaneous MC reactivity in the immediate aftermath of anaphylaxis. Nonetheless, the data are sparse and precise biological mechanisms underlying this phenomenon and duration of suppression of skin tests are not known. The best practice guidelines regarding an optimal timing for performing skin tests postanaphylaxis were largely obtained from expert opinion. In this article, we aimed to review the clinical literature surrounding PAMA and to critically evaluate evidence regarding intracellular events in MCs from in vitro data, to provide biologically plausible mechanisms that might contribute to this condition.

CURRENT GUIDELINES FOR OPTIMUM TIME POINT FOR SKIN TESTING POSTANAPHYLAXIS

A position paper on diagnosis of hymenoptera venom allergy by the European Academy of Allergy and Clinical Immunology (EAACI) recommended performing skin tests at least 2 weeks following a bee or wasp sting reaction to avoid the possibility of false-negative results. Because the length of the refractory period may be longer, EAACI guidelines stated that negative results of early skin tests should be interpreted with caution and a repeat testing should be considered after 6–8 weeks, if the clinical history is suggestive of type I HSR.³ The International Consensus on Drug Allergy report issued by a working group of the International Collaboration in Asthma, Allergy and Immunology, the American Academy of Allergy, Asthma and Immunology, the American College of Allergy, Asthma and Immunology and the World Allergy Organisation recommended delaying allergy diagnostic work-up to 4–6 weeks after complete recovery from all clinical symptoms and signs of a suspected drug HSR, the authors acknowledge that this advice is based on level D evidence.⁴ Similar recommendations were issued by an expert group from the French Society for Anaesthesia and Intensive Care (Société Française d'Anesthésie et de Réanimation) and the French Society of Allergology (Société Française d'Allergologie).⁵ In contrast, the British Society for Allergy and Clinical Immunology and the Association of Anaesthetists of Great Britain and Ireland's (AAGBI) most recent guidelines on investigation of suspected anaphylaxis during anaesthesia advised that allergy testing could be carried out as soon as possible after successful postanaphylaxis recovery; nevertheless, a repeat testing can be considered at a later date in cases of doubtful early negative skin test results.^{6,7} It is noteworthy that the previously



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published AAGBI guidance in 2003 recommended delaying testing for 4–6 weeks; however, the recent guidelines did not provide reasons for this change.

EXISTING EVIDENCE

To review the clinical literature surrounding PAMA, we conducted a systematic literature search in February 2019 using the electronic database PubMed. Publication year limits were not applied, and we included only review articles, clinical studies and case reports published in English. Articles on animal experimental models were not included in our search. PAMA has been described in the context of two clinical models including hymenoptera venom allergy and peri-operative anaphylaxis; therefore, search terms were identified accordingly. Our search strategy combining keywords: (anaphylaxis OR hypersensitivity OR allergy OR reaction) AND (anaesthesia OR perioperative) AND skin test retrieved a total of 489 results. Using the same search terms, but substituting (anaesthesia OR perioperative) with (hymenoptera OR bee OR wasp), resulted in 491 articles. By screening titles and abstracts, we specifically searched for studies comparing skin test results at different time points following anaphylaxis. We also hand-searched the reference lists of all relevant articles for any additional publications potentially missed by the electronic search. As a result, we identified two case series and five case reports that were eligible for inclusion. The search for ‘empty MC syndrome’ and ‘PAMA’ did not show any results.

Model 1: hymenoptera venom anaphylaxis

PAMA was first reported in the medical literature in the 1960s in a patient with hymenoptera venom allergy who had a ‘post-sting refractory period of anergy’ during which the skin test results were falsely negative for a few weeks post-reaction.^{8 9} Few decades later, Goldberg & Confino-Cohen investigated 38 patients with a history of systemic reaction to hymenoptera sting and performed skin prick test, intradermal test and serum-specific IgE (ssIgE) measurement within 1 week and 4–6 weeks after the index reaction, demonstrating positive allergy tests during both visits in the majority of patients. Notably, 9 out of the 38 patients had positive ssIgE with negative skin test results on the initial visit; however, their skin tests became positive 4–6 weeks later. Based on this observation, the authors concluded that an accurate diagnosis of hymenoptera venom hypersensitivity can be confirmed by testing within 1 week in most cases; however, a repeat testing should be considered 4–6 weeks later if early testing is negative in spite of a high clinical index of suspicion.¹⁰ Remarkably, no further similar case series or larger-scale studies were carried out since publication of this report in 1997,

and these recommendations continued to be integrated into clinical practice guidelines.

