

BRIEF COMMUNICATION

Vaccines against SARS-CoV-2 are safe to administer in patients with antibodies to pegaspargase

Hope D. Swanson¹ | Hana Hakim²  | Diego R. Hijano² | Ted Morton² |
Shane Cross¹ | Hiroto Inaba³ | Sima Jaha^{3,4}  | Ching-Hon Pui³ | Seth E. Karol³ 

¹Department of Pharmacy and Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

²Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

³Department of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

⁴Department of Global Pediatric Medicine, St. Jude Children's Research Hospital, Memphis, Tennessee, USA

Correspondence

Seth E Karol, 262 Danny Thomas Place, Mail Stop 260, Memphis, TN 38105, USA.

Email: seth.karol@stjude.org

Funding information

American Lebanese Syrian Associated Charities; National Cancer Institute, Grant/Award Number: CA21765 and CA250418

Abstract

Objective: Allergic reactions to pegaspargase during ALL therapy are typically due to antibodies against polyethylene glycol (PEG), which is also used as a stabilizing agent in mRNA-based SARS-CoV-2 vaccines. To evaluate the safety of these vaccines in patients with anti-pegaspargase antibodies.

Methods: We retrospectively reviewed the records of patients treated for ALL who had received SARS-CoV-2 vaccinations. All patients had antibodies against pegaspargase assayed during ALL therapy prospectively and in response to clinical allergies. Symptoms of intolerance to vaccination were gathered retrospectively from chart abstraction.

Results: SARS-CoV-2 vaccination was well tolerated in all 78 patients with prior exposure to pegaspargase as part of their leukemia therapy. No reactions were observed in the 54 patients without a history of anti-pegaspargase antibodies or in 19 patients with antibodies who received mRNA vaccination. 1 patient who received the polysorbate containing Janssen vaccine experienced mild symptoms after vaccination not meeting the criteria of clinical allergy which spontaneously resolved within 25 minutes.

Conclusion: SARS-CoV-2 vaccination is safe in this population.

Both Pfizer-BioNTech and Moderna mRNA COVID-19 vaccines contain polyethylene glycol (PEG) as an inactive ingredient. Recommendations from the Centers for Disease Control and Prevention list severe allergic reaction to a component of the vaccine as a contraindication to administration.¹ PEG is thought to be one of the causes of allergic reactions to the mRNA vaccines.^{2,3} Patients treated for acute lymphoblastic leukemia/ lymphoma (ALL) are exposed to PEG in the form of pegaspargase, a critical component of all pediatric ALL therapy. The most common side effect of pegaspargase therapy is a

hypersensitivity reaction.⁴⁻⁶ Such apparent hypersensitivity reactions can reflect either infusion reactions without an identifiable immunologic component or be driven by antibodies to pegaspargase.^{4,7} Because allergy to PEG is the primary driver of allergic reactions to pegaspargase,⁷ there are safety concerns for administering PEG-containing COVID-19 vaccines to patients with a history of pegaspargase hypersensitivity reactions during ALL therapy.⁸ However, alternative vaccine options are limited as the Pfizer-BioNTech is the only SARS-CoV-2 vaccine currently available to children. This limitation leaves

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2022 The Authors. *Cancer Medicine* published by John Wiley & Sons Ltd.

TABLE 1 Patient demographics

Patient demographics	N = 78 (%)
Age at leukemia diagnosis (years)	
Median	9.1
Range	1.3–18.5
Age at time of first vaccine (years)	
Median	14.6
Range	5.2–25.8
Sex	
Male	47 (60.3)
Female	31 (39.7)
Self-declared race/ethnicity	
White	51 (65.4)
Black	17 (21.8)
Hispanic	6 (7.7)
Asian	3 (3.8)
American Indian	1 (1.3)
Diagnosis	
B-ALL	57 (73)
T-ALL	15 (19.2)
Early T-cell precursor-ALL	2 (2.6)
B-LLy	2 (2.6)
T-LLy	2 (2.6)
Number of vaccine doses documented in St. Jude medical record	
1	22 (28.2)
2	46 (59)
3	10 (12.8)
Manufacturer of the vaccine	
Janssen	7 (9)
Moderna	6 (7.7)
Pfizer-BioNTech	65 (83.3)
Time from last pegaspargase dose to first vaccine administration (Years)	
Median	3.7
Range	0.22–12.1
History of allergic reaction to pegaspargase, CTCAE version 3	9 (11.5%)
Grade 2	3 (33.3%)
Grade 3	6 (66.7%)
Pegaspargase antibodies positive at any time during treatment	24 (30.8%)
Time from last known positive antibodies to first vaccine dose (years)	
Median	4.3
Range	0.65–12.3

TABLE 1 (Continued)

Patient demographics	N = 78 (%)
Pegaspargase antibodies remaining positive at last test performed	6 (7.6%)
Time from last known positive antibodies to first vaccine dose (years)	
Median	3.2
Range	1.5–7.7

Abbreviations: ALL, acute lymphoblastic leukemia; LLy, lymphoblastic lymphoma; CTCAE, common terminology criteria for adverse events.

a substantial number of patients at high risk of severe COVID-19 disease^{1,9–11} without the protection of highly effective vaccines.

