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 Implications

mRNA coronavirus disease 2019 vaccines, which contain polyethylene glycol, can safely be administered to patients allergic to pegaspargase without risk-stratification measures, potentially in any health care 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% to 15% of patients, with polyethylene glycol (PEG) identified as a primary antigen in these reactions.[1,2] Both the Pfizer-BioNTech and Moderna mRNA coronavirus disease 2019 (COVID-19) vaccines contain PEG.[3] Although 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 (eg, Janssen) do not contain PEG, but do contain polysorbate, which is structurally similar to PEG, though unlikely to cause cross-reactivity.[4,5] Although 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 and Prevention 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,[7] 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 pegasparagase-allergic reactions. However, given limited evidence to date that PEG is a relevant allergen in COVID-19 vaccine reactions, it is unclear whether such contraindication is necessary.[4]

This observational study aimed to identify COVID-19 mRNA vaccine-eligible patients with a documented pegaspargase allergy, to determine whether 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 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 I. Of the 31 vaccinated patients, 28 received Pfizer-BioNTech, 2 received Moderna, and 1 received Janssen vaccines. No patients who received either mRNA vaccine developed an immediate allergic reaction. All patients who received Pfizer-BioNTech or Moderna vaccine received both doses, and 25 of 31 had tolerated MiraLax (contains PEG3350) after their pegaspargase allergy diagnosis. The 1 patient receiving the Janssen vaccine reported self-limiting nausea more than 4 hours after vaccination, which was not considered an immediate allergic reaction. No patient received premedication before 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 of 12 receiving their vaccination under allergist supervision, 2 of 12 declining vaccination due to the contraindication, 1 of 12 awaiting Janssen vaccination by preference, and 1 of 12 deferring vaccination while on active chemotherapy.

This institutional case series found that the severe acute respiratory syndrome coronavirus 2 vaccines were safely administered in at least 31 persons with a known history of Common Terminology Criteria for Adverse Events Grade 2 or higher pegaspargase allergy, without resultant immediate allergic reactions. Furthermore, most were vaccinated without allergist supervision, few were even observed for more than the standard 15 minutes common for COVID-19 vaccines, and none underwent either excipient or vaccine skin testing or received premedication before vaccination. Interestingly, few patients were aware that the pegaspargase allergy was a vaccination contraindication, and in the cases where the vaccine was given without allergist supervision, it remains uncertain whether 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, which also may be the primary mechanism for allergic reactions to pegaspargase).[8]

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

TABLE I. Baseline characteristics

Characteristic	Vaccinated (n = 31)	Unvaccinated (n = 28)
Age (y), median (range)	18 (12-22)	16 (12-28)
Sex		
Male	14 (45.2)	18 (64.3)
Female	15 (48.4)	10 (35.7)
Nonbinary	2 (6.4)	0
Race		
American Indian or Alaska Native	0	1 (3.6)
Asian	1 (3.3)	0
Black or African American	2 (6.4)	0
Hispanic or Latino	6 (19.3)	3 (10.7)
Other	3 (9.7)	1 (3.6)
White	19 (61.3)	23 (82.1)
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 (y)	6.3 (0.7-14.2)	6.1 (0.3-16.7)
Previous use of PEG (MiraLax, PEG3350)		
Before 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)
Prevaccination allergic reaction to MiraLax, PEG3350	0	0

CTCAE, Common Terminology Criteria for Adverse Events.
Values are n (%) unless otherwise indicated. CTCAE grades were based on version 4.03.

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,[9] who vaccinated 32 patients with a history of pegaspargase allergy under the supervision of an allergist, without premedication, with no allergic reactions occurring. As well, our findings both supplement and help further evolve the findings in the recently published work by Koo et al,[10] 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. The key differentiating features of our report are that we did not perform skin testing in any patient before vaccination, not all subjects were PEG3350 tolerant, and most 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 it designed as a powered trial to provide a robustly narrow CI that would provide high-level evidence of definitive safety of the concept, a limitation common to the other 2 aforementioned studies.[9,10]

Although 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 health care 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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Conflicts of interest: M. Greenhawt 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, Allergenis, Aravax, and Prota, 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*; is member of the Joint Taskforce on Allergy Practice Parameters; and has received honorarium for lectures from ImSci, the Allergy and Asthma Foundation of America, and the MedLearningGroup. The rest of the authors declare that they have no relevant conflicts of interest.
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REFERENCES

1. Swanson HD, Panetta JC, Barker PJ, Liu Y, Inaba H, Relling MV, et al. Predicting success of desensitization after pegaspargase allergy. Blood 2020;135:7-75.
2. Liu Y, Smith CA, Panetta JC, Yang W, Thompson LE, Counts JP, et al. Antibodies predict pegaspargase allergic reactions and failure of rechallenge. J Clin Oncol 2019;37:2051-61.
3. Centers for Disease Control and Prevention. Frequently asked questions about COVID-19 vaccinations: CDC. Updated September 24, 2021. Accessed October 1, 2021. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html
4. Greenhawt M, Abrams EM, Shaker M, Chu DK, Khan D, Akin C, et al. The risk of allergic reaction to SARS-CoV-2 vaccines and recommended evaluation and management: a systematic review, meta-analysis, GRADE assessment, and international consensus approach. J Allergy Clin Immunol Pract 2021;9:3546-67.

5. Stone CA Jr, Liu Y, Relling MV, Krantz MS, Pratt AL, Abreo A, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. J Allergy Clin Immunol Pract 2019;7:1533-1540.e8.
6. Kelso JM, Greenhawt MJ, Li JT, Nicklas RA, Bernstein DI, Blessing-Moore J, et al. Adverse reactions to vaccines practice parameter 2012 update. J Allergy Clin Immunol 2012;130:25-43.
7. Centers for Disease Control and Prevention. Interim clinical considerations for use of COVID-19 vaccines currently approved or authorized in the United States. Accessed September 6, 2021. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html
8. Warren CM, Snow TT, Lee AS, Shah MM, Heider A, Blomkalns A, et al. Assessment of allergic and anaphylactic reactions to mRNA COVID-19 vaccines with confirmatory testing in a US regional health system. JAMA Netw Open 2021;4:e2125524.
9. Mark C, Gupta S, Punnett A, Upton J, Orkin J, Atkinson A, et al. Safety of administration of BNT162b2 mRNA (Pfizer-BioNTech) COVID-19 vaccine in youths and young adults with a history of acute lymphoblastic leukemia and allergy to PEG-asparaginase. Pediatr Blood Cancer 2021;68:e29295.
10. Koo G, Anvari S, Friedman DL, Zarnegar-Lumley S, Szafron V, Kahwash BM, et al. mRNA COVID-19 vaccine safety in patients with previous immediate hypersensitivity to pegaspargase. J Allergy Clin Immunol Pract 2022;10:322-5.