Model 2: perioperative anaphylaxis

There is lack of high-quality data on the optimal timing for allergy testing following a suspected perioperative anaphylaxis, but it is common practice to postpone testing 4–6 weeks postreaction unless there is a clinical urgency.^{11–14} Lafuente *et al* performed serial skin testing on 44 patients with suspected perioperative anaphylaxis; a culprit agent was identified in 25 subjects by skin testing. Fifteen out of these 25 patients showed positive results during their first visit (0–4 days postanaphylaxis), 22/25 tested positive on the second visit (4–8 weeks later), whereas 12 showed positive results on both visits. There were 10/25 subjects who has a positive skin test only after 4–8 weeks, demonstrating a possible PAMA.¹⁵ Furthermore, there are few published case reports (table 1) describing this interesting phenomenon.^{16–19}

POSSIBLE UNDERLYING IMMUNE MECHANISMS

There are no published data to directly explain underlying molecular mechanisms underlying PAMA. Although not evidence based, experts anecdotally assumed that it can be explained by depletion of MC granules following anaphylaxis. In the following sections, we explore some plausible immune mechanisms (see figure 1). It is likely that reduced MC reactivity is due to a combination of these mechanisms, in addition to other genetic/host factors that have not yet been identified.

Depletion of MC mediators

Several immediate events take place on IgE-mediated MC activation, during which almost all of the granular content can be secreted.²⁰ First, MCs employ a ‘kiss-and-run’ secretory mechanism²¹ which enables immediate release of preformed low-molecular-weight vasoactive amines into the extracellular space; this is shortly followed by classical exocytosis and full expulsion of the granule content. It has been shown that MCs display different modes of exocytosis to control the delivery pace and amount of mediators released, thus enabling a degree of plasticity which is possibly influenced by the local microenvironment, nature and amplitude of stimulation of high-affinity receptor for IgE (FcεRI) receptors.²² Many attempts have been made to study MC recovery following an IgE-mediated degranulation. Data from experimental studies demonstrated that, on repeated stimulation, MCs have the ability to go through cycles of degranulation/regranulation resulting in initiation and perpetuation of an allergic inflammatory response.^{23 24} It has been shown that degranulated MCs can recover and retain

Table 1 Case reports describing a state of a refractory period of mast cell response following perioperative anaphylaxis

Author	Year of publication	Likely culprit agents	Interval between reaction and initial testing (days)	Results of initial skin tests	Interval between reaction and repeat testing (weeks)	Results of repeat skin tests
Fisher ¹⁶	1976	Thiopental, succinylcholine and d-tubocurare	4	All -ve	3	IDT d-tubocurare+
Aalto-Korte and Mäkinen-Kiljunen ¹⁷	2001	Latex	12	All -ve	12	SPT latex+
Culp <i>et al</i> ¹⁸	2007	Cefazolin	6	All -ve	6	SPT cefazolin+
Soetens <i>et al</i> ¹⁹ (two patients)	2012	Chlorhexidine	6	All -ve	11	SPT chlorhexidine+
		Rocuronium	20	All -ve	6	IDT rocuronium+

IDT, intradermal skin test; ITIM, immunoreceptor tyrosine-based inhibitionmotif; SPT, skin prick test.

