Malays J Pathol 2022; 44(3): 527 – 531

CASE REPORT

Legacy effect of short-term alirocumab in familial hypercholesterolaemia: A case report

Muhammad Hanis MUHMAD HAMIDI[1]*, Yung-An CHUA[2], Noor Alicezah MOHD KASIM[2], Huzairi SANI[1], Hapizah MD NAWAWI[2], Sazzli Shahlan KASIM[1]

[1]Department of Cardiology, Faculty of Medicine, Universiti Teknologi MARA (UiTM), Malaysia; [2]Institute of Pathology Laboratory and Forensic Medicine (I-PPerForM) Universiti Teknologi MARA (UiTM), Malaysia.

Abstract

Homozygous familial hypercholesterolaemia (FH) is a rare genetic disorder with aberrantly high level of low-density lipoprotein cholesterol (LDL-C) requiring multiple combined aggressive lipid-lowering therapy to reduce the progression of atherosclerotic cardiovascular disease. Alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) has been approved for treatment of FH, which requires further lowering of LDL-C in addition to diet modification and maximally tolerated statin therapy. We report the response of short-term alirocumab treatment on a young patient with clinically and genetically confirmed FH, who suffered from acute coronary syndrome, and in particular, discussed the hypothesised legacy effect of PCSK9i. The patient was initially treated with a combination of high-intensity statin and ezetimibe for 12 weeks. Subsequently, alirocumab was added to the patient's lipid-lowering regime and he managed to attain guideline recommended LDL-C target within 10 weeks. However, alirocumab was stopped at week 54 due to financial constraint. Interestingly, despite cessation of PCSK9i therapy for a period of 30 weeks, the patient's LDL-C level rose slightly not returning to his baseline level.

Keywords: PCSK9 inhibitors, homozygous familial hypercholesterolaemia, acute coronary syndrome, legacy effect

INTRODUCTION

Familial hypercholesterolaemia (FH) is rare in Malaysia with a prevalence of 1 in 500 for Heterozygous FH and 1 in a million for Homozygous FH.[1] With a population of 32 million in Malaysia, it is estimated that 64,000 individuals may be affected and the majority of them are still undiagnosed.[2] Untreated FH is an important cause for premature coronary artery disease. Untreated patients have a 100 times increased risk of cardiovascular mortality resulting from acute coronary syndrome (ACS).[3] The treatment includes lipid-lowering agents such as statin, ezetimibe, bile acid sequestrants, nicotinic acid, and fibrates. Statins have been effective in reducing low-density lipoprotein cholesterol (LDL-C) level and improving cardiovascular mortality. FH patients with ACS are considered at a very high cardiovascular risk and are required to attain a guideline recommended LDL-C level below 1.8 mmol/L.[4] However, statin alone is not sufficient to achieve LDL-C target in patients with very high serum levels of LDL-C including homozygous FH patients even in combination with ezetimibe, a cholesterol absorption inhibitor.[5] Proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i) has been approved in 2015 by United States Food and Drug Administration for treatment of FH, which require further lowering of LDL-C in addition to diet modification and maximally tolerated statin therapy.[6] We report the response of short-term alirocumab treatment in a young patient with clinically and genetically confirmed FH, who suffered from ACS, and discuss in particular, the hypothesised legacy effect of PCSK9i. In the context of medicine, the 'legacy effect' is defined as a phenomenon of continuous beneficial effect of the intensive

**Address for correspondence*: Muhammad Hanis Muhmad Hamidi, Department of Cardiology, Faculty of Medicine, Universiti Teknologi Mara (UiTM) Sg Buloh Campus, Jalan Hospital, Sg Buloh, 47000 Selangor, Malaysia. Tel. No.: +60196998955. Email: *hanishamidi@gmail.com*

control on disease outcomes or complications even after a long duration of cessation of the intervention.[7]

