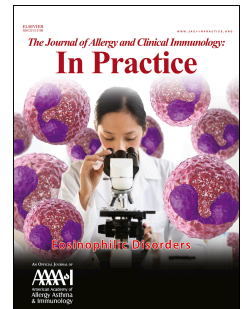


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The Safety Of SARS-Cov-2 Vaccines in Persons with a Known History of Pegaspargase Allergy: A Single Institution Experience

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Clinical Communication:

The Safety Of SARS-Cov-2 Vaccines in Persons with a Known History of Pegaspargase Allergy: A Single Institution Experience

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Conflicts of Interest:

MG: is a consultant for Aquestive; is a member of physician/medical advisory boards for DBV Technologies, Sanofi/Regeneron, Genentech, Nutricia, Novartis, Acquestive, Allergy Therapeutics, Pfizer, US World Meds, Allergenics, Aravax, and Protax, all unrelated to vaccines/vaccine development; is a member of the scientific advisory council for the National Peanut Board; is the senior associate editor for the Annals of Allergy, Asthma, and Immunology, and is member of the Joint Taskforce on Allergy Practice Parameters. He has received honorarium for lectures from ImSci, the Allergy and Asthma Foundation of America, and MedLearningGroup.

The rest of the authors report no conflicts of interest.

Clinical Implications:

Clinical Implications: mRNA COVID-19 vaccines, which contain polyethylene glycol (PEG), can safely be administered to pegaspargase allergic patients without risk-stratification measures, potentially in any healthcare setting that can assess and manage anaphylaxis.

Pegaspargase is a key component to the treatment of acute lymphoblastic leukemia. Allergic reactions to pegaspargase are reported to occur in 10-15% of patients, with polyethylene glycol (PEG) identified as a primary antigen in these reactions.^{1,2} Both the Pfizer-BioNTech® and Moderna® mRNA COVID-19 vaccines contain PEG.³ While anaphylaxis to these vaccines is noted to occur at a rate of 7.9 cases per million, PEG has been speculated but not proven as a cause.⁴ Adenovirus-vector COVID-19 vaccines (e.g. Janssen®) do not contain PEG, but do contain polysorbate which is structurally similar to PEG, though unlikely to cause cross-reactivity.^{4,5} While allergic reactions to vaccines have occasionally been attributed to excipients, some have been implicated based only on theoretical risk, or the excipients are at concentrations below the threshold necessary to provoke a reaction.⁶

The Centers for Disease Control (CDC) and other international health authorities have contraindicated mRNA COVID-19 vaccination in individuals with a history of allergy to the vaccine or a vaccine excipient (<https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>), which would preclude vaccination of persons with a previous reaction to PEG-containing medications, such as pegaspargase.⁵ This could create potential vulnerabilities in terms of COVID-19 susceptibility for immunocompromised leukemia

patients with a history of pegaspargase allergic reactions. However, given limited evidence to date that PEG is a relevant allergen in COVID-19 vaccine reactions, it is unclear if such contraindication is necessary.⁴

This observational study aimed to identify COVID-19 mRNA vaccine-eligible patients with a documented pegaspargase allergy, to determine if they received a COVID-19 vaccine, and define the incidence of allergic reactions among this population. Patients with known pegaspargase allergy in the Children's Hospital Colorado system were identified by electronic medical record review and screened to identify COVID-19 vaccine status and vaccination outcomes. When vaccination status and outcomes were not available in the medical record, patients were contacted by phone to complete a questionnaire. Location of vaccination (primary care or community health setting vs. with an allergy specialist) and any vaccination precautions were also noted, where available. Patients were stratified by baseline severity of the pegaspargase allergy according to Common Terminology Criteria for Adverse Events (CTCAE) grade. This study was approved by the Colorado Multiple Institutional Review Board for the University of Colorado Anschutz Medical campus.

A total of 86 patients were identified as having a documented pegaspargase allergy; of these patients, 59 were successfully screened, with 27 not responding to multiple contact attempts. Thirty-one of 59 received COVID-19 vaccination despite their pegaspargase allergy. Baseline characteristics of these 59 patients are presented in Table 1. Of the 31 vaccinated patients, 28 received Pfizer-BioNTech®, 2 received Moderna® and 1 received Janssen®. No patients who received either mRNA vaccine developed an immediate allergic reaction. All patients who

received Pfizer-BioNTech® or Moderna® received both doses, and 25/31 had tolerated MiraLax® (contains PEG3350) after their pegaspargase allergy diagnosis. The one patient receiving the Janssen® vaccine reported self-limiting nausea >4 hours after vaccination, which was not considered an immediate allergic reaction. No patient received pre-medication prior to vaccination or underwent skin testing for risk stratification, and only 8 patients had 30-minute observation after their dose. Only 1 patient could not recall their pegaspargase allergy, though they remembered an allergy to an unspecified chemotherapeutic agent. Overall, only 12 of the 59 patients knew that a pegaspargase allergy was a contraindication to the vaccine, with 8/12 receiving their vaccination under allergist supervision, 2/12 declining vaccination due to the contraindication, 1/12 awaiting Janssen® vaccination by preference and 1/12 deferring vaccination while on active chemotherapy.

