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Insulin allergy successfully managed using a combination of multi-hexamer-forming insulin degludec and vildagliptin-a case report

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ABSTRACT

Background: With the introduction of recombinant formulations, insulin allergy is rare, occurring in less than 1% of patients treated with insulin. However, it is a serious situation requiring immediate attention, both due to the hypersensitivity reaction and severe life threatening glucose disequilibrium.

Case Presentation: A case of a 68-year-old male known diabetic for 35 years noticed some generalized itching, accompanied with maculopapular, mixed vasculitic, and bullous lesions. Humalog Mix 50/50 was stopped and patient was started on the different combinations but to no avail. Before insulin desensitization, a trial of degludec (IDeg) was given. Fortunately, the patient tolerated IDeg and vildagliptin, and sugars came under control.

Conclusion: This combination of multi-hexamer-forming ultra-long-acting insulin plus a DPP4 inhibitor vildagliptin could be an effective combination in controlling blood sugars in the patients who have severe allergy to multiple drugs, including oral hypoglycemic agents and various insulin preparations.

Keywords: Insulin, allergy, combination therapy, degludec, vildagliptin, case report.

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Background

Due to the immunogenicity of the earlier bovine and porcine, insulin hypersensitivity reactions were quite common, but the incidence of these reactions have reduced significantly after the introduction of recombinant insulins [1,2]. Most of the insulin reactions occur due to the substances added to the insulins but they can also be triggered by insulin itself. Various imm une mechanisms can be implicated in these hypersensitivity reactions [1,2].

Case Presentation

We present a case of a 68-year-old male patient who was a known diabetic for the last 35 years, hypertension 15 years, Benign prostatic hyperplasia 5 years, and chronic kidney disease was presented. There was a significant family history of allergies. Patient's son suffered with multiple allergies for which he had been admitted to intensive care unit on multiple occasions with serious anaphylactic reactions. The medications included insulin Humalog Mix 50/50, 40 units thrice daily, Aspirin 81 mg, Allopurinol 100 mg daily, Amlodipine 5 mg daily, finesteride 5 mg daily, and tamsulosin 0.4 mg daily. Recently because of hyperkalemia, irbesartan was stopped and hydralazine was started 25 mg daily. The patient had been on insulin for the

last 30 years and tolerated it quite well with a fair control. After approximately 5 years of diagnosis, he was started on Mixtard 70/30 and later this was changed to Humalog mix 50/50 for better control. The patient presented to the Emergency Department with acute allergic reaction which was blamed to insulin Humalog Mix 50/50 which was been taken 40 units three times per day. Hydrocortisone and chlorpheniramine was given and discharged. Within a period of 2 weeks, the patient presented to the emergency room (ER) at least three times with similar complaints and each time was given hydrocortisone and an antihistamine, which temporarily relieved the symptoms. Eventually, endocrine and dermatological services were referred for further management. The patient gave a history of acute generalized erythematous, itchy maculopapular rash all over the body. This, according to the patient, came within a few minutes of taking the insulin. This had been going on for the last 4 weeks and got worse. Moreover, some multiple clusters of raised nodular lesions were also noticed on the limbs, more on the lower. In addition, the patient had noticed some bullous lesions mainly on the soles. On examination of the skin, there were generalized maculopapular rashes all over the body. There were also clusters of small red raised petechial lesions on the limbs specially the lower, just above the ankles. On the soles, there were a few small bullous lesions (see Figures. 1 and 2).

Initial investigations only showed eosinophilia and a creatinine clearance of 35 ml/minute. Rest of the immunological workup, including anti DNA, ANA, and compliments C3 and C4, were within normal limits.

The differential diagnosis that was considered initially was allergic reaction to aspirin, allopurinol, or hydralazine. Keeping this in mind, the first step was to withdraw all these drugs. Due to the polymorphic nature of the lesions, specially, vasculitic lesions autoimmune pathology was also on the list. As the patient gave history of the lesions appearing after taking insulin, allergy to insulin was a serious consideration.