Prior publications have reported the safe administration of mRNA vaccines in patients with prior history of hypersensitivity reactions to pegaspargase.^{8,12–14} However, the rate of reactions to these vaccines in patients with anti-PEG antibodies following pegaspargase therapy has not been reported. Prior reports suggest these antibodies develop in more than 80% of patients with clinical hypersensitivity reactions to pegaspargase and 18% of patients receiving pegaspargase without a history of clinical reaction.⁷ We therefore sought to assess the risk of allergic reaction to COVID-19 vaccination in patients previously exposed to pegaspargase with and without a history of anti-pegaspargase antibodies.

Patients treated at St. Jude Children's Research Hospital were evaluated if they had received at least one dose of pegaspargase and a vaccine against SARS-CoV-2. Data collected included pegaspargase doses and dates of administration, details of pegaspargase hypersensitivity reaction, anti-pegaspargase antibody results, manufacturer of COVID-19 vaccine administered, number and dates of vaccine doses, and vaccine reaction symptoms post-vaccination. Clinical notes and allergy documentation were reviewed in the electronic health record for documentation of reaction to SARS-CoV-2 vaccine and history of hypersensitivity reaction to pegaspargase. This study was approved by the institutional review board.

The demographics of the 78 patients who had previously been treated with pegaspargase and received SARS-CoV-2 vaccine are listed in Table 1. Fifty-two patients received at least one dose of anti-SARS-CoV-2 vaccine at St. Jude and 26 patients received their vaccine elsewhere; documentation of administration for these patients was included in the electronic health record. One patient experienced a mild reaction to the Janssen vaccine approximately 25 minutes after administration that included

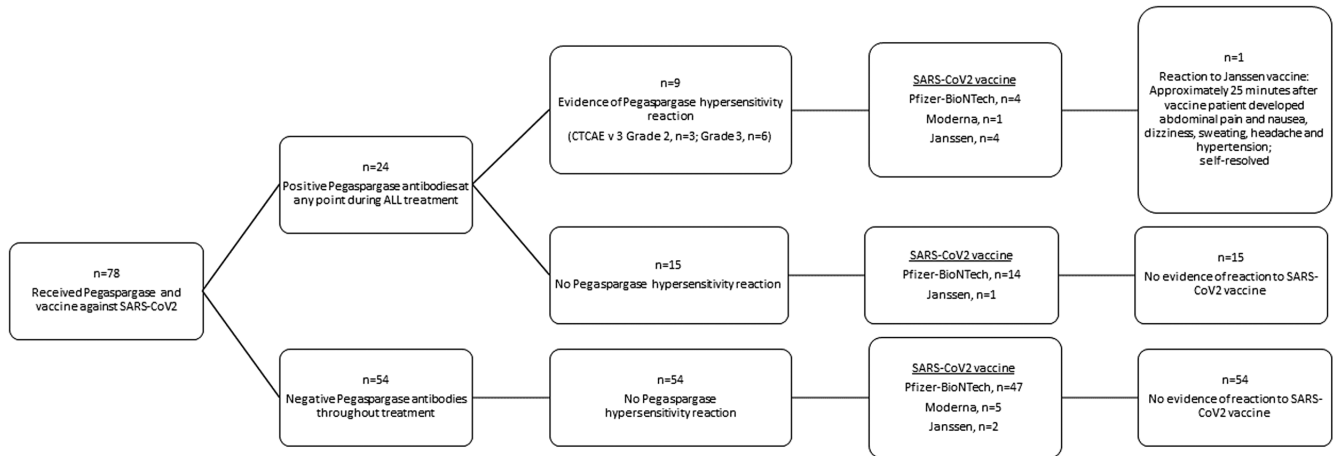


FIGURE 1 Vaccine administration based on the presence of pegaspargase antibodies and hypersensitivity reactions at any point during treatment.

abdominal pain, nausea, dizziness, sweating, and hypertension. These symptoms did not meet CDC criteria for an allergic reaction and resolved without interventions within 30 minutes. The other 77 patients had no adverse reactions to their SARS-CoV2 vaccine.

Of the 24 patients with positive pegaspargase antibodies during their treatment for ALL, 9 experienced clinical hypersensitivity to pegaspargase. Five of these nine patients received an mRNA vaccine that contained PEG; none of them developed a reaction (Figure 1). Of the nine patients with hypersensitivity reaction to pegaspargase, three had tolerated subsequent pegaspargase infusion with desensitization ($n = 2$) or pre-medication ($n = 1$). Six of twenty-four patients, including four with hypersensitivity reactions, had persistently positive pegaspargase antibodies at last assessment 1.5 to 7.7 (median, 3.2) years before they received and tolerated their vaccine. Of these six patients, four with a history of hypersensitivity to pegaspargase received Janssen vaccine, and two without a history of hypersensitivity received Pfizer-BioNTech vaccine.

