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• M. Fujishiro et al.

A case of insulin allergy successfully managed using multihexamer-forming insulin degludec combined with liraglutide

M. Fujishiro, Y. Izumida, S. Takemiya, Y. Kuwano, I. Takamoto, R. Suzuki, T. Yamauchi, K. Ueki and T. Kadowaki

Department of Diabetes and Metabolic Diseases, Graduate School of Medicine,
University of Tokyo, Bunkyo-ku, Tokyo, Japan

Correspondence to: Midori Fujishiro. E-mail: midori-tky@umin.ac.jp

What's new?

- We describe a case of a patient who was allergic to all commercially available insulin formulations except insulin degludec.
- The allergic reactions completely disappeared after switching to insulin degludec.
- The crystallized structure of insulin degludec might mask its antigenicity as a skin allergen.
- Postprandial hyperglycaemia was successfully controlled with glucagon-like peptide-1 receptor agonist liraglutide.

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- Insulin degludec plus liraglutide may be a therapeutic option in patients with insulin allergy.

Abstract

Background Insulin allergy, one of insulin's adverse effects, is rare, especially in patients with Type 2 diabetes, but management is difficult and no effective strategy has yet been established. We experienced an insulin allergy case successfully managed with a novel combination of insulins.

Case report A 38-year-old woman started insulin therapy when diabetes was diagnosed at age 19 years. Despite poorly controlled diabetes because of poor adherence, she hoped to conceive a child and continuous subcutaneous insulin infusion was introduced using insulin aspart at age 32 years. One month thereafter, she developed skin reactions at the subcutaneous insulin infusion catheter insertion site. The patient was then tested for all rapid-acting insulin formulations, all of which triggered local reactions. She decided to continue the continuous subcutaneous infusion of human regular insulin, accompanied by oral cetirizine hydrochloride and betamethasone valerate ointment. The patient was admitted to our hospital at age 38 years with high HbA_{1c} levels. She was tested for all long-acting insulin analogues. All results, except for insulin degludec, were positive. She discontinued continuous subcutaneous insulin infusion and switched to insulin degludec combined with liraglutide. The allergic reactions had completely disappeared and her blood glucose was well controlled by the time of discharge.

Conclusion Our patient was allergic to all insulin formulations except insulin degludec. Her allergic reactions completely disappeared after switching to insulin degludec. The crystallized structure of this insulin might mask its skin allergen antigenicity. Furthermore, her postprandial hyperglycaemia was successfully controlled with liraglutide. We propose multihexamer-forming ultra-long-acting insulin plus glucagon-like peptide-1 analogues as a therapeutic option for patients with insulin allergy.

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Introduction

Insulin allergy is not common, but can emerge in insulin-treated patients. Once insulin allergy develops, glycaemic control becomes very difficult to achieve and no effective management strategy has yet been established [1,2]. Kawanami *et al.* [3] recently reported a patient with Type 2 diabetes with severe insulin allergy in whom blood glucose was successfully controlled with liraglutide, one of the glucagon-like peptide-1 (GLP-1) receptor agonists, which promote endogenous insulin secretion and suppress glucagon secretion from pancreatic islets, suggesting this to be a possible therapeutic option for patients with insulin allergy. In addition, Takatsuki *et al.* [4] reported a patient with insulin allergy who was successfully treated with a semi-synthetic crystalline human insulin zinc (Novolin U), suggesting that the crystallized structure of this human insulin might mask its antigenicity as a skin allergen. In the present paper, we report a patient with poorly controlled Type 2 diabetes who showed positive skin-test reactions to all insulin preparations except for the novel acylated multihexamer-forming insulin degludec (IDeg; Tresiba[®], Novo Nordisk, Bagsværd, Denmark), providing an ultra-long glucose-lowering effect. Indeed, our patient's glycaemic profile was well controlled with combination therapy using IDeg and liraglutide (Victoza[®], Novo Nordisk).