CASE REPORT

The patient was a 25-year-old Malay gentleman, a non-smoker who presented with sudden onset of typical retrosternal chest pain while sleeping. He had a body mass index of 22kg/m^2 with tendon xanthomata and no corneal arcus. His electrocardiogram showed ST-segment elevation over the anterior leads. Coronary angiogram revealed critical left anterior descending artery stenosis and he underwent percutaneous coronary intervention successfully (Figure 1). Family history was significant for first degree relatives with ischaemic heart disease and hypercholesterolaemia (Figure 2). His initial serum lipids (in mmol/L) were as follows: total cholesterol (TC) 14.1, LDL-C 12.5, high-density lipoprotein cholesterol (HDL-C) 1.2 and triglyceride (TG) 1.0. He was clinically diagnosed with FH based on Japan FH diagnostic criteria, Simon Broome and FH Dutch Lipid Clinic criteria. Further molecular confirmation by targeted next-generation sequencing was carried out. TruSeq Custom Amplicon kit was used to prepare the DNA library. MiSeq sequencer (Illumina, CA, USA) was used to run the sequencing. The sequencing analysis confirmed that the patient carried a novel homozygous LDL receptor (LDLR) frameshift mutation (c.2553_2556delGATGinsTCT), which was predicted as a disease-causing variant by Mutation Taster.

He was treated with rosuvastatin 40 mg once daily and ezetimibe 10 mg once daily. At 12 weeks, his LDL-C reduced to 7.0 mmol/L. Alirocumab 75 mg every 2 weeks was added to his medication regime. His LDL-C continued to show marked reduction over time (Figure 3). At 40 weeks, his LDL-C was 1.6 mmol/L. Unfortunately, alirocumab was stopped due to financial constraint at week 54. His LDL-C rose to 3.0 mmol/L (87% increment) at week 56. Interestingly, his LDL-C remained at 3.3 mmol/L up to week 84 (30 weeks after stopping alirocumab) while being only on statin and ezetimibe. There were no major cardiovascular events or side effects to treatment reported during the follow up period.

DISCUSSION

PCSK9i have been demonstrated to be effective in lowering LDL-C in homozygous FH patients, as long as the patient is not carrying a null homozygous LDLR variant.[8,9] The identified frameshift variant c.2553_2556delGATGinsTCT results in loss of stop codon causing LDLR protein elongation at codon 851 - 862.[10] Since the mutation occurred in the last exon (exon 18) of LDLR, the variant is probably pathogenic but unlikely to cause the production of non-functional LDLR.[11] Thus, PCSK9i was still an

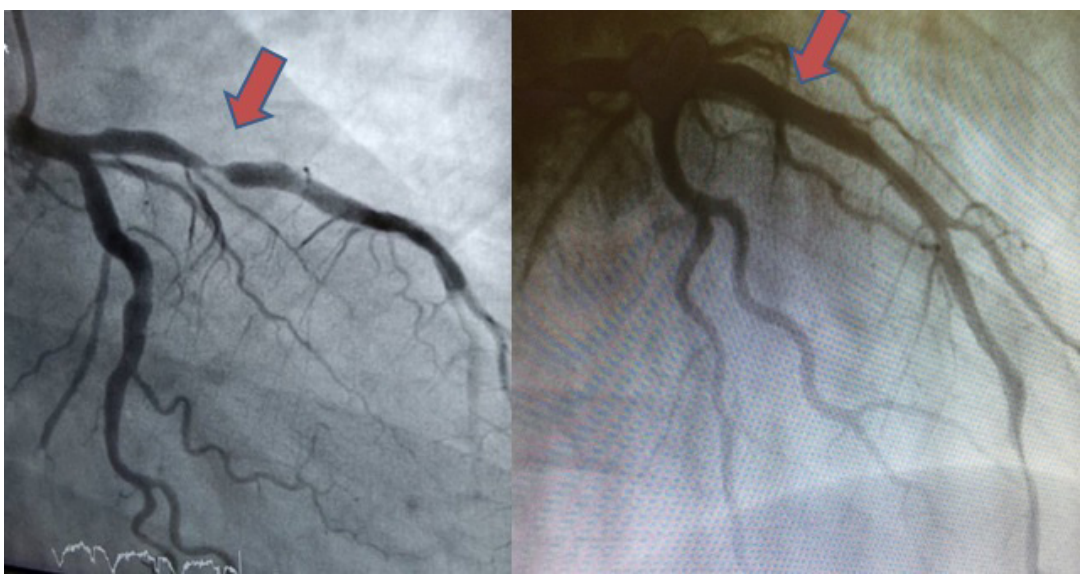

FIG. 1: Coronary angiogram (left) showing critical proximal left anterior descending artery stenosis and post percutaneous coronary intervention (right).

