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A case of coronavirus disease 2019 messenger RNA vaccine tolerance and immune response despite presence of anti-polyethylene glycol antibodies



The role of anti-polyethylene glycol (PEG) immunoglobulin (Ig)M, IgG, or IgE antibodies in coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccine anaphylaxis is unknown. We highlight a case with preexisting anti-PEG antibodies that tolerated vaccination.

A 60-year-old woman with debilitating gout experienced HLA-B*58:01-restricted allopurinol drug reaction with eosinophilia and systemic syndrome. After 2 years, following therapeutic failure with febuxostat, pegloticase was trialed. After 12 days from initial infusion, she developed angioedema and a diffuse erythematous pruritic rash. She self-treated with diphenhydramine, but symptoms persisted for 2 days. She then developed shortness of breath and throat constriction, requiring antihistamines and systemic steroids from an outside emergency department. She was later discharged with steroids, and symptoms resolved after 7 days. After 7 months, she had negative results from skin prick test (SPT) and intradermal test (IDT) to PEG3350. She was not tested to higher molecular weight PEG at this time. Of note, we detected anti-PEG IgG and IgE antibodies using a previously reported dual cytometric bead assay,¹ which had been negative when assessed from biobanked plasma 2 months after the drug reaction with eosinophilia and systemic syndrome episode (Table 1). The target beads for the assay used high-affinity murine

anti-PEG monoclonal antibody-conjugated cytometric bead array beads conjugated with pegloticase as the target antigen.¹ The control beads were conjugated with the same anti-PEG antibodies without pegloticase.¹ The positive signal criterion is defined as “target beads MFI (median fluorescence intensity) more than or equal to 1.2 times control beads MFI” and “free PEG inhibition reduces more than or equal to 50% of target beads MFI.”¹

Given the potential risk from anti-PEG IgE antibodies with future infusions, pegloticase desensitization was completed and followed by tolerance to 3 infusions, each 2 weeks apart.² However, pegloticase was discontinued when hyperuricemia and gout symptoms persisted. After 6 weeks from desensitization, anti-PEG IgM was present. Anti-PEG IgG titer increased over 6 months after desensitization; however, results from PEG3350 SPT/IDT and PEG8000 SPT were negative (Table 1). After negative SPT/IDT results, she tolerated oral challenges with 0.17 g/1.7 g of PEG3350. Serum anti-PEG IgM and IgG remained high with absent IgE. Dose 1 (0.3 mL) of Pfizer-BioNTech COVID-19 mRNA vaccine was associated with injection site soreness and headache. Immediately before dose 2, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein antibodies were positive by multiplex bead assay, suggesting a vaccination response (Table 1).³ Serum anti-PEG IgM and IgG remained high with absent IgE. Dose 2 of the vaccine 0.3 mL intramuscularly was tolerated without an event. Four weeks after dose 2, positive anti-PEG IgG, negative anti-PEG IgM and IgE, and persistent immune response to the vaccine using a SARS-CoV-2 multiplex bead assay were found (Table 1).³

Pegloticase is a recombinant mammalian uricase derived from a genetically modified strain of *Escherichia coli* complexed to a 10,000 Da PEG molecule.⁴ It has a half-life of 8 to 14 days and is infused every 2 weeks.⁴ Pegloticase is known to be associated with infusion and hypersensitivity reactions.⁵ Using data from the US Food and Drug Administration Adverse Event Reporting System, we found that between 2010 and 2019, 5% of all adverse events were reported as anaphylaxis; most of the events were infusion reactions or decreased efficacy. The underlying mechanism for the delayed hypersensitivity reaction to pegloticase in our patient remains unclear. However, the patient had confirmed absence of serum anti-PEG IgE before exposure to pegloticase and then presence of anti-PEG IgE after her reaction. Therefore, the decision to desensitize before the next infusion of

Disclosures: Dr Phillips reports receiving grants and funding from the National Institutes of Health (R01HG010863, R01AI152183, U01AI154659, R13AR078623, UAI109565) and the National Health and Medical Research Council of Australia; receiving royalties from UpToDate; receiving consulting fees from Janssen, Vertex, Biocryst, Regeneron, and Verve; being a co-director of IID 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.

Funding: Dr Phillips reports receiving grants and funding from the National Institutes of Health (R01HG010863, R01AI152183, U01AI154659, R13AR078623, UAI109565) and the National Health and Medical Research Council of Australia. Dr Stone reports receiving funding from Agency for Healthcare Research and Quality, and Patient-Centered Outcomes Research Institute 1K12HS026395-01 and is the recipient of an American Academy of Allergy, Asthma & Immunology Foundation Faculty Development Award. The funders played no role in any aspect of this manuscript. This article reflects the views of the authors and should not be construed to represent the Food and Drug Administration's views or policies. Institutional Review Board: This case study is covered under Vanderbilt University Medical Center IRB#161455, 131836, 150754.

