Pegaspargase is a vital component of a multidrug chemotherapy regimen for treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LL). Pegaspargase is manufactured by chemically conjugating *Escherichia coli*–derived L-asparaginase with polyethylene glycol (PEG5000). By itself, *E. coli*–derived L-asparaginase is associated with high rates of hypersensitivity reactions. The pegylated form has extended half-life and improved immunogenicity profile compared with the native form, resulting in lower rates of hypersensitivity reactions. Tolerance of pegaspargase after a hypersensitivity reaction to *E. coli*–derived L-asparaginase suggests different antigenic sites. However, pegaspargase is also commonly associated with immediate hypersensitivity reactions, with incidence ranging from 3% to 41%. Infusion reactions to pegaspargase might therefore be due to PEG given the presence of anti-PEG antibodies in several studies, but may also be due to reactivity against asparaginase itself. Reactions to pegaspargase are of an antibody-mediated type, consisting of anaphylactic, angioedematous, or urticarial reactions. Treatment also varied from antihistamines to epinephrine. Of the 19 patients, 16 (84.2%) reported having experienced a reaction with the PEG3350 component.

The demographics, index reaction history, and testing results of the 19 patients are summarized in Table 1. Of the patients evaluated with the protocol above, 9 (47.4%) were female and the average age was 16.5 years (range: 12–33 years). An average of 6.6 years (range: 1–20 years) had passed since their index pegaspargase reaction. Apart from 1 patient, the reactions were all immediate hypersensitivity phenotype, with the typical onset of symptoms within 1 to 60 minutes of drug receipt. Of the 19 patients, 15 (78.9%) experienced a reaction with the first or second dose of pegaspargase. The patients had varying levels of symptom severity, but 18 reactions involved 2 or more systems. Treatment also varied from antihistamines alone to epinephrine in 8 of 19 (42.1%) of the patients receiving epinephrine. Of the 19 patients, 16 (84.2%) reported having tolerated PEG3350 subsequent to their reaction to pegaspargase.

Of the 19 patients, 14 had negative skin testing before immunization and the remaining 5 patients who had tolerated PEG3350 went on to immunization without skin testing. All 19 patients tolerated their first dose of Pfizer-BioNTech mRNA COVID-19 vaccine with no symptoms. Subsequently, the patients were given the option to receive their second doses in the regular vaccination centers with 30-minute observation, and all 19 patients tolerated their second doses uneventfully.

