

Skin Testing and Specific-IgE Following IVIG or Omalizumab

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Each month we present highlights from the Ask the Expert section of the American Academy of Allergy, Asthma & Immunology (AAAAI) Web site written by the Ask the Expert editors. For more questions and answers, visit www.aaaai.org/ask-the-expert.aspx.

Question:

I recently had a 36-year-old patient who in the past has had severe allergic reactions, apparently anaphylaxis, to brim, tuna, and shrimp on separate occasions but can tolerate hard shellfish, such as crab and mussels. People at work bring shellfish to work at a medical clinic, and she is concerned about exposure. She also has a history of breast cancer on tamoxifen and chronic inflammatory demyelinating polyneuropathy treated with intravenous immunoglobulin (IVIG) every 2 weeks from her neurologist, dose unknown but presumably a high dose. She also has allergic rhinitis for a number of years. She requested aeroallergen and seafood testing. She was completely negative via skin prick/percutaneous allergy testing to a panel of 50 aeroallergens, 6 shellfish, and 8 fish, with an adequate histamine wheal control of 5 mm, and 0 mm wheal with saline. In a previous Ask the Expert question, for a patient treated with omalizumab (Xolair), it was recommended to stop omalizumab for approximately 5 half-lives, or 4 to 6 months, before performing specific-IgE skin testing. I found minimal literature on allergy testing in patients receiving high-dose IVIG.¹ Skin tests in the abstract were less reactive than normal after 6 months of IVIG, but the authors did not retest subjects after IVIG was discontinued. Should I tell this patient to return in 6 months because she may be stopping her IVIG soon and we will test again? What about patients on replacement dose of IVIG (~400 mg/kg/mo).

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Conflicts of interest: D. K. Ledford is employed by the University of South Florida College of Medicine and the Veterans Administration; has provided expert witness testimony for Wicker, Smith, O'Hara, McCoy, and Ford on the topic of asthma death; has provided expert witness testimony for Shook Hardy Bacon on the topic of drug allergy; has provided expert witness testimony for Saieva and Stine on the topic of metal allergy; has provided expert witness testimony for Vedrine Associates on the topic of drug allergy; has received consultancy fees from Genentech and AstraZeneca; has received Speaker's fees from TEVA, Boehringer Ingelheim, Novartis, AstraZeneca, Genentech, and Sanofi/Regneron; has received research support from AstraZeneca; is on the Editorial Board for *Annals of Allergy, Asthma and Immunology*; is coeditor of *Asthma: Co-Morbidities, Co-existing Conditions and Differential Diagnosis*; is editor, *Allergens and Allergen Immunotherapy*; is volume editor, *Encyclopedia of Allergy, Immunology and Vaccines*; is coeditor, *Asthma and Allergy Basics*; and is an UpToDate contributor.

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Please comment on stopping omalizumab before allergy skin testing and if necessary for how long. Finally, please compare the effects on both skin and Immunocap testing with replacement-dose IVIG (as in common variable immunodeficiency), high-dose IVIG, and omalizumab. Thank you.

Answer:

Thank you for your questions. There are no definitive answers to the issues about which you are concerned. IVIG in doses of 2 g/kg is used to modulate autoimmune disease and presumably this is via Fc receptors on B cells and immune regulatory cells. Whether this modulates specific-IgE production is unknown. The abstract you cite¹ supports the idea of IgE suppression by IVIG but is not sufficient to make any conclusion or make recommendations on the duration of time required before the effect, if any, dissipates. There are several studies *in vitro* showing downregulation of IgE production,² but clinical reports also show no effect of IVIG on IgE production.³ Five half-lives are generally necessary to eliminate a treatment, but there may be additional time required for immunomodulator effects to disappear because half-life is a pharmacokinetic concept and not always dependent on biologic activity. Therefore, I think it is reasonable to repeat testing in 5 to 6 months if there is a need for identifying specific-IgE. I think it is possible that a serum assay may show sensitivity sooner than skin test reactivity. However, this is pure speculation on my part.

The omalizumab effect on skin test reactivity has been investigated in more detail.⁴ However, at the currently approved asthma dose of omalizumab, 0.016 mg/kg/IU/mL, skin test reactivity is not eliminated. There is a published study using omalizumab at current recommended dose and double-dose, 0.032 mg/kg/IU/mL.⁴ Skin test reactivity decreased inconsistently, and the skin test reactivity seemed inversely related to the total IgE, that is, greater suppression with greater serum total IgE. This effect may be due to the likely greater density of a single allergen specific-IgE on basophils and mast cells in the setting of a lower total IgE. There was no evidence that higher doses of omalizumab lead to a long-term, persistent effect on skin test reactivity and skin test response returned "promptly" to baseline after discontinuation. The time course of skin test suppression was not studied in detail, with the data showing return of skin test reactivity within 140 days following a 6- to 20-fold reduction in the initial dose. However, serial, repeat testing was not performed to determine how quickly this occurred. Complete recovery of skin test reactivity would likely require 5 half-lives or approximately 100 days. *In vitro* testing would be affected similarly

although it may not show as much delay in both reduction and reoccurrence, because free IgE is reduced within days of omalizumab treatment. MacGlashan et al⁵ estimated that as little as 1% of occupancy of the approximately 250,000 high-affinity IgE receptors on basophils, and presumably on skin mast cells, is sufficient to result in degranulation of the cell when exposed to allergen. Ong et al⁶ showed 24% reduction in wheal and flare responses to allergen skin testing with approved omalizumab dosing but did not describe a relationship with total IgE. There are some data and modeling suggesting that long-term treatment with omalizumab may modulate specific-IgE production, but the duration of this effect is unknown following discontinuation of omalizumab.⁷

In summary, the effect of high-dose IVIG or replacement doses of IVIG on skin test reactivity or specific-IgE production is unknown but likely greater with high-dose therapy due to broader immunomodulation. Five half-lives of therapeutics, including IVIG and omalizumab, are required to eliminate from serum, but biologic half-lives may be shorter or longer. Because IgG has a half-life of 20 to 26 days, I would suggest waiting at least 100 to 120 days before repeat testing, although longer would be ideal.

I hope this information is of some help to you and your practice.

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