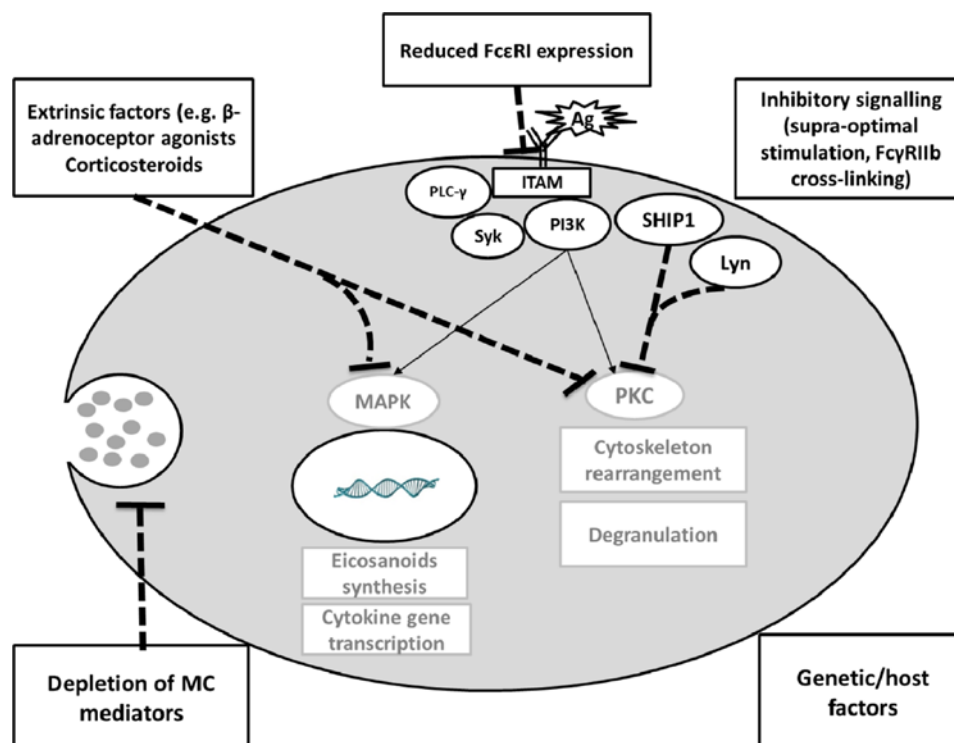


Figure 1 Illustration of the different putative mechanisms underlying PAMA. Some experts anecdotally assumed that this phenomenon can be explained by depletion of MC granules following anaphylaxis. Many attempts have been made to study MC recovery following repetitive and excessive IgE-mediated degranulation; however, the evidence for this association is still inconclusive. It is plausible that exposure to high allergen concentrations in anaphylaxis can cause a temporary shift towards dominance of inhibitory signalling for few weeks, thus contributing to PAMA observed in some patients. There is accumulating experimental evidence that supraoptimal antigen stimulation can attenuate FcεRI-mediated MC response through engagement of the Lyn/ITIM/SHIP inhibitory signalosome. Furthermore, we hypothesised that reduced FcεRI expression may play a role in the pathogenesis of PAMA, but there are no available experimental studies to support this assumption. Other possible contributory factors might be cross-linking of FcεRI to the inhibitory FcγRIIb. The possible role of pharmacotherapeutic agents used in the treatment of anaphylaxis (including β-adrenoceptor agonists and corticosteroids) has also been explored. We propose that this interesting phenomenon can be probably explained by a combination of these mechanisms, in addition to other genetic/host factors that have not yet been identified. Bold dotted lines indicate inhibitory effect. Ag, antigen; FcεRI, high-affinity receptor for IgE; FcγRIIb, low-affinity inhibitory IgG receptor; ITAM, immunoreceptor tyrosine-based activation motif; Lyn, a member of the Src family of protein tyrosine kinases; MAPK, mitogen-activated protein kinase; MC, mast cell; PAMA, postanaphylaxis mast cell anergy; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PLC-γ, phospholipase C-γ; SHIP1, Src homology 2-containing inositol polyphosphate-5'-phosphatase 1; Syk, spleen-associated tyrosine kinase.

their ability to release the granular enzyme β-hexosaminidase and upregulate interleukin (IL)-6 and IL-13 gene expression on a second activation signal 24–48 hours later.²⁵ In another study, maximal release of stored mediators occurred within minutes, and subsequent granule retrieval and recycling via rapid endocytosis resulted in the release of their contents within the scale of a few hours to days to maintain prompt secretory response on restimulation.²⁶ In contrast to endocytic recycling, it is evident that the time needed for granule biogenesis, maturation and full MC recovery is much longer. Hammel *et al* investigated recovery of rat MCs following repetitive and excessive IgE-mediated stimulation. In the immediate phase, they observed significant reduction in MC size due to granule loss, and thereafter, complete reconstitution and granule replenishment occurred gradually over a period of 4–5 weeks.²⁷ More recent experiments showed that the full recovery process could actually take several weeks, or even months.^{28–29}