Case report

A 38-year-old woman had a 20-year history of Type 2 diabetes mellitus. When diagnosed, at age 19 years, she had started intensive insulin therapy with human regular insulin (Novolin[®] R, Novo Nordisk) and neutral protamine Hagedorn (NPH; Novolin[®] N, Novo Nordisk) insulin because she was of childbearing age; however, she stopped taking this treatment 3 months later. At age 22 years, she re-started insulin therapy with premixed biphasic human insulin (Novolin[®] 30R, Novo Nordisk) injected twice daily. Her treatment was changed to premixed insulin analogue biphasic insulin aspart (NovoMix[®] 30, Novo Nordisk) because of the risk of hypoglycaemia. This article is protected by copyright. All rights reserved.

Nordisk) at age 29 years. At age 31 years, intensive insulin therapy was re-started using insulin aspart (NovoRapid®, Novo Nordisk) and NPH insulin with multiple daily injections. At age 32 years, continuous subcutaneous insulin infusion (CSII) was initiated using insulin aspart, classified as category B treatment for pregnant women with diabetes by the US Food and Drug Administration (FDA), because she hoped to conceive a child. One month after starting CSII using insulin aspart, she developed itchy wheal-and-flare reactions at the CSII catheter insertion site, suggesting insulin allergy with or without reactions only against the CSII catheter. Although insulin aspart was changed to human regular insulin with CSII, a similar skin reaction occurred, and she was then tested for all commercially available rapid-acting insulin formulations, all of which triggered local flare, erythema, wheal and/or pruritus reactions, which gradually expanded to maximum diameters of 15 mm when judged at 48 h after injection (Table 1), despite negative drug-induced lymphocyte stimulation tests for these preparations. She decided to continue CSII of human regular insulin which triggered the least severe reaction with the lowest possibility of antibody formation, accompanied by oral cetirizine hydrochloride, an antihistamine classified as category B treatment for pregnant women with diabetes by the FDA, and betamethasone valerate ointment. Unexpectedly, her glycaemic control soon worsened and she chose to use insulin aspart as CSII because of the superiority of insulin aspart as compared with human regular insulin for improving HbA_{1c} values in insulin pump users [5,6]. At age 38 years when her HbA_{1c} level exceeded 97 mmol/mol (11%), she was admitted to our hospital with the goal of identifying the best way to manage her diabetes.

Her mother also had diabetes and was treated with insulin. The patient had never smoked or used alcohol. She was 163 cm in height and weighed 79.3 kg with a BMI of 29.8 kg/m² and a waist circumference of 95.5 cm. On physical examination, neither the biceps nor the Achilles tendon reflex could be elicited. She had branch retinal vein occlusion accompanied

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by subretinal haemorrhage. Laboratory data were essentially normal without eosinophilia. Mild fatty liver damage was revealed by laboratory data and confirmed by abdominal ultrasonography. Chest X-ray and echocardiographic findings were both within normal limits. Fasting blood glucose was 191 mg/dl with a serum C-peptide level of 1.1 ng/ml. These values were elevated to 242 mg/dl and 1.9 ng/ml, respectively, 120 min after a mixed-meal tolerance test. Her HbA_{1c} level was 104 mmol/mol (11.7%) and glycated albumin was 28.2%, indicating poorly controlled diabetes. Human insulin-specific bound immunoglobulin (Ig) E was undetectable. Insulin-specific IgG was 11.7 U/ml with a 16.2% insulin binding rate, not a significant elevation.

Type 2 diabetes had been diagnosed based on obesity, with a maximum BMI of 30.8 kg/m² at age 22 years, as well as her family history of diabetes. On admission, she was taking 2250 mg daily of metformin and 65 units/day of insulin aspart with CSII. After starting a 1400 kcal diet (24 kcal/kg ideal body weight), the total daily insulin amount was reduced to 38 units with a 125 mg/dl fasting glucose level, which suggested β -cell function recovery from hyperglycaemia-induced toxicity in response to a strictly controlled diet. She was then started on once-daily injection of the GLP-1 receptor agonist liraglutide, which is reportedly effective for treating patients with insulin allergy [3]. Skin test results for all commercially available long-acting insulin analogues indicated allergic reactions to both insulin detemir (Levemir[®], Novo Nordisk) and insulin glargine (Lantus[®], Sanofi, Paris, France) manifesting as itchy erythematous lesions with diameters of 20 and 22 mm, respectively, when judged at 48 h after injection (Table 1); however, there was no reaction to IDeg. IDeg provides ultra-long glucose-lowering effects, extending beyond 40 h, that are attributable to the formation of multihexamers [7]. She started treatment with IDeg as basal insulin at an initial dose of 6 units/day on day 13 of hospitalization. Glycaemic control was well maintained with a fasting blood glucose of ~120 mg/dl and postprandial glucose of 180 mg/dl when the IDeg