Our data support the tolerability of PEG-containing mRNA vaccines for SARS-CoV-2 in patients with a history of anti-pegaspargase antibodies with or without a history of clinical hypersensitivity. Our finding is consistent with prior publications indicating mRNA vaccines for SARS-CoV-2 are safe to administer in patients with history of clinical pegaspargase allergic reactions.^{12,13} Our data clarify that such administration is safe even in patients who had a prior immune reaction to PEG. PEG and polysorbate 80 have similar structure with polyether groups; cross reactivity of allergic reactions to PEG and polysorbate 80 have been reported.^{15,16} Thus, cross reactivity to polysorbate in the vaccine manufactured by Janssen can occur in patients with prior pegaspargase hypersensitivity. It is possible such a cross-reaction was the cause of

the observed symptoms in one of our five patients with anti-pegaspargase antibodies. These data support the recommendation that patients with hypersensitivity reaction to pegaspargase should also be considered for additional monitoring after Janssen vaccine administration. Our data also support the safety of vaccine administration in such patients.

Limitations of our study include a variable interval between anti-pegaspargase antibody measurement and vaccination as well as a limited sample size, particularly for patients with a history of clinical allergic reaction. A strength of our data is the ability of available antibody data to confirm that patients had previously experienced true immune-mediated hypersensitivity reactions to pegaspargase as opposed to infusion reactions, which may have similar clinical manifestations but are typically milder in degree.⁷ Taken together, our data indicate that neither a history of anti-pegaspargase antibodies nor clinical hypersensitivity reaction should be a barrier for vaccination against SARS-CoV-2.

AUTHOR CONTRIBUTIONS

HDS and SEK designed the study, analyzed data, performed analyses. All authors contributed data and participated in manuscript preparation and revision.

ACKNOWLEDGMENTS

Support for this work from: ALSAC, NIH CA21765, CA250418.

CONFLICT OF INTEREST

SEK served as a consultant for Servier. The other authors indicate no relevant financial disclosures.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Hana Hakim  <https://orcid.org/0000-0001-7146-5452>

Sima Jeha  <https://orcid.org/0000-0003-2835-5869>

Seth E. Karol  <https://orcid.org/0000-0001-8113-8180>

REFERENCES

1. Services CfDcaPUSDoHH. Interim clinical considerations for use of COVID-19 vaccines. *CDC*. 2022;2022. Accessed July 7, 2022. <https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html>
2. Risma KA, Edwards KM, Hummell DS, et al. Potential mechanisms of anaphylaxis to COVID-19 mRNA vaccines. *J Allergy Clin Immunol*. 2021;147(6):2075-2082 e2072.
3. 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.
4. Kloos RQH, Pieters R, Jumelet FMV, de Groot-Kruseman HA, van den Bos C, van der Sluis IM. Individualized asparaginase dosing in childhood acute lymphoblastic leukemia. *J Clin Oncol*. 2020;38(7):715-724.
5. Jeha S, Pei D, Choi J, et al. Improved CNS control of childhood acute lymphoblastic leukemia without cranial irradiation: St Jude Total therapy study 16. *J Clin Oncol*. 2019;37(35):3377-3391.
6. Vrooman LM, Blonquist TM, Stevenson KE, et al. Efficacy and toxicity of Pegaspargase and Calaspargase pegol in childhood acute lymphoblastic leukemia: results of DFCI 11-001. *J Clin Oncol*. 2021;39(31):3496-3505.
7. 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.
8. 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.
9. Mukkada S, Bhakta N, Chantada GL, et al. Global characteristics and outcomes of SARS-CoV-2 infection in children and adolescents with cancer (GRCCC): a cohort study. *Lancet Oncol*. 2021;22(10):1416-1426.
10. Moreira DC, Millen GC, Sands S, Kearns PR, Hawkins DS. The care of children with cancer during the COVID-19 pandemic. *Am Soc Clin Oncol Educ Book*. 2021;41:1-10.
11. Meena JP, Kumar Gupta A, Tanwar P, Ram Jat K, Mohan Pandey R, Seth R. Clinical presentations and outcomes of children with cancer and COVID-19: a systematic review. *Pediatr Blood Cancer*. 2021;68(6):e29005.
12. 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.
13. Rush C, Faulk KE, Bradley ZK, Turner A, Krumins M, Greenhawt M. The safety of SARS-CoV-2 vaccines in persons with a known history of pegaspargase allergy: a single institution experience. *J Allergy Clin Immunol Pract*. 2022;10(2):630-632.
14. 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.
15. Ieven T, Van Weyenbergh T, Vandebotermiet M, Devolder D, Breynaert C, Schrijvers R. Tolerability of polysorbate 80-containing COVID-19 vaccines in confirmed polyethylene glycol-allergic patients. *J Allergy Clin Immunol Pract*. 2021;9(12):4470-4472 e4471.
16. 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 e1538.

How to cite this article: Swanson HD, Hakim H, Hijano DR, et al. Vaccines against SARS-CoV-2 are safe to administer in patients with antibodies to pegaspargase. *Cancer Med*. 2022;00:1-4. doi: [10.1002/cam4.5011](https://doi.org/10.1002/cam4.5011)