

Case Report

Role of omalizumab in insulin hypersensitivity: a case report and review of the literature

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Abstract

Background Insulin allergy is a rare yet severe side effect of exogenous insulin use. Management typically involves use of alternative antihyperglycaemic agents, symptom control with antihistamines, use of different insulin formulations, and induction of tolerance with incremental doses of insulin. This treatment regimen is not always successful, and the use of omalizumab, an anti-IgE monoclonal antibody, has been used to induce tolerance to insulin.

Case report G.M. is a 62-year-old man with Type 2 diabetes mellitus. His condition was not optimized on oral agents, and insulin therapy was required. G.M. had anaphylaxis to insulin NPH, and subsequent skin-prick testing was positive to insulin aspart, insulin NPH, insulin glulisine, insulin detemir, regular insulin, insulin glargine 100 units/ml and insulin glargine 300 units/ml. He received incremental doses of several insulin formulations; however, he experienced diffuse urticaria preventing optimal glycaemic control. Three successful cases have been described in the literature of omalizumab inducing tolerance to exogenous insulin; therefore, G.M. was started on omalizumab. He subsequently tolerated treatment doses of insulin glulisine and insulin detemir with no allergic reactions and with improvement in glycaemic control.

Conclusion To our knowledge, this is the first described case of allergy to insulin glargine 300 units/ml and reiterates the potential use of omalizumab in insulin allergy. Further research is warranted to determine if omalizumab should be considered standard of care in difficult-to-treat insulin hypersensitivity.

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Introduction

Insulin hypersensitivity reactions are rare yet severe side effects of exogenous insulin use. Reactions have decreased in frequency since the introduction of humanized insulin, but varied responses—from localized injection site reactions to anaphylaxis—still occur [1]. Management of insulin hypersensitivity involves a step-wise escalation of treatment, depending on the severity of the reaction. This treatment paradigm typically includes: a trial of different insulin moieties; the use of high-dose antihistamines to minimize symptoms; and the induction of tolerance with incremental doses of insulin, often with an insulin pump [2]. This treatment strategy is not always successful, and omalizumab, an anti-IgE recombinant humanized monoclonal antibody, has been used to induce tolerance to exogenous insulin in people with diabetes mellitus [3–5].

We describe the first case, to our knowledge, of insulin hypersensitivity to the recently approved insulin glargine 300

units/ml. We also describe the fourth case of omalizumab successfully inducing tolerance to exogenous insulin. This article serves to describe our clinical case, review the literature on omalizumab use in insulin hypersensitivity, and describe future considerations of omalizumab use in difficult-to-treat insulin allergy.

Case report

Within minutes of receiving insulin NPH, a 62-year-old man with Type 2 diabetes experienced anaphylaxis with acute dyspnoea and diffuse urticaria that prompted a call to emergency medical personnel. He received intravenous diphenhydramine and intramuscular epinephrine which abated symptoms. He was subsequently monitored in the emergency department and was discharged with a course of prednisone, a prescription for an epinephrine autoinjector and a referral to the Clinical Immunology and Allergy clinic.

G.M.'s medical history comprised Type 2 diabetes, hyperlipidaemia, bilateral carotid artery stenosis, and gastro-oesophageal reflux disease. His daily medications

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What's new?

- This paper describes a novel therapy, omalizumab use, that may be useful in difficult-to-treat insulin allergy.
- The paper describes the first reported hypersensitivity reaction to insulin glargine 300 units/ml.

included NPH twice daily, insulin aspart once daily, atorvastatin, rabeprazole, clopidogrel and cetirizine. At the time of the anaphylaxis, his disease was not optimized, with an HbA_{1c} concentration of 74 mmol/mol (8.9%). He had been started on metformin and liraglutide in the past but had stopped these medications because of side effects. NPH and aspart had been started 6 and 3 months prior to the anaphylactic reaction, respectively. A brief trial of glargine 100 units/ml was unsuccessful as a result of urticaria. There was no personal history of atopic or autoimmune disease.

In the Clinical Immunology and Allergy clinic, skin-prick testing was completed and positive wheal and flare responses were present at 10 min to multiple insulin derivatives including: insulin NPH; insulin aspart; insulin glulisine; insulin detemir; regular insulin; insulin glargine 100 units/ml; and insulin glargine 300 units/ml. The results were validated with an appropriate histamine and saline control. Skin-prick testing to protamine was not completed because G.M. had positive wheal and flare responses to non-protamine-containing insulin moieties. Serum specific IgE for insulin and protamine were not tested because this assay was unavailable in the local hospital.

