Homozygous Familial Hypercholesterolaemia: A Case Report

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Introduction

Homozygous Familial Hypercholesterolaemia (HoFH) is a rare but life limiting condition characterised by severely elevated circulating concentrations of atherogenic low-density lipoprotein cholesterol (LDL-C) leading to premature cardiovascular disease (CVD). Despite maximal medical therapy with high dose statin, Ezetimibe and in some instances lipoprotein apheresis most patients with HoFH still have suboptimal LDL-C control[1]. The advent of pro-protein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) has revolutionised the management of familial hypercholesterolaemia (FH)[2].

Here we present a case of genetically confirmed HoFH in a 47-year-old gentleman. His treatment journey exemplifies the significant reduction in LDL-C which can be achieved with PCSK9i therapy.

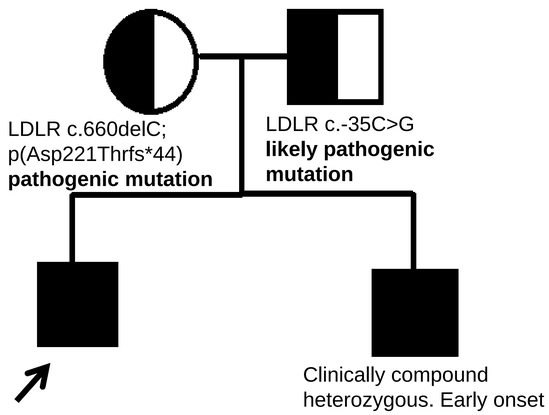
Case Description

Patient X presented age 11 with tendon xanthoma and a total cholesterol of 19 mmol/L. He was given a clinical diagnosis of HoFH and commenced on fortnightly non-selective plasma exchange (PEX). With their advent he was started on high dose statin therapy in the 1990s and later Ezetimibe in the 2007. Despite maximal dose therapy with Rosuvastatin 40mg and Ezetimibe 10mg his pre-PEX LDL-C remained poorly controlled at an average of 8.8 mmol/L.

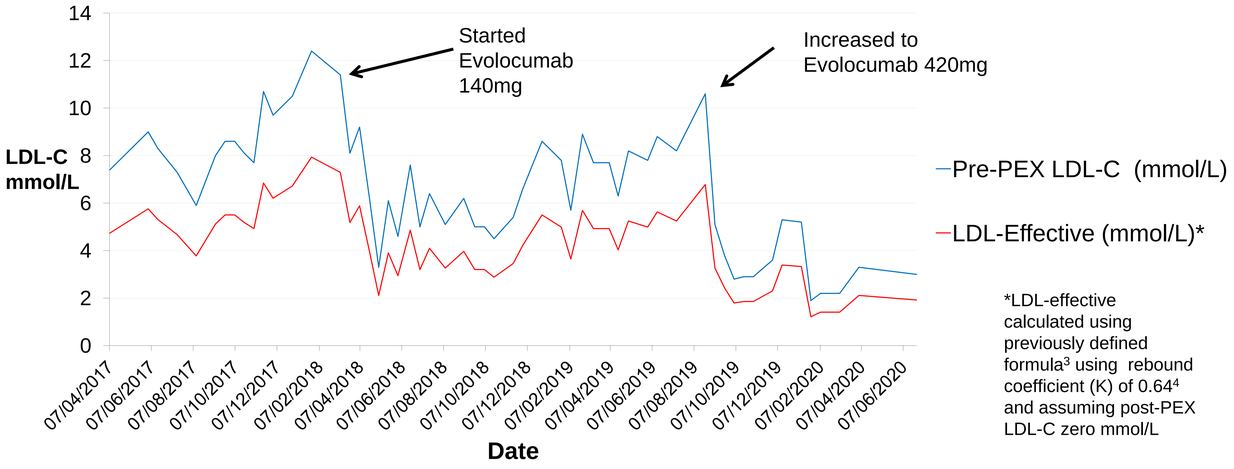
Genetic testing in 2012 confirmed the diagnosis of HoFH and showed 2 LDLR (low-density lipoprotein receptor) mutations. (LDLR c.660delC; p(Asp221Thrfs*44) **pathogenic mutation** and c.-35C>G **likely pathogenic mutation)**. Details of his known family history can be seen in the family tree opposite.