All the possible inciting drugs, including aspirin, allopurinol, and hydralazine, were withdrawn. Moreover, the patient was also asked to put hold on finasteride and tamsulosin. The allergic reactions did not subside. Subsequently, insulin regimen was changed to a basal bolus combination comprising of glargine and glulisine. Unfortunately, patient reacted to this combination, hence, glargine was withdrawn first but when patient continued to have the reaction, glulisine was switched to as a part but to no avail. Even human regular insulin and lyspro were tried without any improvement. During this period, the patient was advised to be admitted for possible desensitization of insulin but the advice was not taken. As the glucose control was decompensated, in desperation gliclazide MR and vildagliptin were started and were quickly escalated to the maximum dosage. Despite this blood sugar remained high at 350-400 mg/dl. A trial of insulin degludec (IDeg) was given after which the patient was admitted for desensitization. A small dose of four units was given which was tolerated without any undue reaction and all the skin lesions were subsided (Figures 3 and 4). The dose was later increased to 10 units which controlled the blood sugar very well along with vildagliptin for post prandial control.

Discussion

Insulin allergy is quite rare and there are no guidelines for managing these patients [1]. The clinical presentation can be very complicated as patients may be on multiple medications and there can be an overlap of multiple hypersensitivity mechanisms [1,2]. Presentation may occur several months or years after starting insulin therapy, or immediately after the first injection. Basal insulin glargine with short-acting analogues have both been utilized to treat insulin allergic patients [3-5]. This was the first strategy that was tried, unfortunately in the present case, reaction occurred to both glargine and all other available insulins. Patient was offered insulin desensitization as it is a good option for patients with multiple insulin allergies [6–8]. However, the patient refused to be admitted to the hospital. Subsequently, insulin was withdrawn, and patient was started on gliclazide MR and vildagliptin without any improvement in the blood sugar. The only insulin preparation that was remaining to be tried was IDeg. After initiating therapy with IDeg, there were no allergic reactions and the previous skin lesions subsided considerably. This may be due to the unique crystallized structure of IDeg which has the same amino acid sequence as human



Figure 1. Peticheal lesions on the lower limb.



Figure 2. Vesico bullous lesions.



Figure 3. Healed lesions on the leg.



Figure 4. Healed lesion on the sole.

insulin except for the removal of threonine in the position 30 of the B chain and the attachment, via a glutamic acid linker of a 16-carbon fatty diacid (hexadecanoic diacid) to lysine in the position 29 of the B chain [9] (Figure 5). This alteration allows for the formation of multi-hexamers in subcutaneous tissues [10] which may have concealed its antigenic potentials.

To the authors' knowledge, this is the first case report that used a combination of IDeg insulin with vildagliptin a DPP4 inhibitor in a patient with type-2 diabetes with

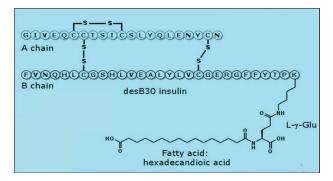


Figure 5. Molecular structure of IDeg.

decompensated glycemic control due to severe insulin hypersensitivity. This case identifies an innovative approach for managing a very difficult diabetic patient with multiple drug allergies, including most of the insulins and oral anti diabetic agents.

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List of Abbreviations

IDeg degludec ER emergency room

Conflict of interest:

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Informed consent was obtained from the patient.

Ethical approval

Medical Services Department for Armed Forces, Scientific Research Center, Research Ethics Committee, Ref no RECT 2015, Reg No H-02-T-078, Date 11/3/2015.

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Summary of the case

Patient	1	Male, 68 years
Final diagnosis	2	Insulin Allergy
Symptoms	3	Allergic reaction, maculopapular rash
Medications	4	Insulin degludec, vildagliptin
Clinical procedure	5	Insulin desensitization, oral medication
Specialty	6	Endocrinology