Because of the presence of PEG2000 in the mRNA COVID-19 vaccines, it is important to investigate whether there is any potential immunological cross-reactivity in patients who have previously experienced hypersensitivity reactions to pegaspargase. This case series is the first to demonstrate that patients with immediate hypersensitivity reactions to pegaspargase appear to safely tolerate PEG3350.
| Center | Age (y) | Sex | Date of reaction | Onset of symptoms (min) | Signs and symptoms | Treatment received | Subsequent PEG exposure? | PEG skin testing result* | 1-h observation outcome | 24-h follow-up phone call | Postvaccination follow-up phone call |
|--------|---------|-----|------------------|-------------------------|--------------------|-------------------|------------------------|------------------------|--------------------------|--------------------------|----------------------------------|
| VUMC   | 13      | F   | 2017 2nd dose    | 10                      | Difficulty breathing, facial flushing | Diphenhydramine   | Yes, Miralax          | Negative               | No symptoms              | No symptoms              | No symptoms                     |
|         | 13      | M   | 2014 2nd dose    | 5                       | Erythema, flushing, shortness of breath | Diphenhydramine, hydrocortisone | Yes, Miralax          | Negative               | No symptoms              | No symptoms              | No symptoms                     |
|         | 17      | F   | 2014 2nd dose    | 10                      | Shortness of breath, lip, and tongue swelling | Diphenhydramine, hydrocortisone, ranitidine, epinephrine | Yes, Miralax          | Negative               | No symptoms              | No symptoms              | No symptoms                     |
|         | 13      | M   | 2016 2nd dose    | 5                       | Rash, throat tightness, vomiting | Diphenhydramine, hydrocortisone | Yes, Miralax          | Negative               | No symptoms              | No symptoms              | No symptoms                     |
|         | 13      | M   | 2016 1st dose    | 20                      | Shortness of breath, flushing, tongue swelling, tachycardia | Systemic steroid | Yes, Miralax          | Negative               | No symptoms              | No symptoms              | No symptoms                     |
| VUMC   | 13      | M   | 2021 2nd dose    | 30                      | Facial erythema, facial swelling, shortness of breath, vomiting | Diphenhydramine, hydrocortisone, epinephrine | Yes, Miralax          | Negative               | No symptoms              | No symptoms              | No symptoms                     |
|         | 33      | F   | 2001 11th dose   | 1                       | Shortness of breath, unconsciousness | Epinephrine        | Yes, Miralax          | Negative               | No symptoms              | No symptoms              | No symptoms                     |
| VUMC   | 25      | F   | 2011 2nd dose    | 2                       | Diffuse erythema, pruritus, hypotensive | Methylprednisolone, epinephrine | Yes, Miralax          | Negative               | No symptoms              | No symptoms              | No symptoms                     |
|         | 17      | M   | 2018 1st dose    | 2                       | Facial and lip swelling, difficulty breathing, urticaria, emesis | Diphenhydramine, hydrocortisone | No                  | Negative               | No symptoms              | No symptoms              | No symptoms                     |
| VUMC   | 14      | F   | 2018 3rd dose    | 15                      | Diffuse urticaria, nausea, hypotension | Diphenhydramine   | Yes, Miralax          | Negative               | No symptoms              | No symptoms              | No symptoms                     |
| TCH    | 16      | F   | 2018 2nd dose    | 3                       | Facial flushing, periorbital edema, cough, emesis | Diphenhydramine, hydrocortisone | Yes, Miralax          | Negative               | No symptoms              | No symptoms              | No symptoms                     |
|         | 16      | M   | 2007 2nd dose    | 1st: 12hrs              | Urticaria, difficulty breathing, cough, wheezing | Diphenhydramine, hydrocortisone, epinephrine | Yes, Miralax          | Negative               | No symptoms              | No symptoms              | No symptoms                     |
|         | 13      | M   | 2013 4th dose    | 5                       | Urticaria, difficulty breathing, cough, wheezing | Diphenhydramine, hydrocortisone, epinephrine | No                  | Negative               | No symptoms              | No symptoms              | No symptoms                     |
|         | 12      | M   | 2014 2nd dose    | 5                       | Facial and orbital erythema, upper lip swelling, tongue pruritus | Diphenhydramine, hydrocortisone | No                  | Negative               | No symptoms              | No symptoms              | No symptoms                     |
| TCH    | 16      | F   | 2013 1st dose    | 15                      | Erythema, urticaria, pruritus, periorbital edema | Diphenhydramine   | Yes, Miralax          | Not done†              | No symptoms              | No symptoms              | No symptoms                     |
|         |         |     | 2014 2nd dose    |                         |                                      |                   |                     |                       |                         |                         |                                  |

(continued)
| Center | Age (y) | Sex | Date of reaction | Signs and symptoms | Onset of symptoms | Pruritus, coughing, facial \(5^*\) symptoms | Treatment received | 1-h observation outcome | 24-h follow-up phone call outcome | Vaccine dose 1 result |
|-------|--------|-----|-----------------|---------------------|-----------------|-------------------------------------|------------------|----------------------|--------------------------|---------------------|
| TCH   | 17     | M   | 2016            | Pruritus, coughing  | 3rd dose        | Diphenhydramine, methylprednisolone, ranitidine, epinephrine | Yes, Miralax     | Not done;‡, α       | Not done;‡, α         | No symptoms            |
| TCH   | 16     | F   | 2015            | Throat tightness, pruritus, vomiting | 1st dose       | Diphenhydramine, methylprednisolone, ranitidine, epinephrine | Yes, Miralax     | Not done;‡, α       | Not done;‡, α         | No symptoms            |
| TCH   | 21     | M   | 2018            | Palpitations        | 1st dose        | Diphenhydramine, methylprednisolone, ranitidine, epinephrine | Yes, Miralax     | Not done;‡, α       | Not done;‡, α         | No symptoms            |
| TCH   | 16     | F   | 2015            | Throat tightness, pruritus, vomiting | 2nd dose       | Diphenhydramine, methylprednisolone, ranitidine, epinephrine | Yes, Miralax     | Not done;‡, α       | Not done;‡, α         | No symptoms            |

