NLA Symposium on Familial Hypercholesterolemia

Familial hypercholesterolemia: Current treatment options and patient selection for low-density lipoprotein apheresis

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KEYWORDS:
Familial hypercholesterolemia; LDL; Apheresis; Statins; Patient selection

Abstract: Options for treatment of severe heterozygous and homozygous familial hypercholesterolemia prior to the statin era were limited by significant side effects and morbidity. The advent of both the statins and technology for the selective removal of LDL via apheresis have revolutionized management but challenges remain.

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Current treatment options

It is useful to look at the past, before looking to the present and the future, to remind ourselves of what therapies were for severe heterozygous familial hypercholesterolemia (FH) and homozygous FH before the statin era. Partial ileal bypass, portocaval shunt, liver transplantation, gene therapy, and plasmapheresis—all of these options had considerable morbidity attached to them. The most acceptable one, plasmapheresis, has now been replaced with selective low-density lipoprotein (LDL) apheresis. Portocaval shunt reduced LDL by up to 40% in patients with homozygous FH, but there was the possibility of hepatic encephalopathy, and over the long term, pulmonary hypertension.

Partial ileal bypass is like a super bile acid sequestrant, preventing reabsorption of bile salts. It was the intervention in a large, randomized, controlled angiographic study, the Program on the Surgical Control of the Hyperlipidemias (POSCH) trial. LDL in this trial was lowered 38% by partial ileal bypass, and high-density lipoprotein (HDL) was increased 4%. The angiographic and clinical end points were positive in this study.

Another one of the older therapies, which is very much still a current therapy for FH, is the combination of niacin and bile acid sequestrants. This was the best therapy available before the statins. In a seminal study by Kuo et al published in 1981, LDL was reduced 45%, which was very similar to statin therapy, and there was a 22% increase in HDL. This finding, however, was with 10 g of bile acid sequestrant three times a day and the administration of 3 to 7 g of immediate-release niacin, that is, a labor of love and very difficult to accomplish.

The statin era changed everything for FH. Now with a simple small pill with virtually no side effects, a 40% to 54% LDL reduction can be achieved in heterozygous FH patients. Statins have also been tested extensively in children with FH. Lovastatin, simvastatin, atorvastatin, and rosvastatin have all been studied in adolescents and were determined to provide 27%, 41%, 40%, and 50% reductions in LDL, respectively. Statins were well tolerated, and no deleterious effect has been seen on development. Currently, there are studies on statins underway in prepubescent children as well.
None of the clinical event trials with statins was done specifically in an FH population. Therefore, what evidence do we have of benefit for these patients? The Simon Broome cohort in United Kingdom referred to the data on the relative risk of coronary heart disease (CHD) mortality for FH patients before and after widespread use of statins. Between 1980 and 1991, there was an eightfold increase in risk of CHD mortality for FH patients between the ages of 20 to 59 years relative to non-FH subjects the same age. Between 1992 and 1995, that changed to a fourfold increase. Even more cause for optimism are data from the Netherlands in which myocardial infarction (MI)-free survival in statin-treated FH patients is virtually indistinguishable from the general population.

Diet is always a critical component of therapy in FH patients. Statins are effective; their effectiveness is improved by appropriate diet. An important metabolic unit study performed early in the statin era makes this point. It used a double crossover design: high fat versus low fat, and lovastatin versus placebo. The high-fat diet was 43% of calories from fat with a high saturated content, and the low-fat diet was 25% calories from fat and high polyunsaturated content. Lovastatin was equally effective in the high- and the low-fat diets, providing 30% reduction in LDL in both. However, the LDL in the lovastatin-treated patients on the high-fat diet was 154 mg/dL, and the LDL in the lovastatin-treated subjects on the low-fat diet was 120 mg/dL, or 22% lower. This diet effect is similar to lower-dose statin effect and underscores the importance of diet in the management of FH.

