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HEALTH PROMOTION AND PREVENTIVE CARDIOLOGY

CASE REPORT: CLINICAL CASE

Life-Threatening Reaction to Lifesaving Medication

Stepwise Approach to Severe Adverse Reactions to PCSK-9 Monoclonal Antibodies

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ABSTRACT

Typical side effects of proprotein convertase subtilisin/kexin type 9 monoclonal antibodies including influenza-like illness and injection site reactions, are minor and well tolerated. This case, however, highlights a less common but severe reaction, indicating the need for clinicians to understand and manage potential rare side effects noted with biologics. (JACC Case Rep. 2024;29:102614) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 70-year-old half-Lebanese, half-Syrian gentleman with hyperlipidemia came to our preventive cardiology clinic for consultation after a severe reaction to evolocumab a year before presentation. In his third decade of life, baseline low-density lipoprotein cholesterol (LDL-C) was ~400 mg/dL and physical exam was remarkable for bilateral corneal arcus. Family history included siblings with high LDL-C on statins, paternal grandfather dying from myocardial infarction at 58 years, and daughter on atorvastatin 80 mg oral daily since 12 years of age. No family history of atopy noted. Dutch lipid score was 21 (definite familial hypercholesterolemia [FH]). Apart from a suboptimal diet (due to increased red meat intake), lifestyle was fairly optimal. Further risk assessment showed coronary artery calcium score of 3,350.77, mild-moderate carotid atherosclerosis, and lipoprotein(a) of 233.1 nmol/L. Diet was optimized and treatment with ezetimibe 10 mg, rosuvastatin 40 mg, and aspirin 81 mg daily was initiated, achieving a post-treatment LDL-C of 130 mg/dL. To further lower atherosclerotic cardiovascular disease risk,

TAKE-HOME MESSAGES

- Severe immune-mediated reactions can occur in the setting of biologics requiring an algorithmic approach to isolate the etiology and determine plausible future treatment options.
- In patients with severe lipid disorders, alternative treatments must be entertained and inclisiran is a reasonable option for those experiencing severe reactions to PCSK9 mAbs because it has a different mechanism of action.

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ABBREVIATIONS AND ACRONYMS

FH = familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

mAbs = monoclonal antibodies

PCSK9 = proprotein convertase subtilisin/kexin type 9

evolocumab 140 mg subcutaneous biweekly was added. Within 24 hours of the first dose, the patient reported flu-like symptoms that resolved with acetaminophen after 6 days. With the second dose, he was hospitalized after 3 days of nausea, vomiting, flu-like symptoms, and fevers (highest 102.9°F), which started 24 hours after administration (Figure 1).

DIFFERENTIAL DIAGNOSIS

Given the timing of the reaction relative to the administration of evolocumab, this was thought to be an immune-mediated adverse drug reaction or an allergic reaction. The hospital team caring for the patient ruled out underlying infection, malignancy, and heart failure during hospital admission.

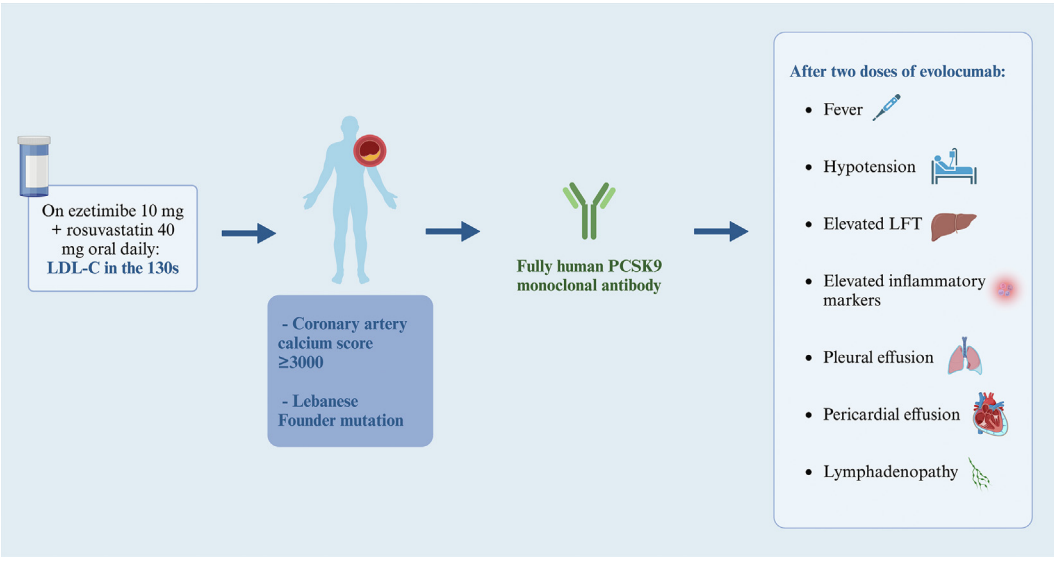
HOSPITAL COURSE: INVESTIGATIONS AND MANAGEMENT

