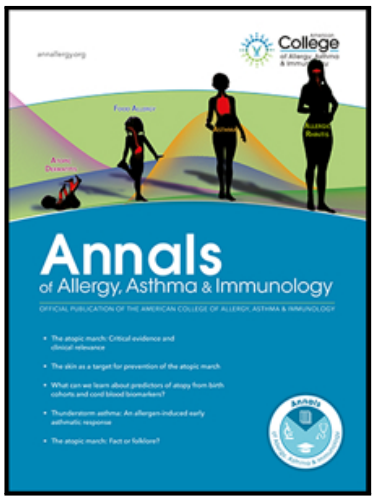
Journal Pre-proof



The role of anti-polyethylene glycol (PEG) IgM, IgG, or IgE antibodies in COVID mRNA vaccine anaphylaxis is unknown. We highlight a case with preexisting anti-PEG antibodies that tolerated vaccination

Kristen B. Corey MD , Grace Koo MD ,
Cosby A. Stone Jr. MD, MPH , Susan F. Kroop MD ,
William H. Fissell MD , Steven Kozlowski MD ,
Zhao-Hua Zhou PhD , Elizabeth J. Phillips MD

PII: S1081-1206(22)00445-8
DOI: https://doi.org/10.1016/j.anai.2022.05.013
Reference: ANAI 3960

To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 18 January 2022
Revised date: 8 May 2022
Accepted date: 16 May 2022

Please cite this article as: Kristen B. Corey MD , Grace Koo MD , Cosby A. Stone Jr. MD, MPH , Susan F. Kroop MD , William H. Fissell MD , Steven Kozlowski MD , Zhao-Hua Zhou PhD , Elizabeth J. Phillips MD , The role of anti-polyethylene glycol (PEG) IgM, IgG, or IgE antibodies in COVID mRNA vaccine anaphylaxis is unknown. We highlight a case with preexisting anti-PEG antibodies that tolerated vaccination, *Annals of Allergy, Asthma Immunology* (2022), doi: https://doi.org/10.1016/j.anai.2022.05.013

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 American College of Allergy, Asthma & Immunology. All rights reserved.

Journal Pre-proof

The role of anti-polyethylene glycol (PEG) IgM, IgG, or IgE antibodies in COVID mRNA vaccine anaphylaxis is unknown. We highlight a case with preexisting anti-PEG antibodies that tolerated vaccination.

Kristen B. Corey, MD[1]‡, Grace Koo, MD[1]‡, Cosby A. Stone, Jr. MD, MPH[1], Susan F. Kroop, MD[2], William H. Fissell MD[3], Steven Kozlowski, MD[4], Zhao-Hua Zhou, PhD[4], Elizabeth J. Phillips, MD[5,6,7]

‡Co-first authors

[1]Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

[2]Division of Rheumatology, Department of Medicine, Vanderbilt University Medical Center, Nashville USA

[3]Division of Nephrology, Department of Medicine, Vanderbilt University Medical Center, Nashville USA

[4]Office of Biotechnology Products, Office of Pharmaceutical Quality, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA

[5]Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[6]Department of Pathology, Microbiology, and Immunology, Vanderbilt University School of Medicine, Nashville, Tennessee, USA

[7]Institute for Immunology & Infectious Diseases, Murdoch University, Murdoch, Western Australia 6150

Journal Pre-proof

Journal Pre-proof

Corresponding Author Information:

Dr. Elizabeth J Phillips

1161t Avenue S, A2200 MCN

Nashville, TN 37232

E-mail: elizabeth.j.phillips@vanderbilt.edu

Tel: +1 (615) 322-9174

Fax: (615) 343-6160

Funding Source:

EJP reports grants and funding from the National Institutes of Health (R01HG010863, R01AI152183, U01AI154659, R13AR078623, UAI109565) and the National Health and Medical Research Council of Australia.

CAS received funding from AHRQ/PCORI 1K12HS026395-01 and is the recipient of an AAAAI Foundation Faculty Development Award.

