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PSYCHOSOCIAL AND SUPPORTIVE CARE: BRIEF REPORT

Oncologist counseling practice and COVID-19 vaccination outcomes for patients with history of PEG-asparaginase hypersensitivity

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Abstract

Vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an effective strategy to prevent serious coronavirus disease 2019 (COVID-19) and is important for oncology patients. mRNA-based COVID-19 vaccines are contraindicated in those with a history of severe or immediate allergy to any vaccine component, including polyethylene glycol (PEG)2000. Patients with acute lymphoblastic leukemia/lymphoma receive asparaginase conjugated to PEG5000 (PEG-ASNase) and those with PEG-ASNase-associated hypersensitivity may be unnecessarily excluded from receiving mRNA COVID-19 vaccines. We, therefore, surveyed oncologists on COVID-19 vaccine counseling practice and vaccination outcomes in COVID-19 vaccination-eligible patients and show safe receipt of mRNA vaccines despite PEG-ASNase hypersensitivity.

KEYWORDS
ALL, COVID vaccine, LLy, pegasparaginase, SARS-CoV-2 vaccination

1 | INTRODUCTION

Asparaginase is a key therapeutic component for acute lymphoblastic leukemia and lymphoma. However, asparaginase can be associated with hypersensitivity reactions, including anaphylaxis, particularly with the most commonly used formulation of *Escherichia coli*-derived L-asparaginase conjugated to polyethylene glycol (PEG-ASNase).[1–6] It is unclear if hypersensitivity reactions to PEG-ASNase are due to asparaginase or PEG.[7,8] Furthermore, some patients experience non-antibody-mediated PEG-ASNase infusion reactions,[9] which may lead to an inaccurate classification of PEG-ASNase allergy.

Abbreviations: ASNase, asparaginase; COVID-19, coronavirus disease 2019; EUA, emergency use authorization; FDA, U.S. Food & Drug Administration; PEG, polyethylene glycol; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VUMC, Vanderbilt University Medical Center.

Concern for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in patients with cancer and impaired immunity is significant and warranted.[10–12] Primary vaccination with mRNA coronavirus disease 2019 (COVID-19) vaccines manufactured by Pfizer-BioN-Tech[13] and Moderna[14] has led to significantly reduced severity of COVID-19 illness and death.[15] However, these vaccines contain a PEG formulation, PEG2000, to stabilize the lipid nanoparticle carrier molecule for the mRNA spike protein construct.[16] PEG was hypothesized to be a potential allergen in previously sensitized patients in early reports of anaphylaxis to mRNA COVID-19 vaccines.[17]

The Centers for Disease Control and Prevention includes severe or immediate allergic reaction of any severity to a component of the COVID-19 vaccine as a contraindication to vaccine administration.[18] This raised concern about the safety of mRNA COVID-19 vaccines in patients with prior PEG-ASNase hypersensitivity. The American Society of Hematology recommended patient referral for skin testing to PEG to determine safety of mRNA vaccine administration.[19] Recently published consensus recommendations from a multidisciplinary panel of experts in anaphylaxis management advise against pre-vaccination excipient skin testing outside of the research setting, given the unknown exact cause of hypersensitivity and variable predictive value of skin testing.[20]

In a recent study from Vanderbilt University Medical Center (VUMC) and Texas Children's Hospital, 19 patients with a prior designation of PEG-ASNase allergy were referred to allergy clinics; 14 patients had skin testing performed, yielding negative results with subsequent safe administration of mRNA COVID-19 vaccine.[7] Five patients had previously tolerated oral laxative, PEG3350, so no skin testing was performed and there was no reaction to vaccine.[7] The Hospital for Sick Children implemented a screening questionnaire to assess PEG-ASNase allergy severity or reaction to PEG3350.[21] One allergy referral was made for a patient with PEG-ASNase and PEG3350 hypersensitivity; the remaining 32 PEG-ASNase-allergic patients received vaccine under medical observation without skin testing, and no allergic reaction was reported.[21] The aim of our study was to better understand oncologists' vaccine counseling and referral practices for patients with prior PEG-ASNase hypersensitivity and to report any allergic reactions to vaccine. This study was approved by the VUMC Institutional Review Board.