On admission, vitals were as follows: blood pressure 126/80 mm Hg, respiratory rate 22 breaths/min, heart rate 106 beats/min, and fever of 100.7°F. Physical examination revealed mild distress and submandibular lymphadenopathy. Abnormal laboratory findings are shown in Table 1. Eosinophils were normal. Polyspecific direct Coombs test and blood cultures were negative. Urine cultures were positive for Morganella Morganani (10,000 to 50,000 colony-forming units). Pro-B-type natriuretic peptide was within range for patient's age and body mass index (27.98 kg/m^2). Our patient had pericardial and pleural effusions and lymphadenopathy on imaging (Table 2).

Considering the lab abnormalities, all home medications were stopped. The patient was discharged after 5 days. Although his bacteriuria was asymptomatic, in the setting of severe illness, he was treated with 4 days of oral antibiotics (cefuroxime and doxycycline). Pericarditis was treated with colchicine (for 1 month) and prednisone taper (for 4.5 months). Four months post-hospitalization, laboratory abnormalities normalized, and echocardiography showed resolution of pericardial effusion. Therefore, all lipid-lowering therapy excluding evolucomab was resumed.

One year after his discharge he was referred to our center for further management. In the 6 months leading up to presentation, the patient was on rosuvastatin 40 mg and ezetimibe 10 mg daily. The laboratory findings were as follows: total cholesterol 206 mg/dL, triglyceride 88 mg/dL, high-density lipoprotein 68 mg/dL, LDL-C 134 mg/dL, non-high-density lipoprotein 138 mg/dL, and high-sensitivity C-reactive protein 1.9 mg/dL. Because of the proximity of symptoms to administration of evolocumab

FIGURE 1 Summary of Case



Created with BioRender.com. LDL-C = low-density lipoprotein cholesterol; LFT = liver function test; PCSK9 = proprotein convertase subtilisin/kexin type 9.

TABLE 1 Abnormal Labs

Lab	Result	Reference Range
Hemoglobin	11.2	14.0-18.0 g/dL
Red blood cell count	3.95	4.60-6.20 M/cmm
Hematocrit	35.7	42.0%-52.0%
Ferritin	1332.0	30-400 ng/mL
Iron	44	59-158 μg/dL
Total iron binding capacity	180	250-450 μg/dL
Haptoglobin	623	43-212 mg/dL
Erythrocyte sedimentation rate	73	0-20 mm/h
Procalcitonin	0.17	0.00-0.08 ng/mL
Lactate	2.2	0.5-1.9 mmol/L
High-sensitivity C-reactive protein	12.1	<0.50 mg/dL
Pro-brain natriuretic peptide	557.9	≤125 pg/mL
Immunoglobulin A	489	70-320 mg/dL
Immunoglobulin G	1777	600-1,540 mg/dL
Immunoglobulin M	49	50-300 mg/dL
Aspartate transferase	221	≤40 U/L
Alanine transaminase	521	≤41 U/L
Alkaline phosphatase	287	40-129 U/L
Nuclear antibody with reflex to immunofluorescence assay	Positive	Negative
Anti-nuclear antibody pattern	Nuclear, Homogeneous	Negative

on both occasions, the most likely explanation was an adverse reaction. Given the extensive family history, baseline physical examination findings, and elevated LDL-C we suspected heterozygous FH and sent the patient for genetic testing.

