

# The Allergenic Role of the Drug Excipient in a Case of Allergy in Pcsk-9 Inhibitor

**Salihu Kushtrim<sup>1</sup> and Abdullahu Valon<sup>\*2</sup>**

<sup>1</sup>*Clinical Research Department, Cardiology, Icahn School of Medicine at Mount Sinai*

<sup>2</sup>*Clinic of Neurosurgery, University Clinical Center Kosovo*

**\*Corresponding author**

Abdullahu Valon, Clinic of Neurosurgery, University Clinical Center Kosovo

**Submitted:** 25 Sep 2020; **Accepted:** 01 Oct 2020; **Published:** 08 Oct 2020

**Abbreviations**

- CVD: Cardiovascular disease
- PCSK-9: Proprotein convertase subtilisin/kexin type 9
- LDL-R: Low-density lipoprotein receptor
- LDL: Low-density lipoprotein
- DM: Diabetes Mellitus
- HTN: Arterial hypertension
- COD: Coronary artery disease
- PCI: Percutaneous intervention
- ER: Emergency room
- BP: Blood Pressure
- Q2W: Every 2 weeks
- QD: once a day

**Introduction**

Hyperlipidemia is a well-established risk factor for the development of cardiovascular disease (CVD) [1]. Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors are novel drugs in use against hyperlipidemia [2]. The gene for this enzyme is encoded by the PCSK9 gene that is located on chromosome 1. This gene contains one of 27 loci associated with increased risk of coronary artery disease [3, 4]. PCSK-9 is expressed in many tissues and it has the ability to bind to low-density lipoprotein

receptor (LDL-R) and to reduce its number on the extracellular side of cell membranes. This results in a decreased ability of the cells to uptake low-density lipoprotein (LDL) and in this way, in a higher concentration of LDL in blood circulation [5]. Therefore, blocking PCSK-9 can lower blood LDL concentrations thus having an important medical importance [6]. We present a case of allergy on Alirocumab only, one of PCSK-9 inhibitors.

**Case Report**

A 67-year old patient with a previous medical history of hepatitis C, gastric ulcer, diabetes mellitus (DM), arterial hypertension (HTN), hyperlipidemia, coronary artery disease (CAD), with successful percutaneous intervention (PCI) with stent placement. On examination she was afebrile with sitting blood pressure of 117/68 mmHg, sitting heart beats of 94/min and regular, respiratory rate of 20 respirations per minute body mass index of 25.3 kg/m<sup>2</sup>. Physical exam revealed plantar tendon xanthomas, bilateral corneal arcus, Achilles tendon xanthomas which was suggestive of familial hypercholesterolemia. Lab workup is shown in tables 1, 2 and 3. A significant increase in LDL cholesterol was evident of the past 15 years, despite the use of Atorvastatin 80mg which was switched to Rosuvastatin 40 mg and Ezetimibe 10mg for past 4 years [7, 8].

**Table 1: Lipid Panel**

Component	Ref Range	12/05/16	12/10/16	07/06/17	28/03/18	07/11/19	19/06/20
Cholesterol	125-200 mg/dL	445	268	258	293	173	326
Triglycerides	35-135 mg/dL	118	97	174	155	121	164
HDL Cholesterol	>60 mg/dL	38	66	54	48	62	50
LDL Cholesterol	35-120 mg/dL	373	182	169	213	89	243
CHOL/HDL Ratio	<4.0	9.3	4.1	4.7	6.1	2.8	6.5
LDL/HDL Ratio	<2.5	7.8	2.8	3.1	4.4	1.4	4.8

It is evident that the LDL Cholesterol levels during these years had hit a base level. The need for another more potent therapy was evident. Therefore, a PCSK-9 Inhibitor – Alirocumab 150mg SC Q2W was prescribed on May/2018. After the first dose, an urticarial eruption had occurred within 6 hours and resolved within

24 hours. It was proved that this general urticarial eruption was caused by Alirocumab after the second dose of this medication 4 weeks later. We switched it to Evolocumab 150 mg SC Q2W. The allergic reaction did not occur with Evolocumab. The complete blood and platelet count is shown in tables 2 and 3.

**Table 2: Complete Blood Count**

Result	Value	Ref Range
White Blood Cell	4.6	4.5-11.0 x 10 <sup>3</sup> /uL
Red Blood Cell	4.35	3.70-5.50 x 10 <sup>6</sup> /uL
Hemoglobin	12.6	11.7-15 g/dL
Mean Corp. Volume	86.8	79.0-98.0 fl
Mean Corp. Hemoglobin	29.0	27.0-32.0 pg
Mean Corp. Hgb. Conc.	33.4	32.0-35.0 g/dL
Red Distrib. Width	12.9	11.5-15.0 %
Platelets	224	150-450 x10 <sup>3</sup> /uL
Mean PLT Volume	10.5	7.4-12.0 fl
Neutrophil %	49.7	40.0-78.0 %
Lymphocyte %	43.2	15.0-50.0 %
Monocyte %	5.1	2.0-11.0 %
Eosinophil %	1.6	0.0-5.0 %
Basophil %	0.4	0.0-5.0 %
Neutrophil #	2.3	1.9-8.0 x 10 <sup>3</sup> /uL
Lymphocyte #	2.0	1.0-4.5 x 10 <sup>3</sup> /uL
Monocyte #	0.2	0.2-1.0 x 10 <sup>3</sup> /uL
Eosinophil #	0.1	0.0-0.6 x 10 <sup>3</sup> /uL
Basophil #	0.0	0.0-0.2 x 10 <sup>3</sup> /uL

