

[‡]Pneumologie
Hôpital de la Croix-Rousse
Hospices Civils de Lyon
Lyon, France
[§]Université Lyon 1
Lyon, France
[¶]INSERM U 1111-CIRI
Lyon, France
emilie.perino@gmail.com

References

- [1] Lieberman PL, Jones I, Rajwanshi R, Rosén K, Umetsu DT. Anaphylaxis associated with omalizumab administration: risk factors and patient characteristics. *J Allergy Clin Immunol*. 2017;140:1734–1736, e4.
- [2] Baker DL, Nakamura GR, Lowman HB, Fischer SK. Evaluation of IgE antibodies to omalizumab (Xolair®) and their potential correlation to anaphylaxis. *AAPS J*. 2016;18:115–123.
- [3] Yamasuji Y, Higashi Y, Sakanoue M, et al. A case of anaphylaxis caused by polyethylene glycol analogues. *Contact Dermatitis*. 2013;69:183–185.
- [4] Price KS, Hamilton RG. Anaphylactoid reactions in two patients after omalizumab administration after successful long-term therapy. *Allergy Asthma Proc*. 2007;28:313–319.
- [5] Harrison RG, MacRae M, Karsh J, Santucci S, Yang WH. Anaphylaxis and serum sickness in patients receiving omalizumab: reviewing the data in light of clinical experience. *Ann Allergy Asthma Immunol*. 2015;115:77–78.
- [6] Kim HL, Leigh R, Becker A. Omalizumab: practical considerations regarding the risk of anaphylaxis. *Allergy Asthma Clin Immunol*. 2010;6:32.
- [7] El-Qutob D. Off-label uses of omalizumab. *Clin Rev Allergy Immunol*. 2016;50:84–96.
- [8] Palacios Castaño MI, Venturini Díaz M, Lobera Labairu T, González Mahave I, Del Pozo G, Blasco Sarraimián A. Anaphylaxis due to the excipient polysorbate 80. *J Invest Allergol Clin Immunol*. 2016;26:394–396.
- [9] Wenande E, Kroigaard M, Mosbech H, Garvey LH. Polyethylene glycols (PEG) and related structures: overlooked allergens in the perioperative setting. *Case Rep*. 2015;4:61–64.
- [10] Wang Y, Li C, Yi Y, et al. Comparative study on pseudoanaphylactoid reactions induced by medicinal Tween 80 and injectable Tween 80. *Zhongguo Zhong Yao Za Zhi*. 2012;37:1890–1893, [in Chinese].

Safe and effective intradermal influenza vaccine desensitization for delayed influenza vaccine allergy



We report a case of an 18-year-old Japanese male with delayed hypersensitivity to influenza virus vaccine, who completed 7 years of successful annual vaccine desensitization using intradermal trivalent split-virion influenza vaccine (Fluzone, Intradermal, Sanofi Pasteur, Cambridge, Massachusetts). Informed consent was obtained for this report. At 4 years of age, the patient was hospitalized for evaluation of possible compartment syndrome in Japan for his first reaction to the intramuscular influenza vaccine when large circumferential swelling developed over a period of 24 to 48 hours after vaccination, which was successfully treated with intravenous steroids. Although a previous intramuscular influenza vaccination was tolerated before this episode, subsequent influenza vaccination was deferred. The patient was eating eggs without any problems and followed a regular diet. Three years later, he experienced a severe influenza illness requiring admission to the pediatric intensive care unit with intubation. At 9 years of age, he required emergency evaluation for 2 days of worsening respiratory distress, wheeze, productive cough, and temperatures as high as 103°F, with blood pressure 109/55 mm Hg, heart rate 100/min, oximetry 93% on room air, and respiratory rate 20/min. Physical examination was notable for bilateral tonsillar exudate and increased work of breathing with retractions. Enzyme immunoassay was positive for influenza B antigen, and chest x-ray showed right upper lobe and right perihilar opacities consistent with pneumonia. He was again hospitalized, with oxygen therapy, intravenous fluids, and antibiotics. After discharge, he underwent further pediatric allergy outpatient evaluation, where he was found to have specific immunoglobulin E (IgE) sensitizations to latex (1.97 ku/L), porcine gelatin (0.49 ku/L), and egg white (0.7 ku/L), with a total IgE level of 3,778 ku/L. His influenza skin prick test using full-strength Novartis (East Hanover, New Jersey) latex-and-gelatin-free vaccine was negative, with positive intradermal testing (5-mm wheal and 10-mm flare), using a 1:100 v/v dilution of vaccine. After informed consent, the patient underwent intramuscular influenza vaccine desensitization, initially using a multiple-day approach after serial intradermal skin testing to determine a non-reactive starting concentration (Table 1). The patient tolerated the