Table 1
Patient's Anti-PEG Antibodies and Anti-S1 (SARS-CoV-2 Spike Protein) Over Time as Described in the Case

Antibody of Interest	–	–	+++	+++	++	++	±
Anti-PEG IgG ^a	–	++	±	±	+++	+++	++
Anti-PEG IgE ^b	–	>30	–	–	–	–	–
Anti-S1 IgG	n/a	n/a	n/a	n/a	n/a	Positive	Positive
	HLA-B*5801 DRESS	Pre-desensitization	6-wk post-desensitization	9-wk post-desensitization	COVID-19 vaccination dose #1 (6-mo post-desensitization)	3-wk post-COVID-19 vaccination dose #1	4-wk post-COVID-19 vaccination dose #2

Abbreviations: COVID-19, coronavirus disease 2019; DRESS, drug reaction with eosinophilia and systemic syndrome; Ig, immunoglobulin; MFI, median fluorescence intensity; PEG, polyethylene glycol; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

^aFor IgM and IgG: +++ has an MFI signal > 2 × control beads and a titer of >10,000; ++ has an MFI signal > 2 × control beads and a titer of >100 in at least 1 determination.

^bFor IgE: + has an MFI signal > 2 × control beads and the titer is found.

pegloticase was made owing to the potential risk for an IgE-mediated anaphylaxis to PEG products.

The presence of anti-PEG antibodies is a risk factor for infusion reactions, accelerated drug clearance, and decreased drug efficacy.⁵ Our patient developed anti-PEG IgM antibodies after desensitization associated with a lack of urate-lowering response. It has been reported that 41% of individuals receiving pegloticase developed high-titer antibodies associated with lack of urate-lowering activity; in most cases, both IgM and IgG against the PEG moiety of pegloticase were detected.⁵ It is suggested that anti-PEG antibodies are responsible for the accelerated blood clearance phenomenon and complement activation-related pseudoallergy (CARPA) reactions.⁶ These studies support the idea that immune-mediated reactions to PEG and PEGylated medications are antibody mediated. In pegloticase, uricase is linked to 10,000 Da PEG molecules; high titers of anti-PEG antibodies may bind the PEG polymers in a manner that blocks the functional protein component of uricase.

Our patient tolerated both doses of the Pfizer-BioNTech COVID-19 mRNA vaccine and had an antibody response found after each dose. Our case highlights that, individuals with pre-existing reactions or antibodies to PEG or pegylated compounds can be mRNA vaccine tolerant. Our case revealed transient development of anti-PEG IgE after a pegloticase hypersensitivity reaction of unclear etiology and the development of anti-PEG IgM and IgG after desensitization associated with lack of treatment response. This aligns with studies that suggest 40% of individuals develop anti-PEG IgG after a single infusion of a pegylated compound; 5% to 9% of the general population has detectable anti-PEG IgG; and 0.001% of the population controls have detectable anti-PEG IgE.^{1,4} Since the COVID-19 mRNA vaccine rollout, immediate hypersensitivity reactions consistent with anaphylaxis have been described at a rate of 2.5 to 4 per million doses administered.^{7,8} It is postulated that reactions may be owing to an IgE-mediated or a CARPA response toward PEG2000 in the mRNA lipid nanoparticle carrier of these vaccines.⁷ Our case reveals tolerance to not only both doses of the Pfizer-BioNTech COVID-19 mRNA vaccine but also antibody response to SARS-CoV-2 spike protein 3 and 4 weeks after dose 1 and 2, respectively, despite presence of anti-PEG IgM and IgG. She had high PEG IgG and IgM titers but not PEG IgE at the time of vaccination, and she did not have a reaction consistent with CARPA or anaphylaxis of any cause. A recent article suggested that those with preexisting PEG antibodies may boost their IgG response after COVID-19 mRNA vaccination. We did not see a “PEG-boosting” effect in our case, and in fact, 28 days after dose 2, there was a tiny decrease in signal for PEG IgG and IgM.⁹ We highlight COVID-19 mRNA vaccine tolerance and response in the setting of anti-PEG IgG and IgM and that additional research into mechanisms of anaphylaxis to COVID-19 mRNA vaccines is needed.