Ezetimibe appears to be as effective in heterozygous FH as it is in the general population of hypercholesterolemic patients. Most of the studies in which ezetimibe was added onto statin therapy were not performed in FH populations, and therefore data are limited. In the Effect of Ezetimibe Plus Simvastatin Versus Simvastatin Alone on Atherosclerosis in the Carotid Artery (ENHANCE) trial, the addition of 10 mg of ezetimibe to 80 mg of simvastatin lowered LDL an additional 16%. If a similar incremental reduction occurs with rosuvastatin, LDL could be reduced 70% with the combination of this potent statin and ezetimibe in heterozygous FH patients.

Homozygous FH is much more resistant to medical therapy. In homozygous FH both LDL receptor alleles are affected so that there is little to no LDL receptor activity to be up-regulated. Do the statins work in homozygous FH? Initially, with the less potent statins, it was rather discouraging. However, with the advent of the more potent statins, a clinically meaningful effect began to be observed in homozygous FH. In a study of eight homozygous FH patients treated with simvastatin 80 mg and 160 mg, the 80-mg dose produced a 25% reduction in LDL and the 160-mg dose, 31%. Seven of the eight patients were receptor defective, but in one receptor-negative patient, there was a 30% reduction in LDL.

What is the mechanism of LDL reduction when there are no LDL receptors to up-regulate? In both heterozygous and homozygous FH, there is overproduction of apolipoprotein B (apoB), and intrahepatic cholesterol availability is a key regulator in the secretion of apoB containing lipoproteins. Statins, by inhibiting hepatic cholesterol synthesis, limit cholesterol availability and therefore secretion of apoB lipoproteins in the LDL receptor-negative patient.

Rosuvastatin has also been tested in homozygous FH in a very large study (n = 44) performed in South Africa and the United States. Rosuvastatin at an 80-mg dose produced a 21% reduction in LDL in all-comers. In the patients who were not on LDL apheresis or who had not had portocaval shunt, there was a 26% reduction. In a crossover to atorvastatin 80 mg, the results were very similar.

Ezetimibe is also useful in homozygous FH. In one study, patients receiving 40 mg of simvastatin or atorvastatin at baseline were then randomized into three groups in which (1) their statin dose was doubled from 40 mg to 80 mg, (2) ezetimibe was added to the 40-mg dose, or (3) their statin dose was doubled and ezetimibe was added. Doubling the statin gave the usual 7% additional LDL reduction; adding ezetimibe to the 40-mg dose provided a 13% additional LDL reduction, but doubling the statin and adding ezetimibe provided an additional 27% reduction.

Patient selection for LDL apheresis

LDL apheresis is the selective removal of all apoB-containing lipoproteins: LDL, very low-density lipoprotein, and lipoprotein (a). They are lowered acutely by 60% to 75%. There is little effect on other plasma components. This is where this technique is advantageous over the older plasmapheresis methodology. HDL is lowered minimally, and albumin and immunoglobulin are not affected. The time averaged lowering with LDL apheresis is approximately 50%, and there have been a number of small noncontrolled clinical trials in which the authors found improvement in cardiovascular disease.

Indications for LDL apheresis are best considered in the setting of the other guidelines. In the National Cholesterol Education Program Adult Treatment Panel III guidelines, the LDL goal for coronary patients is under 100 mg/dL. In the update in 2004 based on the Heart Protection Study and the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, the LDL goal for coronary patients with acute coronary syndromes or multiple risk factors, especially diabetes, metabolic syndrome, and severe and poorly controlled risk factors, was lowered to 70 mg/dL. In 2005, with publication of the TNT trial, a growing consensus would say that all coronary patients, including stable patients, should have their LDL lowered to 70 mg/dL.

So what are the indications for LDL apheresis? The Centers for Medicare and Medicaid Services established the guidelines in the late 1990s. To qualify for LDL apheresis as a coronary patient, one’s LDL has to be greater than 200 mg/dL after at least a 6-month trial of maximum tolerated medical therapy. In the absence of coronary
disease, LDL has to be greater than 300 mg/dL to qualify for LDL apheresis.