procedure well, with some mild local soreness and local swelling. The following year, a multiple-day approach using an intradermal vaccine was chosen, which was subsequently transitioned to a single-day protocol. With subsequent delayed full-strength large local reactions up to 120 mm at 24 hours after vaccination (60-mm immediate induration) in 2012, additional dilutions were added to the protocol along with pre- and post-desensitization loratadine 10 mg every morning, cetirizine 10 mg every evening, and as needed topical betamethasone dipropionate to help control his occasional large local reactions. This approach seemed to offer some benefit (for example, maximum of 10 mm immediate induration at full-strength dose recorded in 2017 without concern for delayed reactions). In addition to annual vaccine desensitization, the patient has used oseltamivir prophylaxis with suspected exposures to influenza and has not since required any intensive treatment or hospitalization for subsequent influenza-like illnesses.

Influenza vaccine serves a critical role in reducing influenza virus-associated morbidity and mortality. The Centers for Disease Control and Prevention reports that 80% to 85% of the US influenza-associated pediatric deaths reported in the 2016 to 2017 season occurred in unvaccinated patients.¹ Vaccine hypersensitivity can present a barrier to vaccination; however, vaccine skin testing, graded challenge, and desensitization can allow greater clarity in diagnosis and create avenues to successfully vaccinate allergic populations. In recent years, our understanding of influenza vaccine allergy has evolved, and most influenza vaccine hypersensitivity is known not to be caused by egg allergy but by specific IgE-directed responses to vaccine antigens or excipients such as gelatin.² A recent report of 19 Japanese patients with influenza vaccine allergy described elevated specific IgE to influenza vaccine antigens, whole vaccine products from different manufacturers, and hemagglutinin proteins (A, H1, H3, and B) derived from egg and cell culture when compared with 25 age-matched control subjects. No patient with influenza vaccine allergy in this report had a severe egg allergy.³ Although egg allergy is not an indication for influenza vaccine desensitization or dose challenge,⁴ allergy to another influenza antigen vaccine component is one of the few indications for graded challenge or multi-step desensitization, as was performed in our non-egg-allergic patient.

Influenza vaccine hypersensitivity may be a challenging problem, especially to those allergic to the viral antigen. Not only are these

Table 1
Influenza Vaccine Desensitization Protocol

	IM fluvirin desensitization 2010 ^a	ID fluzone desensitization 2017 ^b
PRE-DESENSITIZATION MEDICATION		Begin 2 days before vaccine: Loratadine 10 mg every morning Cetirizine 10 mg every evening ID Fluzone,
DESENSITIZATION PROTOCOL	Day 1: ID skin testing (Fluvirin, latex- and gelatin-free) to determine nonreactive concentration (immediate wheal, flare in mm) 1:10,000: (0/0) 1:1,000 (4/10) 1:100 (10/35) IM Fluvirin, desensitization. Dilution every 20 minutes 0.05 mL 1:10,000 v/v IM 0.05 mL 1:1,000 v/v IM 0.05 mL 1:100 v/v IM 0.05 mL 1:10 v/v IM, 0.05 mL full-strength IM Day 2: 0.1 mL full-strength IM Day 4: 0.15 mL full-strength IM Day 7: 0.2 mL full-strength IM	Dilution every 30 minutes 0.05 mL 1:1,000,000 v/v ID 0.05 mL 1:100,000 v/v ID 0.05 mL 1:10,000 v/v ID 0.05 mL 1:1,000 v/v ID 0.05 mL 1:100 v/v ID 0.05 mL 1:10 v/v ID 0.05 mL full-strength ID 0.05 mL full-strength ID
POST-DESENSITIZATION MEDICATION		3–5 days: Loratadine 10 mg every morning Cetirizine 10 mg every evening For large local reactions: Betamethasone dipropionate, augmented; as needed twice daily up to 5 days

Abbreviations: IM, intramuscular; ID, intradermal.