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Outcomes of allergic-type reactions after messenger RNA coronavirus disease 2019 vaccination at 3 military medical centers



In response to the global coronavirus disease 2019 (COVID-19) pandemic, 2 messenger RNA (mRNA) COVID-19 vaccines were developed and authorized for use.^{1,2} Adverse events following immunization (AEFI) have occurred after receipt of these vaccines to include anaphylaxis that is estimated to occur at a rate of 2.5 to 11 cases per 1 million doses.³ Several studies have found tolerance to vaccine challenge in these individuals, suggesting the reactions are likely not immunoglobulin (Ig)E driven.^{4,5} The Centers for Disease Control and Prevention now considers nonsevere, immediate, allergic-type reactions after a dose of a COVID-19 vaccine a precaution, not a contraindication, to a subsequent dose of the same vaccine.⁶ To further support the growing evidence of second dose tolerance after first dose reaction, we describe the evaluation and outcome of patients referred to 3 Military Health System allergy clinics for consultation for suspected allergic reactions after mRNA COVID-19 vaccination.

This is a multicenter retrospective review of patients referred to the Allergy Clinics of the Walter Reed National Military Medical Center, Naval Medical Center Portsmouth, and Womack Army Medical Center, from January 2021 to November 2021 for AEFI after receipt of either mRNA COVID-19 vaccine. Those with at least 1 symptom consistent with an immediate hypersensitivity reaction within 24 hours of the first dose were included. The likelihood of anaphylaxis was based on the Brighton Collaboration Criteria used to determine the level of certainty of anaphylaxis.⁷ Evaluation and determination of testing, vaccine challenge, or vaccine avoidance was based on the risk assessment of the evaluating allergist. Skin testing was performed to the Pfizer-BioNTech COVID-19 vaccine, polyethylene glycol, and polysorbate. In most of the cases, the vaccine and component testing were done with full-strength prick test followed by 1:100 dilution intradermal.⁸ Vaccine challenge was offered to most patients at full dose, except for 3 patients who received split dosing at the discretion of the treating allergist. Premedication was not routinely used. The institutional review board at the Walter Reed National Military Medical Center determined this study as exempt from review.

There were 391 patients referred for concern of an AEFI after either mRNA COVID-19 vaccine. A total of 65 patients met the inclusion criteria. Most of the patients included in the study were of female sex (78%), and the mean age was 42 (13–78) years. In addition, 58 (88%) of the patients received the Pfizer-BioNTech COVID-19 vaccine. Furthermore, 27 (42%) patients met the Brighton levels 1 to 3 classifications (Table 1). The primary symptoms reported were

sensation of throat closure (45%), pruritus (31%), lightheadedness (30%), flushing (27%), urticaria (24%), shortness of breath (19%), nausea (16%), angioedema (9%), tachycardia (4%), hoarse voice (4%), or a combination. A total of 26 (40%) patients underwent skin prick testing. There was 1 patient (4%) whose skin test result was positive to the Pfizer COVID-19 vaccine on intradermal testing at 1:100, but all other skin testing results were negative; this patient was advised against the second dose. In terms of second dose recommendations, 7 (11%) were advised against by the allergist, 5 (8%) declined, and 53 (82%) underwent vaccine challenge. Moreover, 47 (89%) who underwent vaccine challenge had no symptoms, whereas 6 (11%) experienced recurrence of symptoms. One patient received a 10% dose and within minutes developed throat clearing, sensation of throat closure, ear fullness, but with normal vitals and received epinephrine with quick resolution of symptoms. The remaining 90% of the vaccine dose was withheld. Two patients had mild self-resolved pruritus and urticarial rash. Three described isolated throat closure sensation with normal vitals and no respiratory distress; real-time laryngoscopy result revealed pharyngeal muscle tension without evidence of edema most consistent with vocal cord dysfunction.

Table 1

Characteristics and Second Dose Outcomes of Subjects With Possible Allergic Reaction to mRNA COVID-19 Vaccines

Characteristics	n (% total or range)
Subjects (n = 65)	
Age, average	42 (13–78)
Sex	
Female	51 (78)
Male	14 (22)
Vaccine	
Pfizer	57 (88)
Moderna	8 (12)
Received epinephrine	15 (23)
Met Brighton classification	27 (42)
Brighton level 1	2 (3)
Brighton level 2	22 (34)
Brighton level 3	3 (5)
Skin testing (n = 26)	
Reactive	1 (4)
Non-reactive	25 (96)
Second dose outcome (n = 65)	
Provider advised against	7 (11)
Patient declined	5 (7)
Vaccine challenge	53 (82)
No reaction	47 (88)
Immediate allergic symptoms	6 (12) ^a

Abbreviations: COVID-19, coronavirus disease 2019; mRNA, messenger RNA.

^aOne subject was treated with epinephrine after administration of 10% dose with quick symptom resolution. Two patients had mild self-resolved pruritus and urticarial rash. Three experienced sensation of throat closure and real-time laryngoscopy revealed pharyngeal muscle tension without evidence of edema.

Disclosures: The authors have no conflicts of interest to report.

Funding: The authors have no funding sources to report.

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