**Note:**

- ‡At VUMC, the PEG skin testing protocol included PEG3350 (skin prick only 1.7 and 17 mg/mL), PEG8000 (skin prick only 0.1 and 1 mg/mL), and methylprednisolone acetate (skin prick and intradermal 4 and 0.4 mg/mL).
- At TCH, the PEG skin testing protocol included PEG3350 (skin prick only 1.7, 17, and 170 mg/mL), and methylprednisolone acetate (skin prick 40 mg/mL and intradermal 4 and 0.4 mg/mL).
- PEG skin testing not performed because the patient had known tolerance of PEG3350.
- αThe mechanism behind immediate hypersensitivity reactions to pegaspargase is not clear. Whether these patients might ever demonstrate anti-PEG sIgE or positive PEG skin testing in the early pegaspargase reaction period remains unknown.
- βBeyond the ongoing mechanistic questions underlying pegaspargase reactions, we provide preliminary supportive evidence that patients with a previous immediate reaction to pegaspargase may still have IgM, IgG, or IgE PEG antibodies. This is also important because the clinical relevance of IgM and IgG, which is present at low levels in 5% to 9% of the population, is not clear. Whether these patients might ever demonstrate anti-PEG sIgE or positive PEG skin testing in the early pegaspargase reaction period remains unknown.

**TABLE I. (Continued)**

| Index reaction history | PEG skin testing result* |
|------------------------|-------------------------|
| TCH                    |                         |
| TCH                    |                         |
| TCH                    |                         |
| TCH                    |                         |

**Note:**

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**Table notes:**

- **Center:** TCH, Texas Children’s Hospital; VUMC, Vanderbilt University Medical Center.
- **PEG skin testing result:** At VUMC, the PEG skin testing protocol included PEG3350 (skin prick only 1.7 and 17 mg/mL), PEG8000 (skin prick only 0.1 and 1 mg/mL), and methylprednisolone acetate (skin prick and intradermal 4 and 0.4 mg/mL). At TCH, the PEG skin testing protocol included PEG3350 (skin prick only 1.7, 17, and 170 mg/mL), and methylprednisolone acetate (skin prick 40 mg/mL and intradermal 4 and 0.4 mg/mL).
- **PEG skin testing not performed because the patient had known tolerance of PEG3350:**
- **αThe mechanism behind immediate hypersensitivity reactions to pegaspargase is not clear. Whether these patients might ever demonstrate anti-PEG sIgE or positive PEG skin testing in the early pegaspargase reaction period remains unknown.**
- **βBeyond the ongoing mechanistic questions underlying pegaspargase reactions, we provide preliminary supportive evidence that patients with a previous immediate reaction to pegaspargase may still have IgM, IgG, or IgE PEG antibodies. This is also important because the clinical relevance of IgM and IgG, which is present at low levels in 5% to 9% of the population, is not clear. Whether these patients might ever demonstrate anti-PEG sIgE or positive PEG skin testing in the early pegaspargase reaction period remains unknown.**

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- **PEG skin testing not performed because the patient had known tolerance of PEG3350:**
safety. The objective of our evaluation focused on determining whether patients with labels of immediate reactions to pegaspargase could safely receive mRNA vaccines containing PEG 2000. To our knowledge, PEG testing in pegaspargase reactors has not been reported previously. Because our focus was on COVID-19 vaccine safety, we did not perform skin testing or challenges with pegaspargase, and hence we acknowledge that we did not directly or specifically address the pegaspargase allergy that remains as a warning in the patient chart.

In summary, our case series of safe COVID-19 mRNA vaccination in ALL survivors with a history of immediate reactions to pegaspargase provides reassurance that this is a safe strategy. Although our study achieved the major aim of achieving safe vaccination in ALL survivors, it cannot comment on the pegaspargase allergy label or future safety of pegaspargase or other pegylated drugs. Our study remains further limited in its scope and generalizability by lack of inclusion of children under 12 and those with more recent reactions to pegaspargase who are not yet eligible for COVID-19 vaccination. Although our experience suggests that routine PEG skin testing and evaluations in similar patients are likely to be low yield and may serve only to delay COVID-19 vaccination, select higher risk patients with recent anaphylaxis or patients where fear of the previous pegaspargase reaction acts as a barrier to vaccination may still benefit from specialty allergy assessment or skin testing and observed vaccination.

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