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COVID-19 mRNA Vaccination Appears Safe in Pediatric Patients With Hypersensitivity To PEGylated *Escherichia Coli* L-Asparaginase

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Summary:

PEG-asparaginase (PEGAsp) is an established component of acute leukemia therapy. Hypersensitivity reactions to PEGAsp occur in 10–15% of patients, with polyethylene glycol (PEG) suggested as the antigenic culprit. As COVID-19 mRNA vaccines contain PEG, safety of administration of these vaccines to patients with prior PEGAsp hypersensitivity has been questioned. Between December 21, 2020, and March 3, 2022, 66 patients with acute leukemia and PEGAsp allergy received COVID-19 vaccination. No patients (0/66 0%, 95% CI 0–5.4%) experienced an allergic reaction to the vaccine. COVID-19 mRNA vaccination appears to be safe in pediatric and young adult ALL patients with PEGAsp allergy.

Keywords

COVID-19; mRNA vaccination; acute lymphoblastic leukemia; PEG-asparaginase; PEG-asparaginase allergy; PEG-asparaginase hypersensitivity

L-asparaginases are a fundamental component in the treatment of pediatric acute lymphoblastic leukemia (ALL), and are increasingly incorporated into adult protocols for acute leukemia as well[1, 2]. PEG-asparaginase (PEGAsp), a form of asparaginase covalently linked to polyethylene glycol (PEG) has replaced the primitive E coli L-asparaginase as the drug of choice for ease of administration, improved half-life, decreased incidence of neutralizing antibodies, and decreased immunogenicity[3, 4]. However, hypersensitivity reactions to PEGAsp occur in 10% to 15% of patients, with the PEG component being the suggested antigenic culprit[4].

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Allergy to PEG is generally considered a contraindication to mRNA vaccines against coronavirus disease 2019 (COVID-19)[5, 6]. Whereas anaphylactic reactions to vaccines are generally rare, the rate of anaphylaxis to mRNA vaccines appears to be 10 fold higher; to date, the FDA has reported 11.1 cases and 2.5 cases of anaphylaxis per 1 million vaccines to COVID-19 vaccine BNT162b2 (produced by Pfizer-BioNTech) and mRNA-1273 (produced by Moderna Therapeutics), respectively [3, 7]. Although the exact mechanism of action behind anaphylactic reactions on the mRNA COVID-19 vaccines remains unknown, these vaccines are formulated containing a PEGylated lipid as a stabilizing agent and the PEG is frequently implicated as the candidate allergen[3]. As a result, the safety of COVID-19 vaccination in pediatric oncology patients with history of PEGAsp hypersensitivity has been questioned.

At the same time, patients with ALL are at increased risk of morbidity and mortality due to COVID-19[8-10]. To the extent that COVID-19 vaccination can mitigate disease severity, it is critical that this population to be vaccinated against COVID-19. As a result, it was the divisional policy to recommend COVID-19 vaccination series for all patients as soon as it became available, except for those immediately post-stem cell transplant. Currently, the only COVID-19 vaccinations with FDA emergency use authorization for use in patients under 18 years are mRNA vaccines. Therefore, after careful consideration, patients at the Children's Hospital of Philadelphia who had a previously identified hypersensitivity reaction to PEGAsp were recommended to follow general guidance and receive COVID-19 vaccination as soon as possible. Patients could receive vaccination in the CHOP oncology clinic or at a local pharmacy or clinic. No pre-medication or specific precautions were advised but patients were advised to call our clinic if they experienced any adverse events. Because of uncertainty around the clinical significance of an antibody response, these were not routinely measured in this cohort.

We performed a retrospective analysis to determine outcomes of vaccination in this cohort. Targeted chart review was performed to ascertain date and severity of prior PEGAsp allergic reaction, graded according to the Severity Grading System for Acute Allergic Reactions (see supplemental table 1)[11]. This scale imparts an increased level of granularity and guidance compared to Common Terminology Criteria for Adverse Events (CTCAE) grading system. Data are updated as of October 24, 2022. Vaccination administration was verified through the electronic health record or Pennsylvania Statewide Immunization Information System.

Between December 21, 2020, and March 3, 2022, 66 patients with acute leukemia and PEGAsp allergy received COVID-19 vaccination. Patient demographic, allergic and vaccination characteristics are shown in table 1. The majority, 48 (72.7%) received the Pfizer-BioNTech vaccine, twelve (18.2%) received the Moderna vaccine and in six patients (9.1%) the type of vaccine was not documented. Median age at time of first vaccination was 16.8 years (range: 6.2– 25.2 years), consistent with this data collection occurring before vaccination was available to patients under 5 years. Most patients (78.8%) were in off-therapy active surveillance at the time of vaccine receipt; the remainder were receiving upfront or relapsed therapy.

No patients, (0/66 0%, 95% CI 0 – 5.4%) experienced an allergic reaction or other adverse effect to the vaccine. This includes 52 patients (78.8%) who had an allergic reaction to

PEGAsp but subsequently tolerated an alternative non-PEGylated asparaginase formulation without hypersensitivity. One patient not included in this review experienced a grade 2 allergic reaction to PEGAsp after Pfizer COVID-19 vaccination and went on to receive his second vaccination without complication.