Inhibitory MC signalling events

The FcεRI has been extensively studied due to its central role in MC effector function. This cell surface receptor, which is mainly expressed on MCs, basophils, eosinophils and Langerhans cells,

is capable of binding the Fc region of IgE with an affinity of 10^{10} M^{-1} .³⁰ Allergen-triggered cross-linking of the FcεRI initiates a sequence of intracellular signalling pathways responsible for induction and maintenance of an allergic response. In effector cells such as MCs and basophils, functional FcεRI exists in the form of αβγ₂ tetramer; the extracellular portion of the α-subunit is responsible for high-affinity binding to IgE, and on ligand-mediated dimerisation, the cytoplasmic domains of β and γ-chains are involved in downstream signal transduction via phosphorylation of immunoreceptor tyrosine-based activation motifs by the Src family kinase Lyn. Subsequent signalling events lead to stimulation of the phospholipase C-γ and the phosphoinositide 3-kinase (PI3K) pathways to increase cytosolic calcium concentration and to enhance protein kinase C (PKC) activation, which then result in MC degranulation, de novo synthesis of mediators and upregulation of cytokines and chemokines involved in allergic inflammation.³¹

The dose–response behaviour of many receptors shows a maximum biological response on stimulation with raising titres of respective ligand until a saturation of the response is observed at high ligand concentrations. However, following activation with increasing concentrations of multivalent antigens, the

