

Case Study

Oral Pharmacotherapy as Alternative Treatment for Type 2 Diabetes Mellitus in a 61 Year Old Ethnic Filipino Man with Insulin Allergies

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ABSTRACT

Allergy to insulin occurs in approximately 2% of patients treated with insulin. However, major guidelines fail to emphasize this serious adverse effect. In this article, we report on a 61 year old ethnic Filipino man who developed urticaria and pruritus with a swollen tongue, which necessitated a visit to the emergency department. His clinical diagnosis was confirmed by a high titer of anti-insulin antibodies. His condition was successfully managed by discontinuing insulin and by treatment

with oral hypoglycemic agents, with no additional adverse reactions. At the most recent follow-up visit, his antibody titer had fallen; however, that titer has not normalized. Also, the patient currently does not have urticaria.

Keywords: insulin, insulin allergy, type 2 diabetes, glargine insulin, detemir insulin, insulin antibodies

Recently, Diabetes Canada presented its comprehensive guidelines for the management of diabetes. In these guidelines, the organization detailed the pharmacotherapy for type 2 diabetes mellitus (T2DM).¹ The important role of insulin therapy in the management of T2DM was clearly emphasized, as in the American Diabetes Association (ADA) and European guidelines.^{2,3} However, there was only sparse mention of the adverse reaction of insulin allergy in all the guidelines.¹⁻³ It appears that insulin allergy can occur in as many as 2.0% of patients prescribed insulin and could be a serious adverse reaction.⁴⁻⁶

In this article, we report on a 61 year old man of Filipino descent who developed an insulin allergy, as confirmed by high titers of insulin antibodies. We were able to manage his glycemia adequately without insulin therapy, by instead using oral pharmacotherapy, as we will detail in the coming paragraphs.

Abbreviations

T2DM, type 2 diabetes mellitus; ADA, American Diabetes Association; A1c, glycated hemoglobin; NPH, neutral protamine Hagedorn; TSH, thyroid-stimulating hormone; TPO, thyroid peroxidase; BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter

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Case History

Initially, the patient was undergoing metformin therapy (1 g, twice/d) and glipizide (5 mg, twice/d). However, his glycated hemoglobin (A1c) levels remained at approximately 9% (goal, <7%). Detemir insulin, 15 µU per d, was added to his regimen by his internist; however, he reported experiencing rashes and pruritus within days of starting insulin. Detemir insulin was stopped, and glargine µU-100 insulin, 15 µU per d, was started. After administration of his first dose, the patient again developed urticaria, pruritus, and a swollen tongue; and sought treatment in the emergency department at the Sacramento VA Medical Center. He did not have any airway obstruction and he responded to the combination of steroids, antihistamines, and fluids, so he was discharged to his primary care physician.

The patient was started on neutral protamine Hagedorn (NPH) insulin by his internist; again, he developed urticaria and pruritus. At this point, he was referred to our Metabolic Clinic at the Sacramento VA Medical Center. Based on his history and physical examination results, we considered a diagnosis of insulin allergy. It appears that his rash had started on his limbs and spread to his trunk but did not involve his face. We added saxagliptin, 5 mg per d, and increased his glipizide to 10 mg, twice per d. His A1c value decreased to 8.1% within 4 months.

Then, we added acarbose 25 mg, 3 times per d (the maximum dose the patient could tolerate, due to gastrointestinal adverse effects) and empagliflozin, 10 mg per d, which was titrated up to 25 mg per d on his most recent visit April 2018. His most recent A1c level is 7.4%, and his plasma glucose level is 162 mg per dL. In [Table 1](#), we show his anti-insulin antibody titers since October 2016. Anti-insulin antibodies were assayed by the Esoterix reference laboratory (Calabasas, CA) using a radioimmunoprecipitation assay.

On the initial visit by the patient, in October 2016, his levels of anti-insulin antibodies were 145 μ U per mL (reference range, $<5 \mu$ U /mL). Those levels continued to decrease as the patient continued noninsulin therapy; presently, that value is 13 μ U per mL, 19 months since discontinuing insulin therapy. The marked increase in anti-insulin antibodies (despite having stopped taking insulin 3 weeks previously), the presence of urticaria and pruritus with insulin therapy, and the absence of those conditions at discontinuation of insulin therapy confirm a diagnosis of insulin allergy.

Assays for islet-cell antibodies yielded negative results. A recent C-peptide level draw yielded normal results, at 2.2 ng per mL (1.1–4.4), suggesting that the patient is not insulin deficient. Also, levels of thyroid-stimulating hormone (TSH) and thyroid peroxidase (TPO) antibodies were normal: 1.1 mIU per mL (0.4–5.0) and 10 IU per mL (0–34), respectively. The medical history of the patient included gout, hypertension, and hyperlipidemia.