Funders played no role in any aspect of this manuscript.

Journal Pre-proof

Conflict of Interest:

EJP reports grants and funding from the National Institutes of Health (R01HG010863, R01AI152183, U01AI154659, R13AR078623, UAI109565) and the National Health and Medical Research Council of Australia. She receives 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.

Funders played no role in any aspect of this manuscript.

The other authors have no disclosures to report.

This paper reflects the views of the authors and should not be construed to represent FDA's views or policies.

IRB: This case study is covered under VUMC IRB#161455, 131836, 150754

Keywords: None.

Abbreviations/Acronyms: None.

Word Count: 999

Tables: 1

Figures: None.

A 60-year-old woman with debilitating gout experienced HLA-B*58:01-restricted allopurinol drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. Two years later,

Journal Pre-proof

following therapeutic failure with febuxostat, pegloticase was trialed. Twelve days following initial infusion, she developed angioedema and a diffuse erythematous pruritic rash. She self-treated with diphenhydramine, but symptoms persisted for two 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 seven days. Seven months later, she showed negative prick (SPT) and intradermal (IDT) skin testing 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 (DCBA)[1], which had been negative when assessed from biobanked plasma two months following the DRESS episode (**Table 1**). The target beads for the assay used high-affinity murine anti-PEG monoclonal antibody-conjugated CBA 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) >= 1.2 x Control beads MFI" and "free PEG inhibition reduces >= 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 three infusions, each two weeks apart.[2] However, pegloticase was discontinued when hyperuricemia and gout symptoms persisted. Six weeks following desensitization, anti-PEG IgM was present. Anti-PEG IgG titer increased over 6 months following desensitization, however PEG3350 SPT/IDT, and PEG8000 SPT were negative (**Table 1**). Following negative SPT/IDT, she tolerated oral challenges with 0.17g/1.7g of PEG3350. Serum anti-PEG IgM and IgG remained high with absent IgE. Dose 1

Journal Pre-proof

(0.3mL) of Pfizer-BioNTech COVID-19 mRNA vaccine was associated with injection site soreness and headache. Immediately before the dose 2, SARS-CoV-2 spike protein antibodies were positive via 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 IM was tolerated without event. Four weeks after dose 2 revealed 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 (**Table 1**).[3]

Pegloticase is a recombinant mammalian uricase derived from a genetically modified strain of E. coli complexed to a 10,000 Da PEG molecule.[4] It has a half-life of 8-14 days and is infused every two weeks.[4] Pegloticase is known to be associated with infusion and hypersensitivity reactions.[5] Using data from the US FDA FAERS system, we found that between 2010 and 2019, 5% of all adverse events were reported as anaphylaxis; the majority of 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, then presence of anti-PEG IgE following her reaction. Therefore, the decision to desensitize prior to the next infusion of pegloticase was made due 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 following 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 (ABC) 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 demonstrable following each dose. Our case highlights that individuals with preexisting reactions or antibodies to PEG or pegylated compounds can be mRNA vaccine tolerant. Our case demonstrated transient development of anti-PEG IgE following a pegloticase hypersensitivity reaction of unclear etiology and the development of anti-PEG IgM and IgG following desensitization associated with lack of treatment response. This aligns with studies that suggest 40% of individuals develop anti-PEG IgG following a single infusion of a pegylated compound; 5-9% of the general population has detectable anti-PEG IgG; and 0.001% of the population controls have detectable anti-PEG IgE.[1,4] Since COVID-19 mRNA vaccine rollout, immediate hypersensitivity reactions consistent with anaphylaxis have been described at a rate of 2.5-4 per million doses administered.[7,8] It is postulated that reactions may be due to an IgE-mediated or a CARPA response toward PEG2000 in the mRNA lipid nanoparticle carrier of these vaccines.[7] Our case demonstrates tolerance to not only both doses of the Pfizer-BioNTech COVID-19 mRNA vaccine, but also antibody response to SARS-CoV-2 spike protein three and four weeks following dose 1 and 2, respectively, despite presence of anti-PEG IgM and IgG. She

Journal Pre-proof

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 paper suggested that those with pre-existing PEG antibodies may boost their IgG response following COVID-19 mRNA vaccination. We did not see a "PEG-boosting" effect in our case, and in fact, 28 days following 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.