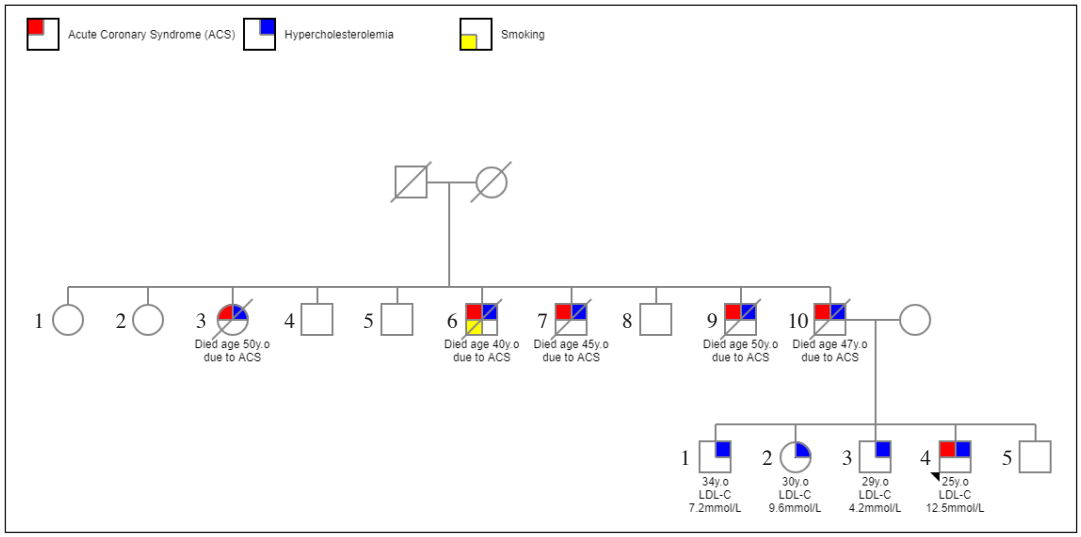

FIG. 2: Index patient pedigree chart.

effective treatment for this homozygous FH patient.

The combined multiple lipid-lowering regime in this patient was shown to effectively reduce LDL-C level up to 87% from the baseline, achieving the guideline target of less than 1.8 mmol/L. The initial use of combined rosuvastatin and ezetimibe had resulted in 50% reduction in LDL-C level over a 3-month period. This result is comparable to EXPLORER study, which looks at the efficacy of rosuvastatin 40 mg monotherapy or in combination with ezetimibe in patients with clinical evidence of atherosclerosis. There were significantly greater percentage in LDL-C reduction achieved with combination therapy than monotherapy (mean percentage decrease 69.8% vs 57.1%, p <0.001).[12] The addition of alirocumab at this stage resulted in a rapid reduction in LDL-C level of 50% over a 2-month period. Alirocumab was investigated in three phase II trials that included patients with background statin therapy or the combination of statin plus ezetimibe. These studies revealed a reduction of LDL-C levels beyond 70% in alirocumab treated patients.[13-15]