Based on our institutional experience, COVID-19 mRNA vaccination appears to be safe in pediatric and young adult ALL patients with a documented PEGAsp allergy, despite the presence of PEG in the vaccine. This finding is consistent with emerging reports in other PEG-allergic patients who have safely undergone vaccination with COVID-19 mRNA vaccines[12, 13], including a Canadian cohort of pediatric ALL patients who safely received a first Pfizer-BioNTech COVID-19 mRNA vaccine at a dedicated vaccination clinic staffed by pediatric oncologists, nurses and psychosocial personnel[14]. This analysis adds to that literature, increasing the population size of individuals challenged with mRNA vaccine, following patients through the two-vaccine series to demonstrate safety, and adding experience with safe delivery of the Moderna vaccine.

PEG is a hydrophilic polymer widely used in the medical, pharmaceutical, food, cosmetic, plastic, and textile industries due to its many advantageous and versatile chemical properties. The incorporation of PEG to the molecular structures of drugs enhances drug delivery and efficacy by increasing the molecular weight, boosting the half-life, and preventing opsonization[2]. PEG can be found in excipients for coatings of tablets, ointment bases, ultrasound gels, organ preservatives, shampoos, fragrances, and cosmetics[2, 7, 15]. A potential explanation for the excellent tolerance of COVID-19 mRNA vaccination in this population is related to the molecular weight of PEG. The molecular weight of PEG ranges from 200 to 35,000 g/mol, with low molecular weight PEGs used to improve cutaneous penetration of chemicals and high molecular weight PEGs (3350 to 6000 g/mol) used to stabilize active ingredients in a variety of medications[2, 15]. PEG of molecular weight 5000 g/mol is found in PEGAsp, PEG of molecular weight 3350 g/mol is found in enteral polyethylene glycol, a frequently used pediatric laxative, and PEG of molecular weight 2000 is used in Pfizer-BioNTech and Moderna's COVID-19 mRNA vaccines[7, 15]. Theoretically, cross reactivity can occur between PEG and PEG derivatives due to the presence of identical molecular branches extending from the hydrocarbon backbone[2], however, the molecular weight may influence the safety of COVID-19 mRNA vaccine administration in PEGAsp allergic patients[7]. This differential effect of PEGs of variable molecular weight is also seen in the 52 (78.8%) of patients who had previously been exposed and tolerated enteral polyethylene glycol as a stool softener.

Another plausible explanation is that the dose of PEG contained in the mRNA vaccines is below the reaction threshold. In addition to molecular weight, amount of PEG and route of administration appear to influence risk of reaction. It may also be that a proportion of the documented PEGAsp hypersensitivity in this institutional cohort are indeed infusion reactions. There are no currently accepted guidelines for differentiating antibody-mediated hypersensitivity reactions and non-antibody-mediated infusion reactions[1]. However, therapeutic drug monitoring which was available for a subset of patients demonstrated reduced asparaginase activity in at least (5/13, 38.5%), suggesting that at least a proportion of these events were true allergy-driven hypersensitivity. Finally,

it may be that the PEG is not always the immunogenic culprit in these products, which is likely in the three patients who also had prior allergic reactions to alternative asparaginase formulations.

Regardless of the explanation, administration of the COVID-19 mRNA vaccine appears to be safe in individuals with a history of allergy to PEGAsp. While prudent to continue administrating the vaccine in a medical facility with trained professionals who can identify a reaction if needed followed by an observational period, as recommended for all individuals receiving the vaccine regardless of allergic histories, our institutional experience suggests that additional precautions are not required for patients with prior allergy to PEGAsp. As efforts are underway to vaccinate all eligible patients to COVID-19 to provide individual protection and reach herd immunity, patients with PEGAsp allergy should not be excluded.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1-

Patient demographic, allergic and vaccination characteristics

	N (% or mean range)	
Total patients	66 (100)	
Type of cancer		
T-cell lymphoblastic leukemia/lymphoma (T-ALL, T-LBL)	13 (19.7)	
B-cell acute lymphoblastic leukemia (B-ALL)	53 (80.3)	
Phase of treatment		
Upfront therapy (pre maintenance)	3 (4.5)	
Upfront therapy (maintenance)	8 (12.1)	
Relapsed therapy	3 (4.5)	
Off therapy	52 (78.8%)	
Mean age at PEGasp reaction in years	11.7 (1.8 – 22)	
Grade of PEGasp reaction		
1	3 (4.5)	
2	20 (30.3)	
3	12 (18.2)	
4	12 (18.2)	
5	0 (0)	
*Unknown	19 (28.8)	
Number of patients exposed to enteral PEG	52	
Tolerated enteral PEG	52 (100)	
Reacted to enteral PEG	0 (0)	
Number of patients exposed to alternative asparginase	55	
Tolerated alternative asparginase	52 (94.5)	
Reaction to alternative asparginase	3 (5.5)	
	1st Vaccine	**2nd Vaccine**
Patients who received COVID-19 vaccine	66	65
Mean age at COVID-19 vaccine in years	16.8 (6.2–25.2)	17.1 (6.3–25.2)
Type of COVID-19 vaccine		
Moderna	12 (18.2)	12 (18.5)
Pfizer/BioTech	48 (72.7)	47 (72.3)
mRNA vaccine not specified	6 (9.1)	6 (9.2)
Number of patients who reacted to COVID-19 vaccine	0 (0)	0 (0)
Mean time from PEGasp reaction to subsequent vaccine in months	58.0 (2–156)	61.1 (3–157)

*Reaction occurred at an outside institution and complete documentation not available