**Table 3. Comprehensive Metabolic Panel**

Result	Value	Reference Range
Hemoglobin A1C	7.7	4.0 – 6.0 %
Bilirubin Total	0.3	0.1 – 1.2 mg/dL
Calcium	9.6	8.5 – 10.5 mg/dL
Creatinine	0.63	0.50 – 1.10 mg/dL
Glucose	101	60 – 100 mg/dL
Alkaline Phosphatase	73	38 – 126 u/L
Potassium	4.9	3.5 – 5.2 mEq/L
Protein Total	7.0	6.0 – 8.3 g/dL
Sodium	139	135 – 145 mEq/L
AST (SGOT)	14	1-35 u/L
Urea Nitrogen	15	6-23 mg/dL
CO2 Total	26.9	22.0 – 32.0 mEq/L
ALT (SQPT)	10	1.45 U/l
EGFR	>60.00	MI/min/1.73m

## Management

The patient was started on Evolocumab 150mg SC Q2W and Rosuvastatin 40 mg + Ezetimibe 10 mg orally QD. Cardiologic therapy that consists of Ranolazine 500 mg tablet, Metoprolol 100 mg, Ramipril 5mg and Aspirin 81 mg was continued.

## Discussion

Treating LDL Cholesterol is key factor to prevent atherosclerosis, the target of LDL Cholesterol on population with cardiovascular risk factors is suggestive to be less than 50mg/dL.1 Currently there are two PCSK-9-i in the USA that are FDA approved. Although both are per se identical, the excipient of mixing the drugs is different which explains why one can cause allergic reactions compare to the other.9 Alirocumab is an aqueous solution that contains the excipients 6mM Histidine, 10% Sucrose , 0.01% Polysorbate 20 and water for injection10. We hypothesize that Histidine is what caused the allergic reaction, as it is known that Histidine is a biochemical precursor of Histamine, the main mediator of allergic reaction.11 In the other hand, the PCSK9 inhibitor Evolocumab contains as excipients proline, glacial acetic acid, polysorbate 80, sodium hydroxide and water for injection.12 As it is evident, the excipient Histidine is absent on Evolocumab, which did not trigger any allergic reaction. In general there was no change in LDL Cholesterol from switching from one to another PCSK9-i. In our case although we are using very aggressive therapy unfortunately we have not yet reach our target.

## Learning objective

Aliracumab and Evolocumab are very potent medications on treating dyslipidemia with very safe use, however allergic reactions can happen to either one and switching them is a safe way to avoid allergic reactions.

## References

1. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Jul 1; 63(25 Pt B):2889-934. [PubMed] [Ref list]
2. Rahul Chaudhary, Jalaj Garg, Neeraj Shah, and Andrew Sumner PCSK9 inhibitors: A new era of lipid lowering therapy World J Cardiol. 2017 Feb 26; 9(2): 76–91. PMID: PMC5329749 PMID: 28289523
3. (Seidah NG, Benjannet S, Wickham L, Marcinkiewicz J, Jasmin SB, Stifani S, Basak A, Prat A, Chretien M (February 2003). "The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation". Proc. Natl. Acad. Sci. U.S.A. 100 (3): 928–33. Bibcode:2003PNAS..100..928S. doi:10.1073/pnas.0335507100. PMC 298703. PMID 12552133.)
4. Mega JL, Stitzel NO, Smith JG, Chasman DI, Caulfield MJ, Devlin JJ, Nordio F, Hyde CL, Cannon CP, Sacks FM, Poulter NR, Sever PS, Ridker PM, Braunwald E, Melander O, Kathiresan S, Sabatine MS (June 2015). "Genetic risk, coronary heart disease events, and the clinical benefit of statin therapy: an analysis of primary and secondary prevention trials". Lancet. 385 (9984): 2264–71. doi:10.1016/S0140-6736(14)61730-X. PMC 4608367. PMID 25748612.
5. Weinreich M, Frishman WH (2014). "Antihyperlipidemic therapies targeting PCSK9". Cardiology in Review. 22 (3): 140–6. doi:10.1097/CRD.000000000000014. PMID 24407047.
6. Gearing ME (2015-05-18). "A potential new weapon against heart disease: PCSK9 inhibitors". Science in the News. Harvard University.
7. Jesús Millán, Xavier Pintó, Anna Muñoz, Manuel Zúñiga, Joan Rubiés-Prat, Luis Felipe Pallardo, Luis Masana, Alipio Mangas, Antonio Hernández-Mijares, Pedro González-Santos, Juan F Ascaso, and Juan Pedro-Botet Lipoprotein ratios: Physiological significance and clinical usefulness in cardiovascular prevention Vasc Health Risk Manag. 2009; 5: 757–765. PMID: PMC2747394 PMID: 19774217
8. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 ACC/AHA/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelinesexternal icon. Circulation. 2018;0:CIR.0000000000000625.
9. [https://www.ema.europa.eu/en/documents/product-information/praluent-epar-product-information\\_en.pdf#:~:text=Alirocumab%20is%20a%20human%20IgG1%20monoclonal%20antibody%20produced,full%20list%20of%20excipients%2C%20see%20section%206.1.%203](https://www.ema.europa.eu/en/documents/product-information/praluent-epar-product-information_en.pdf#:~:text=Alirocumab%20is%20a%20human%20IgG1%20monoclonal%20antibody%20produced,full%20list%20of%20excipients%2C%20see%20section%206.1.%203).
10. Center for drug evaluation and research, Application number 125559Orig1s000. Deputy division director for summary review for Praluent (Alirocumab).
11. Biochemistry, Histidine Aleeza T. Kessler; Avais Raja. Link: <https://www.ncbi.nlm.nih.gov/books/NBK430685/>
12. Summary of product Characteristics for Evolocumab – European Medicines Agency [www.ema.europa.eu](http://www.ema.europa.eu) > documents > product-information

**Copyright:** ©2020 Abdullahu Valon,. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.