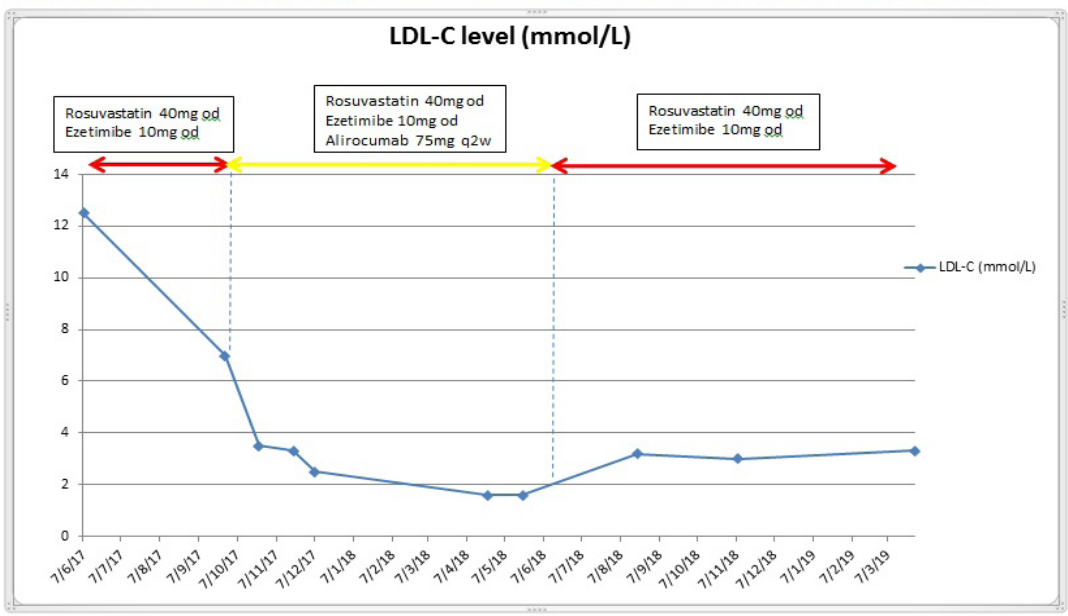

FIG. 3: Index patient LDL-C level (mmol/L) over time according to lipid modifying therapy regimens.

Despite stopping alirocumab for a period of 30 weeks, there was only a LDL-C level increment, which did not return to his baseline level as when treated with only statin and ezetimibe. The LDL-C level (in mmol/L) determined in this patient was estimated from the Friedewald equation where LDL-C equals to TC minus HDL-C minus TG/2.2. Thus, a reference change value (RCV) for a calculated LDL-C could not be determined. RCV for a direct LDL-C level measurement was estimated to be 19-25%.[16,17] Based on this RCV, the initial 87% increment of LDL-C level seen immediately after stopping PCK9i was significant. However, the subsequent 10% increment at week 84 was insignificant implying that LDL-C level remained at a plateau with statin and ezetimibe. This observation is similar to the ODYSSEY Outcome trial, which enrolled 18000 patients with recent ACS who were on high-intensity statin for at least 2 weeks with LDL-C of more than 1.8 mmol/L. At a mean follow-up of 3.3 years, there was a 15% relative risk reduction in the primary composite endpoint of coronary heart disease death, non-fatal myocardial infarction, ischaemic stroke or unstable angina requiring hospitalisation. Intention-to-treat analysis in that study, which included 14.2% of premature discontinuation in the treatment arm showed a non-significant slightly higher endpoint mean LDL-C of 1.7 mmol/L compared to on-treatment analysis of 1.4 mmol/L.[18]

Alirocumab (approximate molecular weight of 146 kDa), a human monoclonal antibody (IgG1) targets PCSK9 at a dose of 75–150 mg subcutaneously once every two weeks, has the onset of action in 4–6 hours and elimination half-life is usually 17–20 days. It undergoes proteolysis in many tissues to form polypeptides and amino acids.[19] This pharmacodynamics property alone would not explain the mechanism underlying the prolonged effect of lipid lowering beyond stopping the alirocumab as observed. The complex role of PCSK9 in cholesterol metabolism may be the underlying mechanism of this observed effect.[20] However, evidence to describe persistent lipid lowering effect beyond discontinuation of PCSK9i therapy is lacking.

Plaque regression and stabilisation are another benefit of lipid-lowering therapy especially statins. It follows a linear relation to the achieved LDL-C and is thought to play a significant role in persistent cardiovascular event reduction in post-trial follow-up.[21] Such a legacy effect was reported in the WOSCOPS study in which patients receiving 5 years of statin therapy continued to have significantly reduced mortality 15 years after the trial was completed.[22] PCSK9i offering a more robust and persistent LDL-C lowering could provide a more profound legacy effect, such that uninterrupted life-long therapy with PCSK9i may not be required. A shorter-term very aggressive LDL-C reduction therapy with PCSK9i and subsequent maintenance with statins and/or ezetimibe could be sufficient for long term reduction of LDL-C levels and adverse cardiovascular risk as proposed by Robinson et al.[21] However, testing this paradigm will require evidence from a range of sources, extended observation of clinical trial cohorts, new imaging studies based on profound LDL lowering and biomarker development.

CONCLUSION

Alirocumab effectively reduced LDL-C up to 87% and has a synergistic effect with statins and ezetimibe in this genetically confirmed homozygous FH patient with ACS. Despite the short-term use of PCSK9i, there was a prolonged effect of lipid lowering up to 30 weeks with no major adverse cardiovascular events in the long term. Thus, early intensive control of hypercholesterolaemia with PCSK9i have continuous beneficial effect even after a long cessation of this intervention.