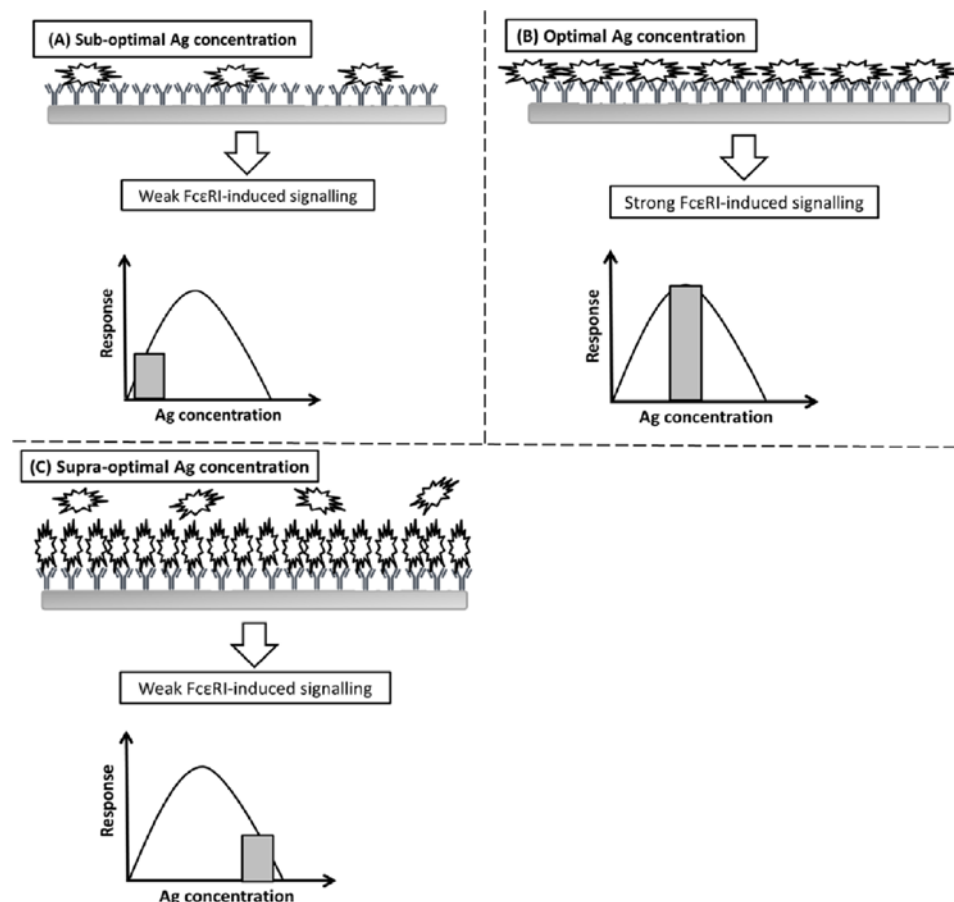


Figure 2 The disproved precipitin model. The first attempt to explain the bell-shaped dose–response behaviour of FcεRI was based on the Heidelberger-Kendall kinetics curve. (A) It was assumed that low antigen levels (ie, high antibody:antigen ratio) would only cross-link few IgE-bound receptors, resulting in generation of weak downstream signalling events. (B) Increasing the polyvalent antigen concentration to optimally cross-link all FcεRIs (equivalence zone) would ensure maximal activation of signal transduction and effector functions. (C) It was thought that weak Ag-triggered signalling would result from formation of monovalent antigen–antibody complexes if the antigen concentration overwhelms the IgE-bound FcεRIs (ie, antigen excess). However, subsequent evidence has confirmed that the dose–response behaviour of FcεRI-mediated MC activation is not based on this precipitin curve model. Ag, antigen; Ab, antibody; FcεRI, high-affinity receptor for IgE; MC, mast cell.

FcεRI-mediated effector response follows a remarkable, bell-shaped dose–response curve (figure 2) displaying weak MC responsiveness at both low and high antigen titres.³² At a low, suboptimal allergen dose, it is reasonable to assume that the weak induction of effector functions (ie, the ascending part of the bell-shaped dose–response curve) is due to cross-linking of only a few IgE-bound FcεRIs, whereas stimulation with an optimum amount of the respective antigen cross-links all receptors, resulting in maximal MC effector response. It is interesting that further increase in the antigen concentrations to supraoptimal range inhibits MC degranulation and cytokine secretion (ie, the descending part of the response curve).

It is plausible that following exposure to allergen load in anaphylaxis, MCs might undergo a period of unresponsiveness (ie, reflecting the descending part of the curve) until normal physiological mechanisms are restored. Previous dose–response studies of FcεRI activation have attempted to explain the duration and the possible mechanisms underlying suppressed MC degranulation after encountering supraoptimal antigen doses.

Reduced FcεRI cross-linking: the precipitin model?

One of the earliest attempts to explain this dose–response behaviour was based on the Heidelberger in-solution immuno-precipitation model.³³ It has been postulated that activation of

MCs at supra-optimal allergen concentrations (ie, antigen excess) can result in the formation of monovalent complexes with IgE and, therefore, allergen-mediated cross-bridging of FcεRI would be significantly reduced, resulting in attenuated signal transduction (figure 2). However, this proposed model was not supported by experimental data and the subsequent evidence has shown that MC hyporesponsiveness to supraoptimal antigen levels is not associated with reduced FcεRI cross-linking.³²

Inhibition of MCs by supraoptimal antigen stimulation

Dose–response experimental studies have demonstrated that the descending section of the bell-shaped curve can be explained by intracellular inhibitory signalling events. It is well known that Src homology 2-containing inositol polyphosphate-5'-phosphatase (SHIP), a critical negative regulator of the PI3K-mediated immune cell activation, plays a key role in MC homeostasis.³⁴ SHIP1^{−/−} mice were shown to have systemic MC hyperplasia, higher serum concentrations of proinflammatory cytokines and enhanced susceptibility to severe anaphylaxis compared with wild-type controls.³⁵ In a more detailed dose–response experiment, Gimborn and colleagues have shown that degranulation of SHIP-deficient murine MCs was not inhibited at supraoptimal antigen concentrations, thus resulting in a complete loss of the descending portion of the dose–response curve.³⁶ Hence, SHIP

has been recognised as one of the dominant negative downstream regulators of FcεRI-induced degranulation under supraoptimal conditions.

The Src family kinase Lyn has been shown to activate SHIP; therefore, it is not surprising that MC degranulation in Lyn^{-/-} mice persisted far longer than in wild-type cells.³⁷ Moreover, protein kinase C-δ (PKC-δ) is another intracellular messenger involved in suppressing antigen-triggered FcεRI-mediated signalling; this has been confirmed in PKC-δ-deficient mice, which displayed augmented MC response even at supraoptimal antigen levels.³⁸ As far as other possible inhibitory signals are concerned, Zhang *et al* studied the role of the Cbl family of adapter proteins in MC cultures from wild-type, c-Cbl^{-/-} and Cbl-b^{-/-} mice. They were able to show that Cbl-b-deficient cells failed to dampen the FcεRI-triggered signal transduction after supraoptimal stimulation.³⁹ There is evidence to suggest that other intracellular proteins such as the SHP-1 tyrosine phosphatase and the Jnk-1 mitogen-activated protein kinase might also be involved in controlling MC degranulation^{40 41}; however, dose-responses were not extended to the supraoptimal range in these studies.