2 | METHODS

Between June and October 2021, North American pediatric oncology providers in any clinical role (nursing, physician, pharmacy) were invited to participate via emails to division and fellowship program directors and posts on the American Society of Pediatric Hematology and Oncology clinical forum. Study data were collected and managed using REDCap electronic data capture tools hosted at VUMC.[22,23] Providers entered responses to the best of their recollection without accessing the medical record for each COVID-19 vaccine-eligible patient with previous PEG-ASNase hypersensitivity reaction. Survey domains included PEG-ASNase reaction, COVID-19 counseling, administration practices, and outcomes. At the time of survey administration, the U.S. Food & Drug Administration (FDA) had provided emergency use authorization (EUA) for Pfizer-BioNTech and Moderna COVID-19 mRNA vaccines for those 12 years and older.

3 | RESULTS

Seventy-five responses were entered into the database, with two ineligible entries due to patient age <12 years. Characteristics of patients and PEG-ASNase hypersensitivity reactions are described (Table 1).

COVID-19 vaccine counseling and administration practice are described in Table 2. Most patients received provider counseling with advice to seek pre-vaccination allergy testing (31.5%) or vaccination under medical observation (26%) or both (21.9%). Ten patients (13.7%) were advised against receiving mRNA COVID-19 vaccine; of these 10 patients, providers further reported that four received the Johnson & Johnson (J&J) vaccine. The remaining six had not yet received vaccine at the time of survey administration due to patient decision (2), lack of availability of non-PEG-containing vaccine (2), and other (2). Four (5.5%) patients were not counseled at all, and two (2.7%) patients were told no precautions were necessary. Of those not counseled ($n = 4$), one patient was not able to be contacted, the others received Pfizer-BioNTech (1), Moderna (1), and J&J (1) vaccines; the two with receipt of mRNA vaccinations did not see an allergist, nor did they have a reaction to vaccine.

Forty-eight patients received any COVID-19 vaccine; 42 received an mRNA vaccine. Of the mRNA vaccine recipients, two-thirds ($n = 28$) were referred to an allergist. Allergist practice included skin testing, oral PEG challenge, medical observation for vaccine administration, antihistamine premedication, or a combination of these practices (Table 2). No hypersensitivity reactions were reported for any patient who received mRNA vaccine. Of the 48 patients who received a first dose of vaccine, 35 received a second dose with no reactions reported.

Twenty-four patients had not received a COVID-19 vaccine at the time of survey completion due to patient decision (7) or medical reasons (3). Other reasons listed for the remaining 14 who had not received vaccine included awaiting allergy evaluation (7), availability of non-PEG-containing COVID vaccine (2), opportunity to receive under medical observation (1), additional information (2), or provider recommendation (1), and lost to follow-up (1).

4 | DISCUSSION

Due to the presence of PEG in mRNA COVID-19 vaccines, pediatric oncologists are faced with how best to counsel patients with prior PEG-ASNase hypersensitivity. Our study, which included patients 12 years and older, indicated that the majority of patients were

TABLE 1 Clinical characteristics of patients and PEG-asparaginase hypersensitivity reactions

	N = 73	*n* (%)
Age (years)		
	12–16	26 (38.4)
	16–24	42 (57.5)
	25–39	5 (6.8)
Cancer type		
	Acute lymphoblastic leukemia	64 (87.7)
	Acute lymphoblastic lymphoma	4 (5.5)
	Other leukemia	5 (6.8)
Current treatment status	Off-treatment	46 (63)
At time of PEG-asparaginase reaction		
Treatment phase		
	Induction	27 (37)
	Consolidation	39 (53.4)
	Delayed intensification	4 (5.5)
	Do not recall	3 (4.1)
Symptoms[a]		
	Flushing	39 (53.4)
	Hives	51 (69.9)
	Nausea/vomiting	37 (50.7)
	Bronchospasm	38 (52.1)
	Hypotension	20 (27.4)
	Do not recall	5 (6.8)
Allergy to other PEG-containing medications		
	No	67 (91.8)
	Do not know	6 (8.2)

Abbreviation: PEG, polyethylene glycol.
[a]Respondents were asked to mark all that apply.

counseled by oncology providers to receive mRNA COVID-19 vaccines under medical observation or after pre-vaccination allergy evaluation and that allergy practice was varied. Importantly, none of the 42 patients who received mRNA vaccine had an allergic reaction despite prior PEG-ASNase allergy. Several patients had not yet been vaccinated while awaiting approval of a non-mRNA COVID vaccine.