^aProtocol used during initial skin testing and desensitization in 2010. Day 1 involved skin testing to identify nonreactive intradermal concentration with subsequent desensitization over several days.

^bIn subsequent years, intradermal desensitization was performed with doses every 20 to 30 minutes, using an 8-dose protocol.

patients at an increased risk of local and systemic reaction to the vaccine, they may theoretically be at increased risk for more severe clinical influenza, possibly because of their hypersensitivity to the viral antigen. In fact, our patient has had 2 pediatric intensive care unit admissions and an intubation associated with influenza illnesses. Our patient demonstrated positive intradermal influenza vaccine skin testing; however, intradermal influenza vaccine testing has been associated with a 15% false-positive rate.⁵ The patient also has latex and gelatin allergies, but these are unlikely to have confounded the assessment because he had positive skin tests to latex-and-gelatin-free flu vaccine.

The protocol described here may provide a safe and effective approach for management of patients with delayed hypersensitivity to the influenza virus; however, while successfully used in our patient, this is a single case report. Also, Fluzone Intradermal Quadrivalent is only licensed for use in persons 18 through 64 years of age.⁶ Although our patient demonstrated evidence of influenza vaccine sensitization by skin testing, his influenza vaccine-related symptoms may not be truly or exclusively IgE mediated, given the delayed nature of his reactions; repeated desensitization potentially could be replaced by simple or graded influenza vaccine rechallenge.² We have deferred such an approach given continued large local reactions during the desensitization procedure. Regardless of approach, using the intradermal influenza vaccine preparation may improve tolerability of repeated doses during the procedure. The critical message is that influenza vaccination can be administered safely in such circumstances. Whether the approach taken is simple vaccine rechallenge, graded challenge,

or formal desensitization may depend on clinical judgment and patient preference.

Tsuzumi Kanaoka, BA*

Kazune Matsuoka†

Marcus Shaker, MD, MS*‡

*Geisel School of Medicine at Dartmouth
Hanover, New Hampshire

†University of Massachusetts Amherst
Amherst, Massachusetts

‡Dartmouth Hitchcock Medical Center
Section of Allergy and Clinical Immunology
Lebanon, New Hampshire

Marcus.Shaker@dartmouth.edu

References

- [1] Flannery B, Reynolds S, Blanton L, et al. Influenza vaccine effectiveness against pediatric deaths: 2010–2014. *Pediatrics*. 2017;139:e20164244.
- [2] Kelso JM, Greenhawt MJ, Li JT, et al. Adverse reactions to vaccines practice parameter 2012 update. *J Allergy Clin Immunol*. 2012;130:25–43.
- [3] Nagao M, Fujisawa T, Ihara T, Kino Y. Highly increased levels of IgE antibodies to vaccine components in children with influenza vaccine-associated anaphylaxis. *J Allergy Clin Immunol*. 2016;137:861–867.
- [4] Kelso JM, Greenhawt MJ, Li JT. Update on influenza vaccination of egg allergic patients. *Ann Allergy Asthma Immunol*. 2013;111:301–302.
- [5] Wood RA, Setse R, Halsey N. Irritant skin test reactions to common vaccines. *J Allergy Clin Immunol*. 2007;120:478–481.
- [6] Food and Drug Administration. Sanofi Pasteur 476 Fluzone Intradermal Quadrivalent. Highlights of prescribing information, 2 March 2017 v0.1. www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM566500.pdf. Accessed December 30, 2017.