The patient has a body mass index (BMI) of 24.6 kg per m^2 and blood pressure (BP) of 112/65 mm Hg, with no evidence of peripheral arterial disease, diabetic retinopathy, or neuropathy. His creatinine level was normal, at 0.81 mg per dL (0.5–1.1), his urine albumin excretion was 25.7 mg per g creatinine (normal, <30 mg/g creatinine), and his serum uric acid level was 5.2 mg per dL (reference range, 3.5–7.2) while undergoing therapy. His protein electrophoresis levels were normal. Also, his low-density lipoprotein (LDL)-cholesterol level was 51 mg per dL and his non-high-density lipoprotein (HDL) cholesterol level was 93 mg per dL. His urine albumin/creatinine ratio was 37.6 before referral and most recently is 25.7 mg per g creatinine. His present medications include empagliflozin, 25 mg per d; saxagliptin, 5 mg per d; acarbose, 25 mg, 3 times per d; metformin 2 g per d; glipizide, 20 mg per d; simvastatin, 40 mg per d; lisinopril, 40 mg per d; and allopurinol, 300 mg per d.

Table 1. Anti-Insulin Antibody Titers in Our Patient, a 61-Year-Old Ethnic Filipino Man

Date	Titer Value ^a
October 2016	145
July 2017	45
November 2017	14
April 2018	13

^aReference range: $<5 \mu$ U/mL.

The patient has a family history of diabetes. Despite this, neither of his parents had any allergy to insulin. Thus, his insulin allergy is not familial.

We are reporting on a patient with proven insulin allergy who is being managed adequately with noninsulin therapy and is experiencing no rashes or diabetic complications. If his A1c level continues to be greater than 7%, we will consider adding liraglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist therapy, in the future.

Discussion

Although insulin allergy is rare, especially in this era of recombinant insulins, it still exists.⁴⁻⁷ The case of our patient exemplifies such an adverse reaction to 3 different insulins, the worst being to glargine, which resulted in a visit to the emergency department.

T2DM is assuming epidemic proportions globally. Although insulin resistance and insulin deficiency are crucial in the pathogenesis of T2DM, insulin deficiency is the final arbiter in clinical progression to overt diabetes.⁸ Further, insulin therapy is the most potent hypoglycemic agent available and is usually used, as in our patient, when HbA1c is greater than 9.0%.¹⁻³

For insulin allergy, insulin desensitization therapy is a reasonable strategy and is the major focus of most reports.⁴⁻⁷ However, the arrival of newer therapies, such as the sodium-glucose cotransporter (SGLT2) inhibitors and GLP-1 receptor agonists, allows for a reasonable trial without tedious insulin desensitization in patients with T2DM.

In our patient, we were successful in lowering his A1c level to 7.4%, from 9.0%, and his albuminuria level to 25.7 mg per g creatinine, from 34.6 mg per g creatinine. Hence, we

are providing an effective strategy to manage his diabetes. We were intrigued that, although the anti-insulin antibodies of the patient have fallen from 145 μ U per mL to 14 μ U per mL, they have not disappeared completely.

The most severe reaction occurred with insulin glargine, which is a modified insulin with 2 added arginine residues to the C terminal of the B chain and substitution of glycine for asparagine at position 21 on the A chain. However, the vast majority of patients prescribed glargine do not experience insulin allergy.^{6,7} Thus, the high titer of anti-insulin antibody in our patient could be due to denatured or complexed insulin, or contaminants such as protamine, zinc, and metacresol, modifying the insulin molecules. It appears that glargine and detemir insulins contain zinc and metacresol.⁴

We are unable to explain the triggering *moiety* (distinct part of a larger molecule) in the insulins prescribed to our patient. There are reports on insulin allergy in the literature; however, none report on insulin antibodies, to our knowledge. Still, it is well known that patients undergoing insulin therapy develop low-titer antibodies, which do not appear to impair efficacy. Hattori et al⁹ reported a frequency of 40.7% antibody positivity (>10.6% antibody-bound insulin) in 118 patients with T2DM who were treated with insulin. In pregnant women treated with insulin, antibody titers were less than 1.6 μ U per mL.¹⁰ In our patient, during his last 2 visits, he had antibody titres less than 15 μ U per mL and he displayed no utricular rash or other such symptoms. Thus, levels greater than the reference range, provided that they are as high as 15 μ U per mL, are unlikely to cause symptoms—our patient had symptoms at levels of 145 μ U per mL.

Our intent in releasing this report is to alert health care providers who manage T2DM with insulin therapy to be aware of insulin allergy, which is rare but can be serious, and can be confirmed by assaying insulin antibodies. Further, with recent advances in pharmacotherapy, there is the opportunity to

manage insulin allergy without insulin desensitization therapy, using novel therapies such as SGLT2 inhibitors and GLP1-receptor agonists in patients with T2DM. **LM**

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