

Insulin allergy

INTRODUCTION

This month's *Annals of Allergy, Asthma, and Immunology* features a very interesting case report by Alvarez-Thull et al of a patient with apparent IgE-mediated hypersensitivity to endogenous insulin. The data presented strongly support the contention that the patient was allergic to *all* forms of insulin, including her own, and is congruent with previous observations reaching the same conclusion in several other patients. The paper provides an opportunity for a brief review of this area and to address related concerns. First, what is the natural history of insulin allergy? Second, how should patients with previous allergic reactions to insulin, who have been desensitized to animal species insulins, be managed when animal species insulins are no longer available for clinical use?

WHAT IS INSULIN ALLERGY?

Allergic reactions to insulin are classified as "local" or "generalized".¹ Local reactions are erythematous, pruritic, and sometime indurated reactions occurring at the site of insulin injection. These may be either monophasic or, more commonly, are biphasic in character. Such local reactions are usually mild and the majority improve or resolve spontaneously within the first several months of treatment. Generalized allergic reactions to insulin range in severity from simple urticaria to life-threatening anaphylaxis. Such generalized allergic reactions are like those that occur with anaphylaxis to penicillin and may be associated with bronchospasm, laryngeal edema, and circulatory collapse. Most local and all generalized allergic reactions to insulin result from the production of insulin-specific IgE antibodies that fix to mast cells and basophils and result in the

release of mediators of immediate hypersensitivity on contact with insulin. These mediators produce the clinical manifestations of insulin allergy.

WHAT ARE THE MECHANISMS OF INSULIN ALLERGY?

There is considerable evidence to support the concept that most, if not all, allergic reactions to animal species insulins result from IgE directed toward antigenic determinants on the insulin molecule *itself* rather than to those of contaminating animal proteins in the insulin preparations. The immunologic response to the insulin molecule probably occurs on the basis of the expression of antigenic determinants on manufactured insulin not present on endogenous human insulin. These determinants may be exposed as the result of the acid ethanol extraction used in the preparation of animal species insulins.² Thus, allergic reactions seem to be more common with animal species than manufactured human recombinant insulin which induce lower levels of insulin antibodies.^{3,4} Insulin aggregates have also been implicated in this immunogenicity.⁵

In a study of two patients with generalized insulin allergy to animal species insulins, both patients had evidence of insulin-specific IgE to human insulin extracted from human pancreas and to human synthetic insulin. One patient reacted to his own insulin extracted from his own serum.²

In vitro studies have also shown that most, if not all, anti-insulin antibodies from diabetic patients treated with animal species insulins react with human insulin in vitro.^{6,7} Furthermore, recombinant human insulin inhibits the in vitro binding of IgG and IgE antibodies to beef and pork insulin in the sera of insulin allergic patients. Thus, the antigenic determinants on bovine and

porcine insulin, which stimulate insulin antibodies, are also present on recombinant human insulin.^{8,9} There are numerous reports of diabetic patients who have experienced allergic reactions to animal species insulins and continue to experience allergic reactions when treated with human (rDNA) insulin.¹⁰⁻¹³

Finally, manufactured human insulins induce IgE antibodies in diabetic patients and on occasion allergic reactions to insulin may occur in patients receiving only recombinant human insulins.^{4,8} The present case report complements that experience.

WHAT IS THE NATURAL HISTORY OF INSULIN ALLERGY?

Little information is available concerning the natural history of insulin allergy. In our own experience, which consists of more than 300 patients (reviewed in reference 1), symptoms resolve in most patients with continued, dose-adjusted insulin therapy or after desensitization. If insulin therapy is continued on a daily basis, symptoms rarely occur thereafter. We would, therefore, be surprised if the insulin-allergic individual in this month's case report required corticosteroid therapy to manage her insulin allergy over the long term.