Subsequently, administration of various subcutaneous insulin derivatives were given in an attempt to optimize

glycaemic control. Incremental doses of insulin glulisine, insulin NPH, insulin detemir and insulin glargine 300 units/ml were tried at various times with no subsequent anaphylactic reactions; however, immediate-onset, diffuse urticaria was present with these insulin derivatives preventing adequate glycaemic control. The best-tolerated insulins were insulin detemir (basal insulin) and insulin glulisine (rapid-acting insulin); however, even with high doses of cetirizine, urticaria was not sufficiently managed. G.M. did not qualify for an insulin pump because he had inadequate insurance coverage; therefore, continuous subcutaneous insulin infusion was not an option. He was also tried on acarbose, and participated in a research trial of a sodium-glucose co-transporter-2 inhibitor, but had to stop both of these medications because of side effects. After almost 3 years of trying various insulin and non-insulin agents, his HbA_{1c} concentration had risen to 86 mmol/mol (10.0%), on gliclazide, detemir 36 units daily and glulisine 30 units daily.

Three previous cases have been described in the literature in which omalizumab successfully induced tolerance to exogenous insulin in individuals with both Type 1 and Type 2 diabetes (Table 1). Because G.M.'s glycaemic control was not optimized, informed consent and approval for omalizumab was obtained, and treatment was initiated. The dosing protocol was 150 mg subcutaneously every 4 weeks, with a total of 16 doses given to date. Titration of insulin glulisine and insulin detemir to therapeutic doses was tolerated and G.M. has not experienced further urticaria or other features concerning for a type 1 hypersensitivity reaction. His HbA_{1c} concentration has declined steadily over the year since starting omalizumab, with a value of 66 mmol/mol (8.2%). Additionally, he is tolerating more insulin than ever before (detemir 86 units daily and glulisine

Table 1 Characteristics and outcomes of individuals with insulin allergy treated with omalizumab

Reference	Age, years; sex	Diabetes mellitus	Symptoms	Diagnosis	Short-term management	Maintenance therapy*
3	27; M	Type 1	Urticaria, anaphylaxis	SPT, insulin specific-IgE	Omalizumab 300 mg s.c. every 2 weeks for 20 weeks	Levocetirizine 5 mg orally daily with cessation of symptoms
4	50; F	Type 1	Urticaria	SPT, insulin specific-IgE	Rituximab (to decrease serum IgE), then mycophenolate mofetil, then omalizumab (dose not specified) for 9 months	Prednisolone 2 mg orally daily with cessation of symptoms
5	62; M	Type 2	Urticaria, anaphylaxis	SPT, insulin specific-IgE	Failure of insulin desensitization (with insulin detemir), then successful treatment with omalizumab 300 mg s.c. every 4 weeks for 6 months	Omalizumab 300 mg s.c. every 9 weeks (maintenance), with cessation of symptoms

F, female; M, male; s.c., subcutaneous(ly); SPT, skin prick test.

*In all three cases, individuals had ultimate cessation of symptoms.

34 units daily). His management plan is to continue omalizumab indefinitely while adjusting his insulin further.

Discussion

Hypersensitivity reactions to insulin are rare complications of exogenous insulin use, and induction of tolerance with incremental doses of insulin has historically been the maximal therapy available in difficult-to-treat insulin allergy. With this treatment, production of insulin IgG antibodies have been described, which may lead to increased insulin resistance in people with diabetes [7]. Additionally, recurrent hypersensitivity reactions have been described after successful desensitization protocols [8]; therefore, there is a need for further treatment methods in difficult-to-treat insulin hypersensitivity that may include the use of omalizumab.

Currently, omalizumab is only approved in the treatment of asthma and chronic spontaneous urticaria [6]; however, case series and ongoing trials are exploring the efficacy of omalizumab in type 1 hypersensitivity reactions. Small trials have suggested a potential role for omalizumab in preventing peanut-induced anaphylaxis and anaphylaxis with allergen immunotherapy [9–12]. Omalizumab has also been used in the prevention of idiopathic anaphylaxis and exercise-induced anaphylaxis [13,14]. Additionally, omalizumab has been used in desensitization protocols for medications including aspirin and carboplatin, in addition to insulin [15,16].

Omalizumab may represent an ideal treatment for inadequately controlled insulin allergy. The medication has low rates of adverse drug reactions, and even in instances of hypersensitivity reactions, desensitization protocols have been successfully used [17,18]; however, there are currently no standardized protocols for omalizumab use in insulin hypersensitivity, and discussion in the literature has been limited to case reports. Larger studies are necessary to develop standardized treatment protocols and assess the need for maintenance therapy.

Our case illustrates the use of omalizumab to induce tolerance to exogenous insulin and describes the first documented case of an immediate hypersensitivity reaction to insulin glargine 300 units/ml. Further research, including cost-benefit analysis, is warranted to determine if omalizumab should be considered standard of care in difficult-to-treat insulin hypersensitivity, and to determine dosing regimens for therapy.

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