Acknowledgement: The author(s) of this publication received research support and funding from 1) Institute of Research Management and Innovation, Universiti Teknologi MARA Malaysia (IRMI, UiTM) [Grant number: 100-RMI/PRI/16/6/2(2/2014)] and 2) UiTM MITRA Grant [Grant number: 600-IRMI/MYRA 5/3/MITRA (003/2017)-1].

Conflict of interest: The authors declared no conflict of interest.

REFERENCES

1. Khoo KL. Hereditary Hyperlipidemia in Malaysia: A historical Perspective of Six Decade of Research and Treatment. Med J Mal. 2014; 69: 57-9.
2. EAS Familial Hypercholesterolaemia Studies Collaboration: Vallejo-Vaz AJ, De Marco M, Stevens CAT, *et al*. Overview of the current status of familial hypercholesterolaemia care in over 60 countries - The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Atherosclerosis. 2018; 277:234-55.
3. Sawhney J, Prasad SR, Sharma M, *et al*. Prevalence of familial hypercholesterolemia in premature coro-

nary artery disease patients admitted to a tertiary care hospital in North India. Indian Heart J. 2019; 71: 118-22.
4. Baigent C, Blackwell L, Emberson J, *et al*. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010; 376: 1670-81.
5. Bandyopadhyay D, Ashish K, Hajra A, Qureshi A, Ghosh RK. Cardiovascular Outcomes of PCSK9 Inhibitors: With Special Emphasis on Its Effect beyond LDL-Cholesterol Lowering. J Lipids. 2018; 2018: 317920.
6. U.S. Food and Drug Administration. FDA approves Praluent to treat certain patients with high cholesterol [Press release]. 2015 July 24. Available from: www.fda.gov
7. Wander GS, Bansal M. Legacy effect in medicine-the expanding horizon. Indian Heart J. 2018; 70(6): 769-71.
8. Raal FJ, Honarpour N, Blom DJ, *et al*. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015; 385: 341-50.
9. Hartgers ML, Defesche JC, Langslet G, *et al*. Alirocumab efficacy in patients with double heterozygous, compound heterozygous, or homozygous familial hypercholesterolemia. J Clin Lipid. 2018; 12: 390-396.e398.
10. Truong PK, Lao TD, Le THA. The major molecular causes of familial hypercholesterolemia. Asian J Pharma Res Health Care. 2018; 10(2):60-8.
11. Al-Allaf FA, Coutelle C, Waddington SN, David AL, Harbottle R, Themis M. LDLR-Gene therapy for familial hypercholesterolaemia: problems, progress, and perspectives. Int Arch Med. 2010; 3(1):36.
12. Ballantyne CM, Weiss R, Moccetti T, *et al*. Efficacy and Safety of Rosuvastatin 40 mg Alone or in Combination With Ezetimibe in Patients at High Risk of Cardiovascular Disease (Results from the EXPLORER Study). Am J Cardiol. 2007; 99: 673-80.
13. Stein EA, Gipe D, Bergeron J, *et al*. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Lancet. 2012; 380: 29-36.
14. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med. 2012; 367: 1891-900.
15. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J Am Coll Cardiol. 2012; 59: 2344-53.
16. Okan D, Mustafa S. Use of reference change value for dyslipidemia follow up. J Turk Clin Biochem. 2019; 17(2):063-9.
17. McCormack JP, Holmes DT. Your results may vary: the imprecision of medical measurements. BMJ. 2020; 368 :m149.
18. Schwartz GG, Steg PG, Szarek M, *et al*. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018; 379: 2097-107.
19. Turner PL, Barry KA. Alirocumab (Praluent) for Treatment of Hyperlipidemia. Am Fam Physician. 2016; 94: 310-1.
20. Nozue T. Lipid Lowering Therapy and Circulating PCSK9 Concentration. J Atheroscler Thromb. 2017; 24(9):895-907.
21. Robinson JG, Heistad DD, Fox KA. Atherosclerosis stabilization with PCSK-9 inhibition: An evolving concept for cardiovascular prevention. Atherosclerosis. 2015; 243: 593-7.
22. Kashef MA, Giugliano G: Legacy effect of statins: 20-year follow up of the West of Scotland Coronary Prevention Study (WOSCOPS). Glob Cardiol Sci Pract. 2016; e201635-e201635.