Drug testing was conducted by an allergist/immunologist. Percutaneous skin prick testing with Duo-Tip II using a negative saline control (0 mm wheal and flare) and a positive histamine (1 mg/mL) control (5 mm wheal, 6 mm flare) was compared with latex and evolocumab. Both revealed a negative test with a 0 mm wheal and flare (Figure 2). In addition, patch testing in a Finn chamber to latex and evolocumab was negative at 72 hours. Genetic testing was positive for a pathogenic FH variant identified in the LDL-receptor gene, a Lebanese founder mutation. Given the subclinical atherosclerosis, elevated lipoprotein(a) and heterozygous FH, we initiated inclisiran, which has a different mechanism of action and not expected to pose risk for a similar reaction. The patient did not experience any symptoms and he is currently 1 month status post-inclisiran with no adverse effects and LDL-C of 67 mg/dL.

TABLE 2 Workup Performed

Electrocardiogram	• Normal sinus rhythm, no significant ST-T changes
Chest x-ray	• Probable left basilar atelectasis • No focal consolidation • Questionable mild cardiomegaly although possibly accentuated by technique
Transthoracic echocardiogram	• Overall left ventricular systolic function and size is normal • Global left ventricular ejection fraction ∼55%-60% • Normal left ventricular wall thickness • Impaired relaxation compatible with diastolic dysfunction (reversed E/A ratio) • Aortic valve: Moderately thickened trileaflet with decreased excursion, mild aortic sclerosis, no regurgitation • Mitral valve: Mild thickening of anterior and posterior leaflets, mobility is normal, trace mitral regurgitation • There is a moderate pericardial effusion, no evidence to suggest tamponade physiology
Multiaxial computed tomography scan of the chest without intravenous contrast	• Moderate-sized pericardial effusion measuring up to 2.5 cm in thickness with apparent mild thickening of the pericardium coupled with apparent loculation and some stranding in the pericardial fat • Small left-sided pleural effusion with mild thickening of the pleura-split like sign • Small right-sided pleural effusion with overlying atelectatic changes versus infiltrates • Multiple shotty mediastinal lymph nodes with a single prominent subcarinal lymph node measuring 2.1 × 3.4 cm • Severe coronary vascular calcifications and moderate calcification of the aortic root • 3.7 cm simple right upper renal pole cyst • Severe thoracic spine scoliosis
Abdominal ultrasound	• Heterogenous appearance of liver, fibrofatty changes • Small right pleural effusion • Simple right renal cyst • No evidence of acute cholecystitis
Esophagogastroduodenoscopy biopsy (due to enlarged carinal lymph node to rule out gastric malignancy)	• Normal esophagus, stomach, and proximal duodenum • No evidence of esophageal or gastric malignancy