The following cases from the LDL apheresis unit at the Massachusetts General Hospital illustrate some of the complexities of decision making and of dealing with the guidelines set by CMS. The first patient is the only patient who was able to obtain insurance company coverage despite the fact that he did not meet the guidelines. He was 42 years old when he was referred for consideration for LDL apheresis. He had a very strong family history: his father had a carotid endarterectomy at 43 years and died of an MI at 53 years of age, and he had four paternal uncles who died of MI in their 40s and 50s. When the patient was 37, he had an angioplasty of a severe lesion in his right coronary artery. At 41, he had a stent to a new severe lesion in the circumflex, presenting with unstable angina. Also at 41, he had another stent in the right coronary, again presenting with an acute coronary syndrome. At 42, he had an atheroembolic renal infarct, and finally, still at age 42, he had a stent to another new high-grade lesion in the right coronary artery, again presenting with unstable angina.

Through all of this, he was on quadruple lipid therapy: atorvastatin 80 mg, ezetimibe, gemfibrozil, and intermediate release niacin. His lipids on this therapy were total cholesterol, 216 mg/dL; LDL cholesterol, 153 mg/dL; HDL cholesterol, 34 mg/dL; and triglycerides, 146 mg/dL. His LDL was 153 mg/dL, so he would not qualify according to the guidelines. Fortunately, his internist, cardiologist, and lipidologist all wrote very strongly worded letters to his insurance company, which agreed to cover apheresis for him. This was begun in the fall of 2006, almost four years ago as of this writing, and the patient has been stable, with his angina much improved. His pre/post lipids are as follows: total cholesterol, 220/100 mg/dL; LDL cholesterol, 143/29 mg/dL; HDL cholesterol, 33/32 mg/dL; and triglycerides, 227/191 mg/dL.

The second case is a common case in LDL apheresis units: the patient with multiple lipid medication intolerance. This is a woman with premature coronary disease, percutaneous intervention at the age of 61, more than 10 years ago, and subsequent interventions in 2004 and 2006. Her untreated lipids qualify her for LDL apheresis because her LDL was 215 mg/dL. Over the course of 10 years, she has been treated with multiple medications, all of which got her LDL well below the cutoff, but she experienced multiple side effects in the process. While taking atorvastatin, she developed generalized muscle weakness several months after starting, which persisted for 2 years until finally she saw a neurologist who stopped the atorvastatin. The symptoms improved in several weeks and were gone in a month. Simvastatin was started, the patient’s muscle weakness recurred, and simvastatin was stopped. Pravastatin was started, the patient’s muscle weakness recurred, and the pravastatin was stopped. Then a new approach, niacin and bile acid sequestrant, was tried in 2004, which caused intolerable constipation and flushing, so they were stopped. Ezetimibe was tried in 2006 but caused abdominal distress, so it was stopped. The patient was tried on the every-other-day rosvastatin, achieved good results, but again, the muscle weakness recurred. For the better part of 10 years her LDL cholesterol was greater than 200 mg/dL. She began apheresis in 2007 and has been doing very well.

The final patient is not on apheresis. She does not qualify by strict criteria. This is a young woman, age 46, who said she has been tested positive for the Ashkenazi FH gene in Israel. No one on her father’s side of the family has lived past 55 years of age; most had their first cardiac events in their 40s, including an aunt. She does not have clinical coronary disease, so technically she is primary prevention, but her coronary calcium score was 80th percentile for her age and sex, and she has a 50% stenosis in her left internal carotid artery. Therefore, this is a very nervous young woman who also, like the previous patient, has gone through years and years of undergoing therapies for her LDL and being intolerant to them. Her untreated lipids are as follows: total cholesterol, 374 mg/dL; LDL, 320 mg/dL; HDL, 37 mg/dL; triglycerides, 83 mg/dL; and lipoprotein (a), 45 mg/dL. She was finally able to tolerate 40 mg of fluvastatin, but her LDL is still 241 mg/dL. Is she primary prevention or is she secondary? Does she qualify? Should she be apheresed? Although the guidelines sound simple, the reality is another matter.

Financial disclosures

Grant/research support for Dr. Hemphill comes from ISIS and the Genzyme Corporation.

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