This study has several limitations, including (a) low response rate, with participation more likely by providers with established counseling and referral practices and the potential for multiple institutional providers to report on the same patient, and (b) reliance upon provider recall of hypersensitivity reactions and allergy evaluations. Specifically, the high proportion of patients reported to have PEG-ASNase hypersensitivity during induction therapy may indicate either poor provider recall or inaccurate classification, as true hypersensitivity is rare at initial exposure and more commonly indicates infusion-related reaction and less likely prior sensitization to PEG.

This study adds to recently published experience[7,21] that mRNA COVID-19 vaccines are safely administered to those with prior PEG-ASNase allergy, providing valuable information to oncologists who counsel these patients. Counseling is complicated by variable symptomatology, severity, and elapsed time from PEG-ASNase reactions. Though the mechanism of PEG-ASNase hypersensitivity remains incompletely understood, anti-PEG IgE may play a role in some cases,[24] creating the potential for IgE-mediated immediate hypersensitivity upon re-challenge. IgE-mediated reactions and skin testing to PEG can wane over time[25]; therefore, recent PEG-ASNase reactions may warrant more careful evaluation and observed vaccination. Given the complexity of PEG-ASNase reactions, we propose observed immunizations in a physician practice with pre-vaccination allergist referral for recent or severe PEG-ASNase reactions. Further study is necessary, particularly with FDA expansion of the EUA for Pfizer-BioNTech COVID-19 vaccine to younger children who may have had more recent PEG-ASNase reactions, to determine the safest strategy that prevents delay of vaccination.

TABLE 2 COVID-19 vaccine counseling and administration practice in patients with history of PEG-asparaginase hypersensitivity reactions

	N = 73	*n* (%)
Counseling	Pre-vaccination allergy testing only	23 (31.5)
	Vaccination with medical observation only	19 (26)
	Allergy testing and medical observation	16 (21.9)
	NOT get mRNA vaccine	10 (13.7)
	Received vaccine without precautions	2 (2.7)
	Not counseled at all	4 (5.9)
	N = 72[a]	*n* (%)
Vaccine received	Yes	48 (66.7)
	Non-mRNA[b]	6 (12.5)
	mRNA[c]	42 (87.5)
mRNA vaccine	*N* = 42	*n* (%)
	Reaction to first dose of mRNA vaccine	0
	Allergist referral	28 (66.7)
	N = 28	*n* (%)
	Skin test only	2 (7.1)
	Skin test + oral PEG challenge	2 (7.1)
	Skin test + oral PEG challenge + medical observation	11 (39.2)
	Skin test + oral PEG challenge + medical observation + antihistamine premedication	1 (3.6)
	Skin test + medical observation	4 (14.2)
	Medical observation only	7 (25)
	Unknown	1 (3.6)
Reasons why vaccine was not received	*N* = 24	*n* (%)
	Medical reason unrelated to vaccine	3 (12.5)
	Patient decision	7 (29.2)
	Other	14 (58.3)

Abbreviations: mRNA, m-ribonucleic acid; PEG, polyethylene glycol.
[a]One response was not provided to question "vaccine received?"
[b]Non-mRNA: Johnson & Johnson/Janssen.
[c]mRNA (Pfizer-BioNTech *n* = 39, Moderna *n* = 3).

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CONFLICT OF INTEREST

Elizabeth J. Phillips has received royalties from Uptodate and consulting fees from Janssen, Vertex, Biocryst, Regeneron, and Verve. She is co-director of IIID Pty Ltd that holds a patent for HLA-B*57:01 testing for abacavir hypersensitivity, and has a patent pending for Detection of Human Leukocyte Antigen-A*32:01 in connection with Diagnosing Drug Reaction with Eosinophilia and Systemic Symptoms without any financial remuneration and not directly related to the submitted work. The other authors have no disclosures to report.

