Familial Hypercholesterolemia And The Use Of Novel Cholesterol Lowering Drugs; A Case Report

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CASE REPORT

AG is a 54–year-old woman who experienced a myocardial infarction at age 37 and was diagnosed with familial hypercholesterolemia(FH) at age 42. Because of cholesterol as high as 799 and intolerance to standard lipid medications, she was started on lipid apheresis treatments in 2005. Despite aggressive therapy including lipid apheresis, she has continued to suffer from progressive CAD with recurrent myocardial infarction and repeated placement of coronary stents (11 in total). Her lipid parameters in January 2014 were:

Total cholesterol	429
Triglycerides	229
HDL	49
LDL	335
Post apheresis LDL	79
Time-averaged LDL (LDL pre and post apheresis/2)	207.5

Based on these numbers and her progressive CAD despite lipid apheresis, the decision was made to add a novel cholesterol lowering agent (NCLA) to her regimen.

BACKGROUND

FH is a genetic disorder characterized by drastic elevations of plasma cholesterol. As the world's most common inherited potentially deadly disease, FH occurs in 1/500 to 1/300 individuals in the general population, with higher rates in certain subgroups due to founder effects.[1] As discussed in a recent article in this journal, 90% of patients with FH have a defective LDL receptor resulting in poor clearance of LDL from the serum.[2]

Basic research and improved technology have led to the development of new drugs to treat FH:

a. Two of these drugs, *mipomersen* and *lomitapide* (branded Kynamro and Juxtapid), have been approved for treatment of homozygous FH, but because of their complexity and expense they can only be prescribed by certified providers.[3]

b. Inhibitors of PCSK9 (proprotein convertase subtilisin/kexin type 9) comprise a third class of drugs that is being actively studied by several pharmaceutical companies but has not been approved yet by the FDA.

Lomitapide inhibits the microsomal transfer protein (MTP) responsible for assembly of the VLDL particle in the hepatocyte. With further metabolism VLDL eventually becomes LDL. Thus, *lomitapide* is highly effective at lowering LDL, and a mean reduction of 40% was noted in phase 3 studies. *Lomitapide* is an oral drug that must be accompanied by a strict low fat diet to avoid GI side effects.

Mipomersen uses antisense technology to inhibit the production of the apoB protein. ApoB is a necessary part of atherogenic lipoproteins including LDL, VLDL, and lipoprotein a. *Mipomersen* is an antisense oligonucleotide which binds to the apoB mRNA resulting in its destruction by ribonucleases. Phase 3 studies have shown a 28-36% reduction in LDL. *Mipomersen* is administered weekly by SQ injection.

PCSK9 is a protein that enhances degradation of the LDL receptor. Individuals with hypofunctioning PCSK9 have increased LDL receptor activity, low LDL cholesterols, and virtual absence of CAD. Patients with genetic mutations resulting in hyperfunctioning PCSK9 have very high LDL cholesterols and suffer from premature cardiovascular disease. Antibody-type inhibitors of PCSK9 have been developed by several companies, and early trials have shown a marked reduction in LDL.[4] LGH has participated in some of these early trials.

CLINICAL COURSE

AG was started on low dose lomitapide 5 mg/day. Lomitapide was chosen because unlike mipomersen it has been approved for use in combination with apheresis. Additionally, we felt that AG could comply with the dietary fat restriction necessary with lomitapide, and fortunately she has tolerated the drug well.

Her lipid numbers are now as follows:

Total cholesterol	236
Triglycerides	257
HDL	29
LDL	156
Post apheresis LDL	32
Time-averaged LDL	94

Thus her pre-apheresis LDL and her time-averaged LDL dropped by roughly 54%. We hope that this impressive response translates into clinical improvement.

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