In 2015 an individual patient treatment request was made to the health board to make a case to start the PCSK9i Evolocumab. Fortnightly 140mg Evolocumab injections were initiated in April 2018 resulting in an average pre-PEX LDL-C of 6.5mmol/L (23% reduction). The dose was increased to 420mg fortnightly in September 2019 resulting in an average pre-PEX LDL-C of 3.5 mmol/L (60% reduction).The frequency of PEX was decreased to monthly and stopped all together in September 2020. His LDL-C remains stable around 3.5 mmol/L on a combination of Evolocumab 420mg fortnightly, Ezetimibe 10mg once daily (OD) and Rosuvastatin 40mg OD.

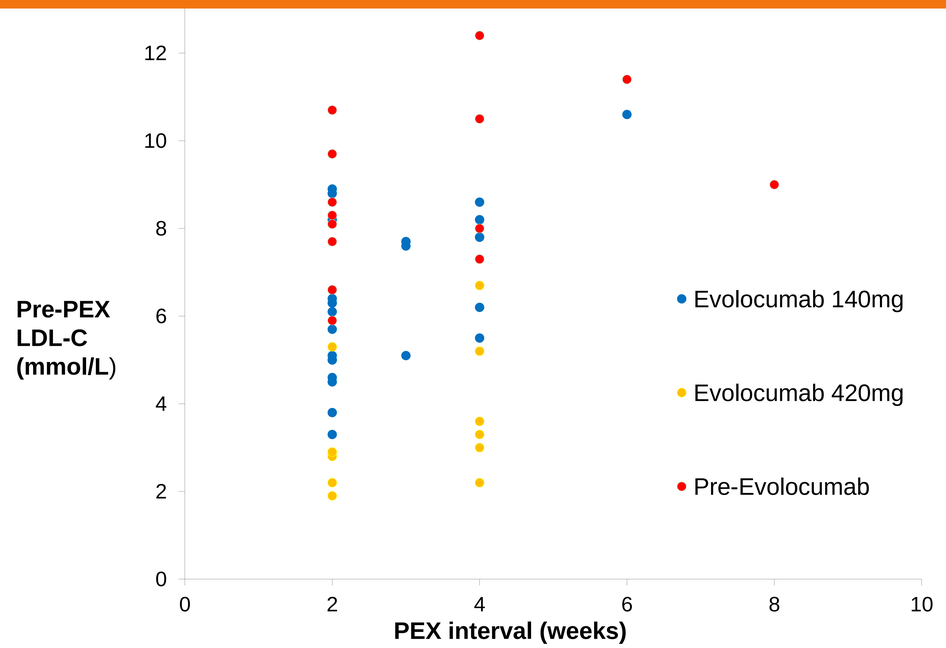
Family tree



Pre-PEX LDL-C and LDL-Effective over time



Pre-PEX LDL-C with varying PEX interval and Evolocumab dose



Discussion

This case demonstrates the profound effects PCSK9 inhibitors can have, not only on biochemistry and reducing cardiovascular risk, but also in improving quality of life. The percentage reduction in LDL-C achieved in patient X (-60%) with Evolocumab is considerably higher than the mean of other HoFH patients studied (- 25%) [5]. Response to Evolocumab in FH is determined by the underlying genotype and relies on at least some residual LDLR function[6]. Patients who are LDLR negative (as opposed to LDLR defective) do not respond to Evolocumab[6] and this can be understood by the underlying mechanism of action of the drug (up regulation of the LDLR to increase hepatic clearance of LDL-C). Therefore Patient X's combination of LDLR mutations must confer a relative preservation of LDLR function compared to many HoFH individuals. Evinacumab is an exciting new drug in development which lowers LDL-C without the need for residual LDLR function. It has been shown to lower cholesterol in LDLR negative HoFH patients who lack response to PCSK9i[7].

Inequalities in healthcare access are highlighted in this case. Patient X had to travel to another health board to attend both a specialist lipid clinic and for PEX sessions. Ideally he would have been treated with selective LDL-C apheresis[1] however this is not currently available in Scotland. There was a significant delay in starting Evolocumab due to difficulties in obtaining funding in patient X's health board. If he had lived in a different health board then he would have been able to start Evolocumab immediately. Evolocumab has allowed patient X to stop fortnightly PEX which has had a positive impacted on his freedom and quality of life.

Conclusion

PCSK9 inhibitors such as Evoloumab effectively lower LDL-C in HoFH patients who have some degree of residual LDLR activity. This reduction in LDL-C confers reduced cardiovascular risk and in certain cases can lead to the discontinuation of apheresis. Unfortunately inequalities in healthcare provision, dependent on geographical area, remain in the National Health Service.

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