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dosage was increased to 14 units/day. She therefore discontinued CSII on day 16 after admission and was discharged the following day. The allergic reactions had completely disappeared by the time of discharge.

Discussion

Although the patient had no laboratory evidence of insulin allergy, as described above, we believe she definitely had an insulin allergy for the following reasons. First, she developed no reactions to saline injection, which suggested that she had no allergies to the metals used in insulin injection devices. Second, she developed skin reactions to all commercially available insulin formulations except IDeg, which suggested an allergy to the insulin molecule itself rather than insulin additives such as cresol, phenol or protamine. Third, several reports have indicated that insulin allergy can emerge without an insulin-specific bound IgE [8,9], which is a typical marker of type I allergy, further supporting the assumption that our patient developed skin reactions as a result of insulin allergy without this typical antibody. In fact, drug-induced lymphocyte stimulation tests, known to be markers of type IV allergy, were negative against all of the rapid-acting insulin formulations. This is not, however, enough evidence to exclude the possibility that she had type IV allergy to insulins because neither the sensitivity nor the specificity of drug-induced lymphocyte stimulation tests for type IV allergy are sufficiently reliable. These positive skin tests suggested, therefore, that she had delayed-onset type I allergy without the insulin-specific bound IgE or type IV allergy with negative drug-induced lymphocyte stimulation tests.

Long-acting insulin glargine and CSII with short-acting insulin analogues have both reportedly been used to manage patients with insulin allergy [10–15]; however, our patient was allergic to glargine and other analogues, such that none of these treatments could be used. After starting treatment with IDeg, the allergic reactions completely disappeared. This article is protected by copyright. All rights reserved.

suggested that the crystallized structure of IDeg might mask its antigenicity, thereby preventing the triggering of allergic reactions. In addition, her postprandial hyperglycaemia was successfully controlled with GLP-1 receptor agonist liraglutide, which stimulates endogenous insulin secretion. On this regimen, she was ultimately able to discontinue CSII.

To our knowledge, this is the first report to document the usefulness of IDeg combined with liraglutide in a patient with Type 2 diabetes whose glycaemic control was adversely affected by severe insulin allergy. Our presentation highlights a novel potential therapeutic strategy against insulin allergy.

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None.

Competing interests

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Table 1 Summary of the patient's skin reactions to all available insulins with their additives

Insulin	Amounts*	Flare size/ pruritus	Additives
NPH	1 unit	5 mm/+	Protamine sulphate, zinc oxide, phenol, glycerol, m-cresol, disodium hydrogen phosphate
Regular	2 units	5 mm/-	Zinc oxide, glycerol, m-cresol
Aspart	2 units	5 mm/+	Zinc oxide, phenol, glycerol, m-cresol, disodium hydrogen phosphate, sodium chloride
	5 units	15 mm/±	
Lispro	2 units	10 mm/+	Zinc oxide, glycerol, m-cresol, disodium hydrogenphosphate
	5 units	10 mm/+	
(tested at age 32 years [†])			
Detemir	0.1 ml/	20 mm/+	Zinc acetate , phenol, glycerol, m-cresol, disodium hydrogen

	10 units		phosphate, sodium chloride
Glargine	0.1 ml/		
	10 units	22 mm/+	Zinc chloride, glycerol, m-cresol
Degludec	0.1 ml/		
	10 units	No reaction	Zinc acetate, phenol, glycerol, m-cresol

(tested at age 38 years)

*Indicates amounts of insulin used for skin tests.

†Insulin glulisine, which acts rapidly, was not tried because this insulin analogue was not available in Japan when the patient was tested for all commercially available rapid-acting insulin formulations during her previous admission.