It has also been shown that attenuated FcεRI-mediated MC response can occur as a result of extensive actin polymerisation and other cytoskeletal rearrangements induced by the supraoptimally cross-linked antigen-antibody complexes.⁴² These findings were verified by Seagrave and Oliver, who were able to show that supraoptimally stimulated MCs retained their ability to degranulate by adding inhibitors of actin polymerisation.⁴³

Suppressive low-affinity IgG receptor (FcγRIIb)-mediated signalling

A large body of evidence, obtained mainly from allergen-specific immunotherapy studies, suggests that allergen-specific IgG antibodies can exert a dampening effect on IgE-dependent MC responses; this is mediated by cross-linking FcεRI to the inhibitory FcγRIIb.⁴⁴⁻⁴⁶ It is, therefore, quite relevant to think about a possible role for FcγRIIb in the bell-shaped dose-response behaviour of MC activation. Gast and coworkers have recently demonstrated that exposure to supraoptimal antigen concentrations causes FcεRI/FcγRIIb coaggregation in an IgG-independent manner, resulting in suppression of MC degranulation via phosphorylation of the Lyn/immunoreceptor tyrosine-based inhibition motif (ITIM)/SHIP inhibitory signalosome (ITIM: immunoreceptor tyrosine-based inhibition motif).⁴⁷ However, it has been demonstrated that human cutaneous MCs do not express functional FcγRIIb⁴⁸ arguing against the involvement of this receptor as a mechanistic explanation for PAMA. In addition to FcγRIIb, MCs express other inhibitory receptors including gp49B1, MC function-associated antigen and paired immunoglobulin-like receptor B⁴⁹⁻⁵¹; however, signalling events from these receptors in response to supraoptimal stimulation have not been studied.

Reduced FcεRI expression

Therapeutic targeting of the high-affinity FcεRI has emerged as a viable option to attenuate MC effector function. Biological agents such as anti-IgE monoclonal antibody (omalizumab), DARPins (designed ankyrin repeat proteins) and Fcε-Fcγ fusion proteins were shown to exert direct and indirect inhibitory influence on FcεRI expression and activation.^{52 53} It is possible that, due to unknown pathophysiological events, the surface expression of FcεRI might be significantly reduced in some patients postanaphylaxis, resulting in transient MC hyporeactivity.

However, there are no available experimental studies to support this assumption.

Extrinsic factors

The treatment of anaphylaxis is based on prompt administration of epinephrine; other drugs that are commonly given as adjunctive therapies include antihistamines, corticosteroids and bronchodilators. In addition to epinephrine, other adrenergic receptor agonists (such as metaraminol) can be used in the management of perioperative anaphylaxis for inotropic support.⁵⁴ It is reasonable to ask, 'Do these pharmacotherapeutic agents have any inhibitory effects on MCs and basophils?' and 'Does the modulation of mediator release, if any, have a role to play in the pathogenesis of PAMA?'

Several experimental studies have demonstrated that β-adrenergic receptor agonists inhibit IgE-mediated histamine release from human MCs; this is believed to be through suppressing PKC translocation and activation.⁵⁵ Grönneberg and Raud showed that pretreatment with β-adrenoceptor agonists inhibited wheal-and-flare responses to intradermal histamine injection in 36 healthy subjects. They found that administration of salmeterol and terbutaline attenuated cutaneous MC responses for up to 24 hours.⁵⁶ Moreover, an experimental study on enzymatically dispersed human skin MCs showed that β-adrenoceptor stimulation resulted in suppression of histamine and prostaglandin D2 release.⁵⁷ There are no published dose-response studies to show the extent of inhibitory effect attained and the total duration of MC hyporesponsiveness, and it is unknown whether these short-acting agents have any role to play in the PAMA phenomenon.

