Hypersensitivity Reactions to the GLP-1 Receptor Agonists Liraglutide and Semaglutide: A Case Series

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Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) lower glucose levels by mimicking the actions of the gut hormone GLP-1, which stimulates insulin biosynthesis and inhibits glucagon, secretion from gastric emptying, and food intake. This group includes liraglutide (Victoza and Saxenda), semaglutide (Ozempic, Rybelsus), dulaglutide (Trulicity), and tirzepatide (Mounjaro), which are structurally analogous to human GLP-1, and exenatide (BydureonBCise and Byetta) and lixisenatide (Lyxumia), which are GLP-1 RAs based on exendin-4, a peptide isolated from the salivary venom of *Heloderma suspectum*, whose structure is similar to that of GLP-1. Homology between human GLP-1 RAs and exendin-4–based GLP-1 RAs is about 53%. All GLP-1 RAs are indicated in type 2 diabetes, except Saxenda (liraglutide), which is indicated in obesity. Administration is subcutaneous, with daily or weekly dosing, except for Rybelsus, which is administered once daily.

Although several cases of allergy to GLP-1 RAs have been reported, only a few included allergology studies. Carvallo et al [1] reported a case of a local delayed hypersensitivity reaction to liraglutide with positive skin test results and negative results with semaglutide, proposing this as an alternative. Steveling et al [2] described a systemic allergic reaction with a positive skin test result for exenatide and a negative result for liraglutide. Shamriz et al [3] reported an allergic reaction to exenatide and lixisenatide in a patient who tolerated liraglutide. Other publications on allergies to liraglutide, dulaglutide, and exenatide did not include allergy tests or demonstrate tolerance of other GLP-1 RAs [4-7].

We report on 5 patients with hypersensitivity to liraglutide, semaglutide, or both. Patients #1, #2, #3, and #4 developed localized pruriginous erythematous infiltrated plaques at the liraglutide injection site; these appeared 24 hours after 1-3 months of treatment. Patient #5 received subcutaneous

semaglutide for 3 months with good tolerance. Owing to drug shortages, he stopped treatment for a few days, after which he started oral semaglutide. Fifteen minutes after receiving his first tablet, he presented generalized hives, facial angioedema, dizziness, and hypotension (90/60 mmHg). The reaction was treated with cetirizine and fluid therapy. An ECG was performed when de novo atrial fibrillation, which required cardioversion, was detected. Subsequently, the patient began to use subcutaneous liraglutide, which he tolerated.

All patients underwent skin prick tests (SPTs) with liraglutide (1/1=6 mg/mL), semaglutide (1/1=1.34 mg/mL), saline, and histamine and intradermal skin tests (IDTs) with liraglutide (1/1=6 mg/mL; 1/10=0.6 mg/mL; 1/100=0.06 mg/mL), semaglutide (1/1=1.34 mg/mL; 1/10=0.134 mg/mL; 1/100=0.0134 mg/mL), and saline [1]. A subcutaneous challenge was performed in patients whose SPT and IDT results were negative, together with a subcutaneous saline control. Patch tests with liraglutide (6 mg/mL) and semaglutide (1.34 mg/mL) in saline were performed on the arm of patients #1 and #3 over a residual lesion. Patch tests were not performed in patients #2 and #4 because the lesions affected the abdomen, where patch testing is technically difficult. The patients gave their informed consent for testing and for their clinical findings to be published.

The results of the SPTs and IDTs with liraglutide and semaglutide are shown in Table S1-Supplementary material.

Patients #1, #2, and #3 were diagnosed with delayed allergy to liraglutide and tolerance of semaglutide. Although sensitization to liraglutide could not be demonstrated with skin tests in patient #1, the allergy was diagnosed through the clinical history and clinical signs.

Patients #2 and #3 presented a positive 1/10 and 1/1 IDT result at the delayed 24-hour reading with liraglutide, confirming the diagnosis (Figure). Patient #4 was diagnosed with allergy to liraglutide and semaglutide, which was confirmed through a positive challenge with liraglutide and positive IDT with semaglutide. Positive dilutions were tested in 3 healthy control individuals, with negative results.

Patient #5 was diagnosed with anaphylactic shock to semaglutide but tolerated liraglutide. IDT was not performed owing to the high risk of the previous reaction.

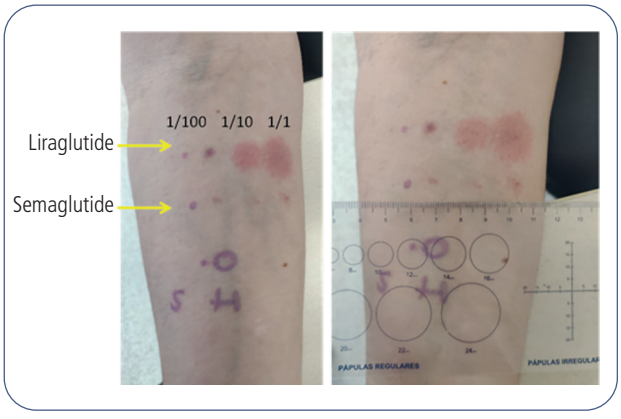

Figure. Intradermal tests with liraglutide in patient #3 (delayed 24-hour reading). H indicates histamine; S, saline.

The use of GLP-1 RAs is increasing worldwide owing to their indication in type 2 diabetes and obesity. Given that GLP-1 RAs can induce allergy, physicians should be aware of potential reactions.

The pathophysiological mechanism of allergy to GLP-1 RAs is unknown. Therefore, in cases of late local reaction to a GLP-1 RA, we recommend performing a patch test on a residual lesion. If the result is negative, performing SPT and IDT with delayed readings would be indicated, with a dilution of 1/1 for SPT and 1/100, 1/10, and 1/1 for IDT. In our series, allergy to liraglutide was detected by IDT at the 1/10 and 1/1 dilutions, but not at 1/100. We would like to emphasize the variability of in vivo test findings, which may not confirm the diagnosis, thus leaving challenge testing as the gold standard.

Although several cases of allergy to liraglutide had previously been reported, only Carvallo et al [1] had performed allergy tests in a case of delayed hypersensitivity reaction with positive skin test results for liraglutide and negative results for semaglutide, proposing this as a possible alternative. Our series included 4 patients with a similar late local reaction at the injection site, 3 of whom also tolerated semaglutide. However, one of the patients also presented allergic sensitization to semaglutide. To our knowledge, we report is the first case of allergy to liraglutide with cross-reactivity to semaglutide. This finding demonstrates variability in the pattern of cross-reactivity between liraglutide and semaglutide, which must be explored on an individual basis. Therefore, referral to allergology is recommended if allergy to any of the human-GLP-1 RAs is suspected.

Ouellette et al [8] reported 2 cases of semaglutide-induced rash confirmed with histology. The authors did not perform allergy tests, and tolerance of alternatives was not verified. To our knowledge, no cases of immediate allergy to semaglutide have been described. In this article, we present the first case of anaphylaxis to oral semaglutide in a patient who tolerated liraglutide. We consider that further studies are needed to establish a clear pattern of cross-reactivity between GLP-1 RAs.

In conclusion, we present the first series of patients with hypersensitivity to human analogue GLP-1 RAs: 1 case of anaphylaxis due to semaglutide with tolerance of liraglutide, and 4 cases of local allergic reaction due to liraglutide, with tolerance of semaglutide in 3 of them.

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Conflicts of Interest

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