What is the likelihood that insulin allergy will recur when human patients are switched from animal species to human (rDNA) insulins? Since no data are available on this topic, our response to this question is obviously an opinion. Insulin desensitization is associated with a decrease in the serum concentration of IgE antibodies to insulin.¹⁴ Since human recombinant insulins have been shown to induce lower levels of these antibodies than animal species insulin,^{3,4} it is unlikely

that administration of human recombinant insulin will induce reactivation of insulin allergy in patients previously receiving animal species insulins.

MANAGEMENT

Several simple precautions are indicated when patients with histories of insulin allergy are switched from one insulin to another, regardless of the type. The first dose of the new insulin should probably be given under observation where personnel are available to treat allergic reactions if they occur. Patients should also be instructed to notify their physician if local reactions develop, as local reactions may be harbingers of more generalized reactions.

Finally, it is prudent for patients with histories of insulin allergy to have epinephrine available in case allergic reactions occur under circumstances when medical assistance is not quickly accessible. Epinephrine auto-injector devices such as EpiPen (Center Laboratories, Division of EM Pharmaceuticals, Inc) may be useful in these patients.

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REFERENCES

1. Galloway JA, deShazo RD. Insulin chemistry and pharmacology; insulin allergy, resistance, and lipodystrophy. Ellenberg and Rifkin's diabetes mellitus: theory and practice. 4th ed. New York, New York: Elsevier Science Publishing Co, Inc; 1990; 497-513.
2. Patterson R, Lucena G, Metz R, Roberts M. Reaginic antibody against insulin: demonstration of antigenic distinction between native and extracted insulin. *J Immunol* 1969; 103: 1061-71.
3. Faholt K, Hoskam JAM, Karamos BG, et al. Insulin specific IgE in serum of 67 diabetic patients against human insulin (Novo), porcine insulin, and bovine insulin: four case reports. *Diabetes Care* 1983;6 (Suppl 1):61-5.
4. Ho LT, Lam HC, Wu MS, et al. A twelve month double blind randomized study of the efficacy and immunogenicity of human porcine insulins in non-insulin dependent diabetes. *Chin Med J (Taipei)* 1991;47:313-9.
5. Ratner RE, Phillips TM, Steiner M. Persistent cutaneous insulin allergy resulting from high molecular weight insulin aggregates. *Diabetes* 1990;39: 728-33.
6. Patterson R, Roberts M, Grammer LC. Insulin allergy reevaluation after two decades. *Ann Allergy* 1990;64: 459-62.
7. Thomas JW, Virta VJ, Nell LJ. Heterogeneity and specificity of human anti-insulin antibodies determined by isoelectric focusing. *J Immunol* 1984; 134:1048-52.
8. Grammer LC, Metzger BE, Patterson R. Cutaneous allergy to human (rDNA) insulin. *JAMA* 1984;251: 1459-60.
9. Grammer LC, Roberts M, Patterson R. IgE and IgE antibody against human (recombinant DNA) insulin in patients with systemic insulin allergy. *J Lab Clin Med* 1985;105:108-13.
10. Garcia-Ortega P, Knobel H, Mirada A. Sensitization to human insulin. *Br Med J* 1984;288:1271.
11. Altman JJ, Pehuet M, Slama G, Tchobrowsky C. Three cases of allergic reaction to human insulin. *Lancet* 1983; ii:524.
12. Wiles PG, Guy R, Watkins SM, Reeves WG. Allergy to purified bovine, porcine, and human insulins. *Br Med J* 1983;287:531.
13. Ganz MA, Unterman T, Roberts M, et al. Resistance and allergy to recombinant human insulin. *J Allergy Clin Immunol* 1990;86:45-52.
14. Patterson R, Mellies CJ, Roberts M. Immunologic reactions against insulin. III. IgE anti-insulin, insulin allergy, and combined IgE and IgG immunologic insulin resistance. *J Immunol* 1973;110:1135.
15. Patterson R, Roberts M, Grammer LC. Insulin allergy: reevaluation after two decades. *Ann Allergy* 1990;64: 459-62.

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