FIGURE 2 Percutaneous Skin Test

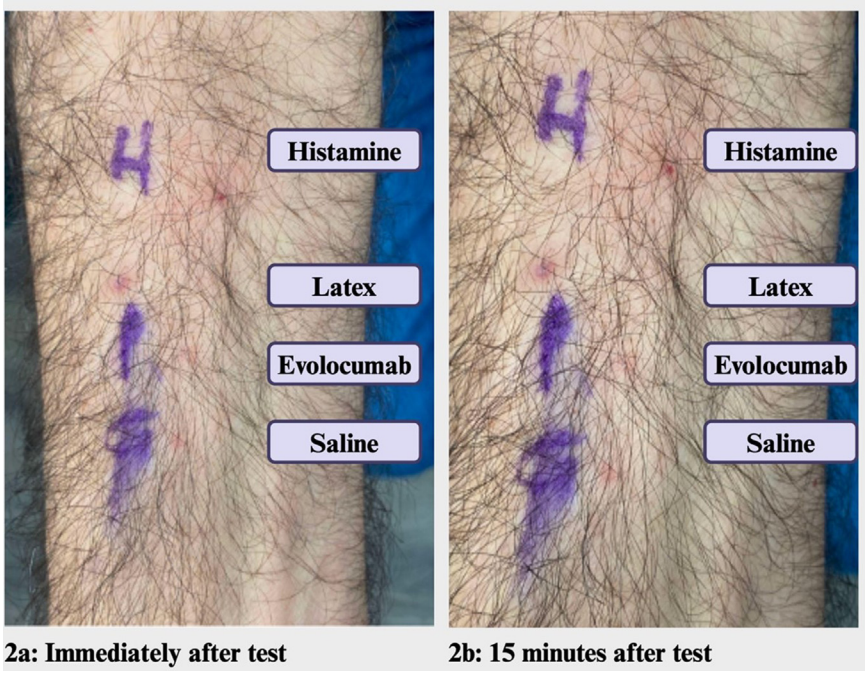


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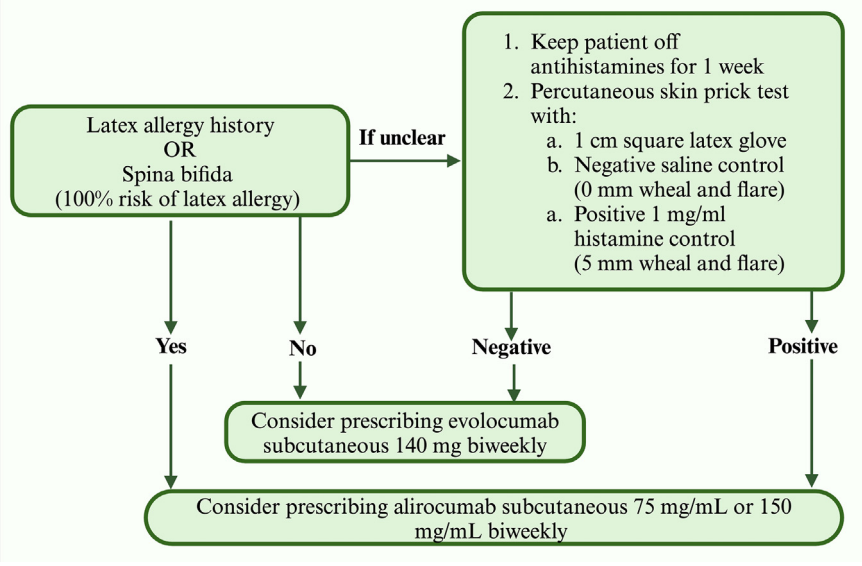
FIGURE 3 Proposed Algorithm for PCSK9 mAb Treatment



Created with BioRender.com. mAb = monoclonal antibody; PCSK9 = proprotein convertase subtilisin/kexin type 9.