Although the evidence of therapeutic benefit is lacking, it is a common practice to administer short course of corticosteroids for treatment of anaphylaxis. It is recognised that administration of corticosteroids for periods in excess of a week exerts inhibitory effects on MCs and can suppress allergic inflammation; this is in contrast to shorter administration that has no discernable effect on MC responsiveness.⁵⁸ This has been confirmed in an ex vivo study by Schleimer *et al*, who demonstrated that incubation of dexamethasone with human MCs for 24 hours did not suppress mediator release.^{59 60} Furthermore, other in vivo studies have shown that administration of corticosteroids for ≤48 hours did not result in attenuated cutaneous MC effector responses.^{61 62} It has been shown that the primary mechanism by which steroids inhibit the MC-dependent wheal and flare response is by reducing the number of cutaneous MCs, with a consequential reduction in total histamine release, rather than direct inhibitory effect on degranulation.⁵⁸

HOW DOES PAMA TRANSLATE CLINICALLY?

Following prompt recognition and immediate management of anaphylaxis, patients should be counselled on avoidance of suspected allergen/s and issued with an emergency treatment plan with an epinephrine autoinjector and antihistamines until specialist evaluation is undertaken in an allergy clinic. In most cases, there is no urgency for diagnostic allergy testing as long as all the safety measures are in place. However, the need for early testing may arise following suspected anaphylaxis during general anaesthesia if the procedure is abandoned and there is a genuine urgency, for example, cancer surgery and aneurysm repair. These uncommon but challenging situations require careful risk-benefit analysis and multidisciplinary discussions involving anaesthetists, allergists and surgeons. We acknowledge the paucity of high-quality data about the optimal timing to perform allergy tests postanaphylaxis, but based on

available evidence, testing at 4–6 weeks seems acceptable in non-urgent cases. If there are no available safer alternatives and early testing is indicated, negative results should be interpreted with great caution and a repeat assessment should be arranged after a minimum of 4 weeks. Nonetheless, much remains to be clarified about the duration of the recovery period of MC following strong stimulation, and whether the degree of suppression of mediator release vary in response to different allergens.

CONCLUSION

Based on very limited evidence and clinical experience, it appears that a relatively small proportion of patients may develop PAMA; however, there are many, yet unanswered questions. Different putative mechanisms for reduced MC reactivity postanaphylaxis were explored in this article, and we propose that this interesting phenomenon can be explained by a combination of these mechanisms, in addition to other genetic/host factors that have not yet been identified. At present, it is unclear if PAMA represents a state of generic (ie, to all allergens) MC hyporesponsiveness postanaphylaxis or if it is allergen-specific. Based on the proposed pathomechanisms explained above, it is tempting to speculate that this temporary phenomenon equates to systemic 'generic' MC hyporesponsiveness, and the affected patient may be protected against IgE-mediated anaphylaxis until normal physiological mechanisms are restored. The latter would be challenging and unethical to prove in a human model of anaphylaxis. Also, does the severity of the index reaction influence period of refractoriness to skin tests? Moreover, what are the patient-specific immunological/genetic contributory factors that could trigger this temporary state of hyporesponsiveness?

Prospective well-designed studies involving serial skin testing at predetermined time points might shed light on the incidence rate and define the duration of MC non-responsiveness in PAMA. Moreover, it would be interesting to know if there is a similar effect on basophil activation test, given its emerging use as a supportive diagnostic tool. Understanding cellular mechanisms underpinning this condition might pave the way in the development of novel biomarkers and novel interventions and therapies for allergic conditions.

Take home messages

- Temporary loss of cutaneous mast cell (MC) reactivity has been described in the context of hymenoptera venom allergy and peri-operative anaphylaxis.
- Plausible mechanisms may include depletion of MC granules, dominance of inhibitory signaling pathways, downregulation of FcεRI expression and other genetic/host factors.
- Unless urgently needed, we recommend delaying allergy diagnostic work 4–6 weeks after anaphylaxis to avoid the possibility of false negative results.

Correction notice This paper has been corrected since it appeared Online First. Author name 'Mamidupudi' has been corrected to 'Mamidipudi'.

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ORCID iD

Omar E Mohamed <http://orcid.org/0000-0001-9102-278X>

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