

Images in Allergy

First Confirmed Case of IgE-Mediated Hypersensitivity to Evolocumab with Cross-Reactivity to Alirocumab

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Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have become popular for aggressive lowering low-density lipoprotein cholesterol levels. Two Food and Drug Administration–approved PCSK9 inhibitors include evolucumab (Repatha) and alirocumab (Praluent), and adverse effects have reported to be rare.¹ We report a case of immediate-type hypersensitivity reaction to evolucumab with cross-reactivity to alirocumab.

A 61-year-old man with a history of hypertension, hyperlipidemia, and triple vessel disease was started on evolucumab subcutaneous injections every 2 weeks. Since his second evolucumab dose, he experienced recurrent episodes of urticaria almost immediately (within minutes) after each consecutive injection. The rash was initially localized around the injection site but progressively worsened after each injection, becoming generalized to the limbs and trunk (Figure 1, A and B). There was no angioedema or systemic symptoms, but the rash would persist for many days until gradual resolution. There was only partial relief despite regular oral antihistamines. The rash healed without any postinflammatory hyperpigmentation. Skin biopsy was declined by the patient. The patient did not have any history of chronic or spontaneous urticaria. Because of suspected adverse reaction to evolucumab, his cardiologist switched the patient to alirocumab subcutaneous injections every 4 weeks. However, he still experienced similar rashes immediately after every alirocumab injection (Figure 1, C).

The patient was referred to our allergy clinic for further evaluation. Basophil activation testing was attempted, but the patient had nonresponding basophils (Online Repository text at www.jaci-inpractice.org). The skin prick test (SPT) and intradermal test (IDT) with evolucumab and alirocumab were performed (Figure 2) according to European Network for Drug Allergy guidance.² SPT using undiluted concentration of evolucumab (140 mg/mL) and alirocumab (75 mg/mL) were both borderline at 3 mm. IDT to evolucumab and alirocumab

were performed at 1:100 and 1:10 dilutions, which were all unequivocally positive (evolucumab IDT both 1:100 and 1:10 = 15 mm wheal expansion; alirocumab IDT 1:100 = 5 mm wheal expansion, 1:10 = 10 mm wheal expansion). Possible latex hypersensitivity was excluded with negative SPT and specific IgE tests to latex. Evolucumab and alirocumab at undiluted and 1:10 dilutions were confirmed to be nonirritative for SPT and IDT in 10 healthy individuals, respectively. In view of his diagnostic skin test results, the patient was advised to avoid both drugs in the future. Desensitization was not attempted as the patient was switched to an alternative lipid-lowering therapy by his cardiologist.

We report the first case of IgE-mediated hypersensitivity reaction to both PCSK9 inhibitors. A suggestive clinical history along with concordant skin test results supports IgE-mediated hypersensitivity to both drugs. To the best of our knowledge, this is the first case of allergy to PCSK9 inhibitors with cross-reactivity by allergy testing. The extended half-life of evolucumab being 11 to 17 days may explain the protracted period of urticaria after each subcutaneous injection.³ In contrast to this case, one previous report claimed the absence of cross-reactivity between evolucumab and alirocumab, but no allergy tests were performed and the diagnosis remains speculative only.⁴ Cases with possible non-IgE-mediated reactions have also been reported.⁵

To date, this is also the first report of allergy skin testing for PCSK9 inhibitors. We established that an undiluted concentration and 1:10 dilution for evolucumab and alirocumab were nonirritative for SPT and IDT, respectively. This is similar to concentrations used for investigating immediate-type reactions with other biologics such as tumor necrosis factor- α antagonists.⁶ Further research is needed to better understand the mechanisms for hypersensitivity and cross-reactivity between the monoclonal antibodies. Development of *in vitro* tests may also aid in diagnosis and clinical management of these patients.

