EDITORIAL

Oman Medical Journal [2017], Vol. 32, No. 6: 447-448

New Treatments on the Horizon for Familial Hypercholesterolemia

Khalid Al-Rasadi* and Khalid Al-Waili

Department of Biochemistry, Sultan Qaboos University Hospital, Muscat, Oman

ARTICLE INFO

Article history:

Received: 29 October 2017

Accepted: 29 October 2017

Online:

DOI 10.5001/omj.2017.86

Familial hypercholesterolemia (FH) is a common genetic disorder with an estimated prevalence of heterozygous FH (HeFH) between 1 in 200–500 and homozygous FH (HoFH) between 1 in 160 000–300 000.[1,2] FH can be diagnosed using clinical criteria based on the presence of personal and first-degree family members with high cholesterol levels, premature coronary heart disease (CHD), and tendon xanthomas.[2–4] The most common mutations observed are in the genes for low-density lipoprotein receptor, apolipoprotein B, and proprotein convertase subtilisin/kexin type 9 (PCSK9).[5] Patients with FH are at 3.5- to 16-fold increased risk of developing CHD. CHD can present before the age of 20 in HoFH and before the age of 55 in HeFH if it is not diagnosed and managed early in life.[1,6,7] Moreover, patients with FH with plasma low-density lipoprotein cholesterol (LDL-C) of 4.9 mmol/L and FH mutation are at approximately three-fold greater CHD risk than patients with similarly high LDL-C levels but do not carry the mutation.[3] This can be explained by their cumulative lifelong exposure to high LDL-C due to the genetic defect.[8] Therefore, it is highly important to screen the family (cascade screening) of the individual confirmed to carry the FH mutation using plasma lipid levels and genetic testing, if available.[9,10] Cascade genetic screening has been shown to be a cost-effective method of diagnosing individuals with FH and starting early lipid-lowering therapies (LLTs).[11,12]

Patients with FH should be advised regarding physical activity, diet, and smoking.[13] Potent maximally tolerated statin doses should be started immediately in adults at the time of the diagnosis. For children, the recommended starting age is 8–10 years, usually with a low dose statin which is then up-titrated to a maximum tolerated dose by the age of 18. Statins can reduce LDL-C up to 50% in HeFH and up to 25% in HoFH.[2,14,15] Observational studies have shown that starting statins early (before the onset of CHD) can improve patient survival.[2] Despite the wide use of statins in patients with FH, many do not achieve the recommended targets.[16] It has been demonstrated that the addition of other LLTs will help patients achieve their recommended targets.[2] The combination of cholesterol absorption inhibitor, ezetimibe, with a statin can decrease LDL-C by 60–70%.[17] In patients with HoFH, treatment with weekly or biweekly lipoprotein apheresis should be considered, which can acutely reduce LDL-C further by 50–70%. The age threshold for starting lipoprotein apheresis may vary from country to country but is recommended as early as five years in children.[18,19] Novel therapies have been approved for use as an adjunctive treatment for HoFH. Lomitapide, a microsomal triglyceride transfer protein inhibitor, which is approved for use from 18 years of age, can reduce LDL-C up to 46%.[18,19] In addition, injectable mipomersen, an antisense RNA therapy is approved in the USA from 12 years old and can reduce LDL-C up to 25%.[17,19] Monoclonal antibodies to PCSK9 are considered the new horizon in the treatment of FH. In the Rutherford-2 study[20] in HeFH patients on evolocumab, LDL-C was reduced by 61–66% and in the Odyssey FH I and II studies with alirocumab, LDL-C was reduced by 60–68%.[21] Furthermore, the administration of evolocumab every two weeks has been shown to reduce plasma LDL-C by 26.3% from baseline in receptor defective HoFH patients.[22] No randomized clinical trials have been conducted in patients with FH due to ethical reasons, but the cardiovascular disease outcome benefits of LLTs have been extrapolated from non-FH patients.

*Corresponding author: ✉k.alrasadi@gmail.com

In summary, FH patients are at a greater risk for CHD and should be diagnosed early and treated intensively to reach very low LDL-C targets using available and optimal LLTs.

