

“COVID-19 vaccine anaphylaxis: IgE, complement or what else?”

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Title: COVID-19 vaccine anaphylaxis: IgE, complement or what else? A reply to: “COVID-19 vaccine anaphylaxis: PEG or not?”

To the Editor:

Thank you for the correspondence of Krantz et al “COVID-19 vaccine anaphylaxis: PEG or not?”.¹

We totally agree with the authors that patients previously allergic to polyethylene glycol (PEG) might react to PEGylated liposomes when exposed to them later on.¹ Since PEGs of different molecular weights are widely distributed, exposure and absorption depending on the size and mode of application can take place *via* the skin, the gastrointestinal mucosa, or other mucosal tissues including conjunctiva, while some substances containing PEG are administered intravenously, subcutaneously, or intramuscularly². This broad range of likelihoods how PEG can be delivered to the immune system opens a wide range of possibilities, where and how to get sensitized to PEG. Interestingly, sensitization to PEG and PEG analogous occurs only very rarely in view of the extremely high rate of expositions to these substances.^{2,3} (Figure 1A).

Since hypersensitivity reactions take place more frequently after intravenous or intramuscular injection of PEGs,² both concentration and molecular weight might play a role. PEGs with lower molecular weights might require in some situations a higher concentration to induce hypersensitivity reactions, while PEGs with higher molecular weights could sometimes induce severe hypersensitivity reactions even at low concentrations (Figure 1B).

The individual thresholds to react to PEGs of different molecular weight and at different concentrations *in vivo* and even during diagnostic skin prick testing varies,⁴ so that a patient primarily sensitized to a PEG with lower molecular weight might react also to a PEG or even pegylated substance of higher molecular weight as described by Krantz et al.⁵ If patients previously sensitized to PEGs of higher molecular weights may react with PEGs of lower molecular weights such as PEG2000 contained in the micellar delivery system of Pfizer/BioNTech or Moderna COVID-19 vaccines, should be further analyzed.

In this context, it might be also possible that the way how PEG is delivered to the immune system is of importance. The PEGylated form as a carrier for drugs injected for example intramuscularly as a “shot” as it is the case for the Pfizer/BioNTech and Moderna COVID-19 vaccines, might increase not only the bioavailability and stability of the active agent that is delivered, but also of the carrier and enhance thereby its resistance to degradation, size, and allergenicity.

In addition to IgE-mediated hypersensitivity reactions, complement activation-related pseudoallergy, called CAPR and mediated by PEGylated nanobodies, which induce anaphylatoxins (C3a and C5a) and anti-PEG IgM and IgG antibodies has been described.⁶ The anti-drug antibodies are responsible for an accelerated blood clearance (ABC) and thereby loss of efficacy of the drug and severe anaphylaxis. If such a complement activation might be induced by the PEGylated Pfizer/BioNTech or Moderna vaccine as a cause of some of the anaphylactic cases, for example in non-allergic individuals, remains to be elucidated (Figure 2A).

If excipients of the new Pfizer/BioNTech and Moderna vaccines including PEG would not be the reason for the hypersensitivity reactions to the vaccine, one immunologic possibility could be the direct interaction of RNA applied with the vaccine with mast cells. In this regard, it has been demonstrated that cytosolic RNA in mast cells during viral infections can be detected by retinoic-acid-inducible gene-1 (RIG-1), which *in vitro* leads to the transient expression of type I interferons and TNF-alpha as well as anti-viral proteins by mast cells.⁷ However, mast cell degranulation did not occur after intracellular RNA recognition in different *in vitro* studies,⁷ so that such a way of mast cells activation and degranulation in response to the mRNA delivered with the vaccine is very unlikely (Figure 2B). This goes along with the clinical observation that the frequency of allergic adverse events in the vaccine and the placebo group in the phase-III-trial of Pfizer/BioNTech BNT162b2 vaccine was quite similar and relatively low in regard to both, frequency and severity,⁸ which would supposedly not be the case if mast cell activation via mRNA would be of relevance.

A general hyperreactivity of mast cells as it is the case in patients with systemic mastocytosis might be another reason for hypersensitivity reactions to this new vaccine observed in a few cases since patients with severe allergic reactions in the medical history and supposedly mastocytosis have not been included in the clinical trials. However, according to the very rare data available in the literature on this topic, vaccines are in general well tolerated by adult patients with different forms of systemic mastocytosis, while mast cell release induced by vaccines has been reported to occur sometimes in children with cutaneous mastocytosis^{9,10}

Last but not least, we would like to thank Kantz et al. for the really helpful table and overview of PEG and polysorbate containing drugs provided. We would like to add one important group of substances, which contain PEG and its analogous to this overview of substances: PEG-coated antihistamine tablets or PEG containing corticosteroids are often part of emergency kits or used as rescue medication to treat anaphylactic reactions but should not be used in patients with documented hypersensitivity reactions to PEGs or its derivatives.

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Figure 1. A. Different routes of exposures of products containing PEG. B. Threshold of reactivity for PEG in relation to concentration and molecular weight. Biorender software was used to create the figure under an academic license.

Figure 2 . A. Possible interaction of mast cells with PEG-2000 or viral RNA. B. Possible complement-activation related pseudoallergy induced by PEGylated nanobodies. Biorender software was used to create the figure under an academic license.