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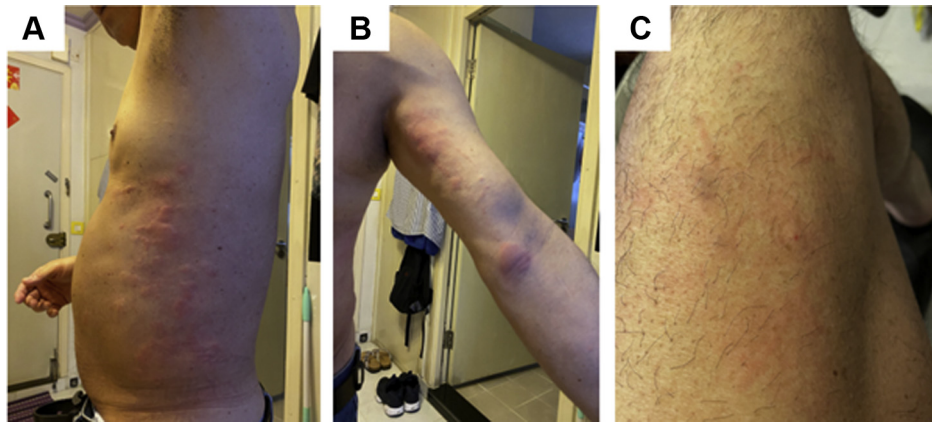


FIGURE 1. Diffuse urticarial rash immediately after subcutaneous injection of evolucumab (**A, B**) and at the injection site of alirocumab (**C**).

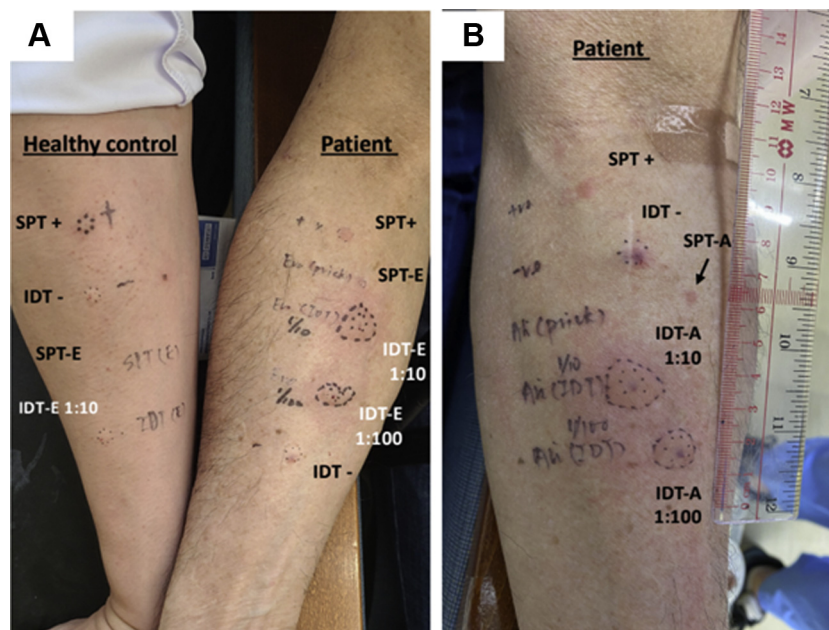


FIGURE 2. Skin prick test (SPT) and intradermal test (IDT) for evolucumab and alirocumab. **A**, Results of SPT and IDT to evolucumab on a healthy control (left) and patient (right). **B**, Results of SPT and IDT to alirocumab in the patient. *IDT-*, Negative control for IDT; *IDT-A*, IDT for alirocumab; *IDT-E*, IDT for evolucumab; *SPT+*, positive control for SPT; *SPT-A*, SPT for alirocumab; *SPT-E*, SPT for evolucumab.

ONLINE REPOSITORY**BASOPHIL ACTIVATION TEST AND
NONRESPONDING BASOPHILS**

Basophil activation testing was performed using the Flow-CAST reagent kit and CD203c reagent set (Buhlmann Laboratories AG, Schönenbuch, Switzerland) according to the manufacturer's instructions. Briefly, fresh EDTA blood samples were incubated with various drug dilutions in the stimulation buffer. All samples were processed within 4 hours. Both a monoclonal anti-FcεRI antibody and N-formyl-methionyl-leucyl-phenylalanine are used as positive control, whereas stimulation buffer without drugs is used as a negative control. After

stimulation, basophils in the blood samples are stained with the cell surface marker CCR3 and the activation markers CD63 and CD203c by specific fluorochrome-conjugated monoclonal antibodies from the reagents. Finally, the expression of CD63 and CD203c on CCR3 positive basophils were determined by flow cytometry (Beckman Coulter, Brea, Calif). The tested drug item would be considered positive when the percentage of cells with CD63 expression is >5% or the stimulation index of CD203c >3.21.

Approximately 5% to 10% of individuals have nonresponding basophils in which no upregulation of CD203c or CD63 occurs in response to IgE-mediated allergen stimulation. However, they may respond to non-IgE-mediated stimulants.