This institutional case series found that the SARS-CoV-2 vaccines were safely administered in at least 31 persons with a known history of CTCAE Grade 2 or higher pegaspargase allergy, without resultant immediate allergic reactions. Furthermore, most were vaccinated without allergist supervision, few were even observed more than the standard 15 minutes common for COVID-19 vaccines, and none underwent either excipient or vaccine skin testing or received pre-medication prior to vaccination. Interestingly, few patients were aware the pegaspargase allergy was a vaccination contraindication, and in the cases where the vaccine was given without allergist supervision, it remains uncertain if either the pegaspargase allergy was disclosed (when it was known by the patient) and/or the clinicians administering the vaccine were aware of the contraindication with this allergy. To date, no evidence supports PEG as an allergen causing IgE-mediated reactions to mRNA COVID-19 vaccines, though a contraindication to

administering these vaccines to PEG allergic individuals persists, and emerging data may support a non-IgE mediated pathway (complement activation related pseudoallergy [CARPA], which also may be the primary mechanism for allergic reactions to pegaspargase).⁷

These data help to provide evidence in support that the contraindication to administering PEG-containing COVID-19 vaccines to pegaspargase allergic individuals may be unnecessary and a potential barrier to vaccination for some patients, and that pegaspargase allergic individuals can be safely vaccinated with mRNA COVID-19 vaccines without allergist supervision or risk-stratification measures. Our data reflect similar findings from the recent study from Mark et al, who vaccinated 32 patients with a history of pegaspargase allergy under the supervision of an allergist, without premedication, with no allergic reactions occurring.⁸ As well, our findings both supplement and help further evolve the findings in the recently published work by Koo et al, who demonstrated similar safety data in 19 pegaspargase allergic patients; however, in their study, 14 patients underwent skin testing to PEG3350, and all vaccination was supervised by an allergist.⁹ The key differentiating features of our report are that we did not perform skin testing in any patients prior to vaccination, not all subject were PEG3350 tolerant, and that the majority of patients received their initial mRNA COVID-19 vaccine dose without allergist supervision. A limitation of our report is that it does not have a large sample size, nor was designed as a powered trial to provide a robustly narrow confidence interval that would provide high-level evidence of definitive safety of the concept, a limitation common to the other two aforementioned studies.^{8,9}

While further research is needed, a preference-sensitive approach to offering mRNA COVID-19 vaccination to pegaspargase allergic-individuals, either under the supervision of an allergist or in any other general healthcare setting where anaphylaxis could be assessed and treated, should be considered. This approach may not have to involve negative skin testing results to PEG3350.

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Table 1: Baseline Characteristics

	Vaccinated (n=31)	Unvaccinated (n=28)
Age, median (range)	18 years (12-22)	16 years (12-28)
Gender		
Male	14 (45.2%)	18 (64.3%)
Female	15 (48.4%)	10 (35.7%)
Nonbinary	2 (6.4%)	0
Race		
White	19 (61.3%)	23 (82.1%)
Hispanic or Latino	6 (19.3%)	3 (10.7%)
Black or African American	2 (6.4%)	0
Asian	1 (3.3%)	0
American Indian or Alaska Native	0	1 (3.6%)
Other	3 (9.7%)	1 (3.6%)
Pegaspargase Allergy Severity		
CTCAE Grade 1	0	2 (7.1%)
CTCAE Grade 2	22 (70.9%)	20 (70.14%)
CTCAE Grade 3	8 (25.8%)	4 (14.3%)
CTCAE Grade 4	1 (3.3%)	2 (7.1%)
Mean Duration of Pegaspargase Allergy (years)	6.3 years (0.7-14.2 years)	6.1 years (0.3-16.7 years)
Previous use of polyethylene glycol (MiraLax®, PEG3350)		
Prior to allergy identified only	4 (12.9%)	4 (14.3%)
After allergy identified	25 (80.6%)	16 (57.1%)
Never used	0	3 (10.7%)
Undetermined	2 (6.5%)	5 (17.9%)
Pre-Vaccination Allergic Reaction to MiraLax®, PEG3350	0	0
Abbreviations: Common Terminology Criteria for Adverse Events (CTCAE) CTCAE Grades were based on version 4.03		