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REFERENCES

1. Abbott LS, Zakova M, Shaikh F, Shewaramani N, Punnett A, Dupuis LL. Allergic reactions associated with intravenous versus intramuscular pegaspargase: a retrospective chart review. *Paediatr Drugs*. 2015;17(4):315-321.
2. August KJ, Miller WP, Dalton A, Shinnick S. Comparison of hypersensitivity reactions to PEG-asparaginase in children after intravenous and intramuscular administration. *J Pediatr Hematol Oncol*. 2013;35(7):e283-e286.
3. Burke MJ, Devidas M, Maloney K, et al. Severe pegaspargase hypersensitivity reaction rates (grade ≥ 3) with intravenous infusion vs. intramuscular injection: analysis of 54,280 doses administered to 16,534 patients on Children's Oncology Group (COG) clinical trials. *Leuk Lymphoma*. 2018;59(7):1624-1633.
4. Hasan H, Shaikh OM, Rassekh SR, Howard AF, Goddard K. Reply to: comment on: comparison of hypersensitivity rates to intravenous and intramuscular PEG-asparaginase in children with acute lymphoblastic

leukemia: a meta-analysis and systematic review. *Pediatr Blood Cancer*. 2018;65(8):e27106.
5. Henriksen LT, Harila-Saari A, Ruud E, et al. PEG-asparaginase allergy in children with acute lymphoblastic leukemia in the NOPHO ALL2008 protocol. *Pediatr Blood Cancer*. 2015;62(3):427-433.
6. Petersen WC Jr, Clark D, Senn SL, et al. Comparison of allergic reactions to intravenous and intramuscular pegaspargase in children with acute lymphoblastic leukemia. *Pediatr Hematol Oncol*. 2014;31(4):311-317.
7. Koo G, Anvari S, Friedman DL, et al. mRNA COVID-19 vaccine safety in patients with previous immediate hypersensitivity to pegaspargase. *J Allergy Clin Immunol Pract*. 2022;10(1):322-325.
8. Liu Y, Smith CA, Panetta JC, et al. Antibodies predict pegaspargase allergic reactions and failure of rechallenge. *J Clin Oncol*. 2019;37(23):2051-2061.
9. Burke MJ, Rheingold SR. Differentiating hypersensitivity versus infusion-related reactions in pediatric patients receiving intravenous asparaginase therapy for acute lymphoblastic leukemia. *Leuk Lymphoma*. 2017;58(3):540-551.
10. Connelly JA, Chong H, Esbenshade AJ, et al. Impact of COVID-19 on pediatric immunocompromised patients. *Pediatr Clin North Am*. 2021;68(5):1029-1054.
11. Madhusoodhan PP, Pierro J, Musante J, et al. Characterization of COVID-19 disease in pediatric oncology patients: the New York-New Jersey regional experience. *Pediatr Blood Cancer*. 2021;68(3):e28843.
12. Wood WA, Neuberg DS, Thompson JC, et al. Outcomes of patients with hematologic malignancies and COVID-19: a report from the ASH Research Collaborative Data Hub. *Blood Adv*. 2020;4(23):5966-5975.
13. Polack FP, Thomas SJ, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med*. 2020;383(27):2603-2615.
14. Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403-416.
15. Thompson MG, Burgess JL, Naleway AL, et al. Prevention and attenuation of Covid-19 with the BNT162b2 and mRNA-1273 vaccines. *N Engl J Med*. 2021;385(4):320-329.
16. Rijkers GT, Weterings N, Obregon-Henao A, et al. Antigen presentation of mRNA-based and virus-vectored SARS-CoV-2 vaccines. *Vaccines (Basel)*. 2021;9(8):848.
17. Sellaturay P, Nasser S, Islam S, Gurugama P, Ewan PW. Polyethylene glycol (PEG) is a cause of anaphylaxis to the Pfizer/BioNTech mRNA COVID-19 vaccine. *Clin Exp Allergy*. 2021;51(6):861-863.
18. CDC. *Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Approved or Authorized in the United States*. CDC; Updated October 30, 2021. Access date: November 15, 2021. https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html
19. American Society of Hematology. *COVID-19 and Pediatric ALL: Frequently Asked Questions*. American Society of Hematology; Updated January 29, 2021. Accessed November 6, 2021. https://www.hematology.org/covid-19/covid-19-and-pediatric-all
20. Greenhawt M, Abrams EM, Shaker M, 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(10):3546-3567.
21. Mark C, Gupta S, Punnett 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(11):e29295.
22. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.
23. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381.
24. Stone CA Jr, Liu Y, Relling MV, et al. Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized. *J Allergy Clin Immunol Pract*. 2019;7(5):1533-1540.e8.
25. Bruusgaard-Mouritsen MA, Jensen BM, Poulsen LK, Duus Johansen J, Garvey LH. Optimizing investigation of suspected allergy to polyethylene glycols. *J Allergy Clin Immunol*. 2022;149(1):168-175.e4.

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