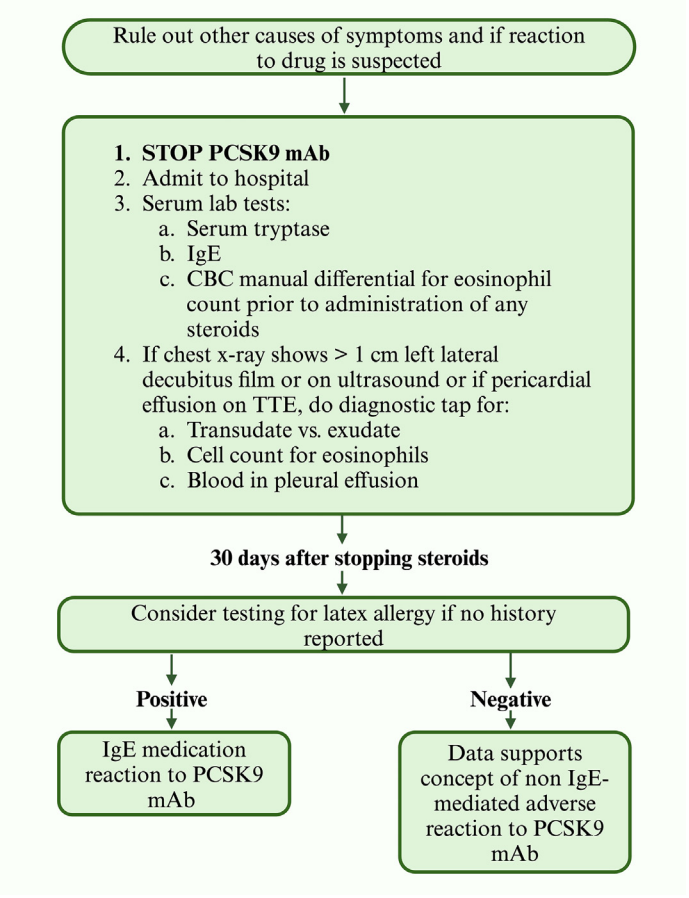
DISCUSSION

Proprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (mAbs), such as evolocumab and alirocumab, are extremely well-tolerated drugs with the common side effects of influenza-like illness and injection site reactions.[1] Unfortunately, our patient developed an uncommon, severe reaction after the second dose of evolocumab. A plausible reason is latex allergy. The needle cover of the autoinjector of evolocumab contains a derivative of latex, a potential risk factor for triggering Gell-Coombs Type I immediate or type IV delayed allergic reactions in latex-sensitive individuals.[2] It is not unreasonable to ask patients if they are latex sensitive before starting evolocumab. In patients who are unsure, pretreatment testing may be warranted (**Figure 3**). This is unlikely in this case, as the patient tested negative to the skin prick and patch test. The PCSK9 mAbs have polysorbate (evolocumab 0.06%-0.068% and alirocumab 0.0%-0.04% depending on dosage), which in rare cases can trigger allergic reactions.[2,3] However, this is also unlikely because a polysorbate sensitivity would have triggered a positive skin prick or patch test to evolocumab. It should be noted that inclisiran does not contain polysorbate.[4]

Although the patient could be developing antibodies to evolocumab, fully human mAbs like evolocumab and alirocumab are less likely to trigger immunogenicity. In the evolocumab arm of the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, new binding antibodies (not neutralizing) developed in 0.3% patients, which did not affect the safety or efficacy of drug.[5] Moreover, bococizumab, a humanized mAb with 3% murine sequence has increased immunogenicity. The SPIRE (Studies of PCSK9 Inhibition and the Reduction of vascular Events) trials, which studied bococizumab, were terminated early due to anti-drug antibody formation.[6] Currently, there are no commercial assays to measure anti-drug antibodies.

Most likely, this is an adverse T-cell-mediated cytokine alpha reaction to evolocumab that is non-immunoglobulin E dependent.[7] Eosinophils were not elevated during the time of acute reaction. If an IgE-mediated systemic reaction is present, serum tryptase levels and diagnostic pericardial and pleural tap would have helped in the diagnosis during the acute phase (**Figure 4**). It is essential to realize that an immune reaction like this one is a diagnosis of exclusion. However, conducting further testing 1 year post reaction would be futile.

FIGURE 4 Proposed Algorithm for Management of Acute Reaction to PCSK9 mAbs



Created with BioRender.com. CBC = complete blood count; IgE = immunoglobulin E; TTE = transthoracic echocardiogram; other abbreviations as in **Figure 3**.

FOLLOW-UP

Our patient is currently pending his second dose of inclisiran and will continue combination therapy. His children are also awaiting genetic testing.

CONCLUSIONS

The severity of the uncommon response experienced by this patient suggests the need for large-scale epidemiological studies to better understand and assess the prevalence and potential risk factors associated with adverse reactions to PCSK9-mAbs and other biologics, as these agents are now more commonly used for LDL-C optimization and multiple other disease states.

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