REFERENCES

1. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab 2012 Nov;97(11):3956-3964.
2. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013 Dec;34(45):3478-3490a.
3. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. Am J Epidemiol 2004 Sep;160(5):407-420.
4. Civeira F; International Panel on Management of Familial Hypercholesterolemia. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis 2004 Mar;173(1):55-68.
5. Rader DJ, Cohen J, Hobbs HH. Monogenic hypercholesterolemia: new insights in pathogenesis and treatment. J Clin Invest 2003 Jun;111(12):1795-1803.
6. Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ 2008 Nov;337:a2423.
7. Huijgen R, Vissers MN, Defesche JC, Lansberg PJ, Kastelein JJ, Hutten BA. Familial hypercholesterolemia: current treatment and advances in management. Expert Rev Cardiovasc Ther 2008 Apr;6(4):567-581.
8. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol 2016 Jun;67(22):2578-2589.
9. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al; National Lipid Association Expert Panel on Familial Hypercholesterolemia. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011 Jun;5(3)(Suppl):S1-S8.
10. Watts GF, Sullivan DR, Poplawski N, van Bockxmeer F, Hamilton-Craig I, Clifton PM, et al; Familial Hypercholesterolaemia Australasia Network Consensus Group (Australian Atherosclerosis Society). Familial hypercholesterolaemia: a model of care for Australasia. Atheroscler Suppl 2011 Oct;12(2):221-263.
11. Nherera L, Marks D, Minhas R, Thorogood M, Humphries SE. Probabilistic cost-effectiveness analysis of cascade screening for familial hypercholesterolaemia using alternative diagnostic and identification strategies. Heart 2011 Jul;97(14):1175-1181.
12. Nherera LM. Saving lives, saving families: the health, social and economic advantages of detecting and treating familial hypercholesterolaemia (FH). Economics Chapter: Estimating the benefits from treatment and increasing the implementation of cascading screening. [cited 2012 December 17]. Available from: http://heartuk.org.uk/files/uploads/documents/HUK_ HealthEconomics_FINAL2012_2702.pdf.
13. Broekhuizen K, Jelsma JG, van Poppel MN, Koppes LL, Brug J, van Mechelen W. Is the process of delivery of an individually tailored lifestyle intervention associated with improvements in LDL cholesterol and multiple lifestyle behaviours in people with familial hypercholesterolemia? BMC Public Health 2012 May;12:348.
14. Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, et al; European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J 2015 Sep;36(36):2425-2437.
15. Martin AC, Gidding SS, Wiegman A, Watts GF. Knowns and unknowns in the care of pediatric familial hypercholesterolemia. J Lipid Res 2017 Sep;58(9):1765-1776.
16. Varghese MJ. Familial hypercholesterolemia: A review. Ann Pediatr Cardiol 2014 May;7(2):107-117.
17. Hamilton-Craig I, Kostner K, Colquhoun D, Woodhouse S. Combination therapy of statin and ezetimibe for the treatment of familial hypercholesterolemia. Vasc Health Risk Manag 2010 Nov;6:1023-1037.
18. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, et al; European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014 Aug;35(32):2146-2157.
19. Al-Ashwal A, Alnouri F, Sabbour H, Al-Mahfouz A, Al-Sayed N, Razzaghy-Azar M, et al. Identification and Treatment of Patients with Homozygous Familial Hypercholesterolaemia: Information and Recommendations from a Middle East Advisory Panel. Curr Vasc Pharmacol 2015;13(6):759-770.
20. Raal FJ, Stein EA, Dufour R, Turner T, Civeira F, Burgess L, et al; RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet 2015 Jan;385(9965):331-340.
21. Kastelein JJ, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. Eur Heart J 2015 Nov;36(43):2996-3003.
22. Catapano AL, Pirillo A, Norata GD. Anti-PCSK9 antibodies for the treatment of heterozygous familial hypercholesterolemia: patient selection and perspectives. Vasc Health Risk Manag 2017 Sep;13:343-351.