References

1. Zhou Z-H, Stone CA, Jakubovic B, Phillips EJ, Sussman G, Park J, et al. Anti-PEG IgE in anaphylaxis associated with polyethylene glycol. J Allergy Clin Immunol Pract. 2021;9(4):1731-1733.e3. doi:10.1016/j.jaip.2020.11.011
2. Botson JK. Pegloticase hypersensitivity desensitisation: an outpatient, 3-bag, 12-step protocol. BMJ Case Rep. 2020 Jun 21;13(6):e234721. doi: 10.1136/bcr-2020-234721
3. Zhou Z-H, Dharmarajan S, Lehtimaki M, Kirshner SL, Kozlowski S. Early Antibody Responses Associated with Survival in COVID19 Patients. PLOS Pathogens doi: 10.1371/journal.ppat.1009766
4. Sundy JS, Ganson NJ, Kelly SJ, Scarlett EL, Rehrig CD, Huang W, et al. Pharmacokinetics and pharmacodynamics of intravenous PEGylated recombinant mammalian urate oxidase in patients with refractory gout. Arthritis Rheum. 2007;56(3):1021-1028. doi:10.1002/art.22403
5. Lipsky PE, Calabrese LH, Kavanaugh A, Sundy JS, Wright D, Wolfson M, et al. Pegloticase immunogenicity: the relationship between efficacy and antibody development in patients treated for refractory chronic gout. Arthritis Res Ther. 2014;16(2):R60. doi:10.1186/ar4497
6. Caballero ML, Krantz MS, Quirce S, Phillips EJ, Stone CA. Hidden Dangers: Recognizing Excipients as Potential Causes of Drug and Vaccine Hypersensitivity Reactions. J Allergy Clin Immunol Pract. Published online March 15, 2021. doi:10.1016/j.jaip.2021.03.002
7. Castells MC, Phillips EJ. Maintaining Safety with SARS-CoV-2 Vaccines. Longo DL, ed. N Engl J Med. 2021;384(7):643-649. doi:10.1056/NEJMra2035343
8. Shimabukuro TT, Cole M, Su JR. Reports of Anaphylaxis After Receipt of mRNA COVID- 19 Vaccines in the US—December 14, 2020-January 18, 2021. JAMA. 2021;325(11):1101. doi:10.1001/jama.2021.19
9. Ju Y, Lee WS, Kelly HG, Pilkington EH, Wragg KM, Subbarao K, et al. Anti-PEG antibodies boosted in humans by SARS-CoV-2 lipid nanoparticle mRNA vaccine. medRxiv. 2022:22268953. doi: https://doi.org/10.1101/2022.01.08.22268953

Journal Pre-proof

Anti-PEG IgM [a]	**-**	**-**	**+++**	**+++**	**++**	**++**	**+/-**
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-weeks post desensitization**	**9-weeks post desensitization**	**COVID-19 vaccination dose #1 (6-months post desensitization)**	**3-weeks post COVID-19 vaccination dose #1**	**4-weeks post COVID-19 vaccination dose #2**

Table 1. Patient's anti-PEG antibodies and anti-S1 (SARS-CoV-2 spike protein) over time as described in the case.

[a] For IgM and IgG: +++ has a median fluorescence intensity (MFI) signal > 2X controls beads and a titer of >10,000; ++ has an MFI signal > 2X control beads and a titer of >300; +/- has an MFI signal > 1.5X control beads and a titer of >100 in at least one determination

[b] For IgE: + has an MFI signal > 2X control beads and the titer is shown

Journal Pre-proof