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Clinical Lipidology Roundtable Discussion

JCL Roundtable: Drug treatment of severe forms of familial hypercholesterolemia

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Abstract: Clinical lipidologists are often asked to manage patients with severely elevated low-density lipoprotein cholesterol (LDL-C) and other apolipoprotein B-containing lipoproteins. Statins at maximum doses and in combination with other drugs may not achieve adequate reductions in LDL-C in such patients. The most dramatic elevations are usually in patients with genetic abnormalities in the LDL receptor gene on both chromosome pairs. LDL-C values well in excess of 400 mg/dL are not fully responsive to current treatments. In the past few months, the Food and Drug Administration has approved 2 new drugs for special use in such patients; these are mipomersen and lomitapide. During the National Lipid Association's Scientific Sessions, 2 highly experienced clinician scientists who have completed research studies with these agents agreed to answer questions pertinent to the prescription use of these agents. These scientists are Dr Anne Goldberg from Washington University in St. Louis and Dr Daniel Rader from the University of Pennsylvania.

Dr. Brown: Dr. Goldberg, what are your initial steps in developing a plan for therapy for a patient with severe hypercholesterolemia who has not responded to treatment with statins.

Dr. Goldberg: Typically, I would take a detailed family history to establish the genetic nature of the problem. I would also make sure that there are no secondary causes of hypercholesterolemia such as hypothyroidism and nephrotic syndrome. I would then consider severe familial hypercholesterolemia (FH) as a cause.

Dr. Rader: I completely agree. However, I do think that it is worth considering certain unusual diagnoses as well. For example, a patient with severe hypercholesterolemia who does not respond well to conventional therapy and who has no family history of hypercholesterolemia is when I would think about the diagnosis of sitosterolemia. It is critically important even though it is rare because that diagnosis has unique therapeutic implications. However, most of our patients with severe hypercholesterolemia have 1 or more mutations in the genes that cause autosomal dominant hypercholesterolemia.

Dr. Goldberg: If patients have typical tendon xanthomas, I would definitely consider FH. I have not seen a patient with sitosterolemia, but he or she also may have tendon xanthomas.

Dr. Rader: It is always important to exclude secondary causes of hypercholesterolemia.

Dr. Brown: What would secondary causes be?

Dr. Goldberg: These include hypothyroidism and nephrotic syndrome, both of which can also exacerbate genetic dyslipidemias. Then I look at medications such

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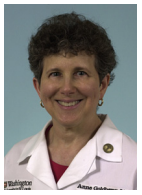
Dr. Brown

cyclosporine and some of the antipsychotic agents. In addition, cholestatic liver disease causes elevated lipoprotein X, which can produce extremely high cholesterol levels and would be measured as low-density lipoprotein cholesterol (LDL-C) in a conventional assay.

Dr. Brown: I suggest we focus now on the patient with no functional LDL receptors. What can clinicians offer the patient with FH who has homozygous or combined heterozygous hypercholesterolemia?


Dr. Goldberg

Dr. Goldberg: Many homozygous patients are combined heterozygotes who have some residual function of their LDL receptors. The most severely affected patients have few or no LDL receptors and do not respond well to lipid-lowering medications. All of them, even if they do not respond much, require high-dose statins plus ezetimibe, bile acid sequestrants, or niacin. For these patients, the usual therapy is the addition of LDL apheresis to the drug therapy. However, we now have 2 additional medications for treating these severely affected patients. These medications are mipomersen and lomitapide.

Dr. Brown: Some unusual patients present with extremely high LDL, including children with LDL-C levels that exceed 800 or 900 mg/dL who do respond to high-dose statins with marked reductions of 50% to 75%. Some patients have LDL receptors that have low binding affinity for the apolipoprotein B (apoB) moiety, and these patients prove more responsive. What are your thoughts about such unusual responses?

Dr. Goldberg: I have seen patients with bad LDL-C levels who do have some response to statins and then have remarkable additional improvement with ezetimibe, which suggests they have high intestinal absorption of cholesterol.


Dr. Rader

Dr. Rader: I agree that using the designator of homozygous FH is generally based on a clinical diagnosis, but this disorder is heterogeneous for the molecular causes. For management, the approach is certainly high-dose statin therapy and adding additional classes of drugs, including ezetimibe and bile acid sequestrants. Historically, if the patients are still hypercholesterolemic, consideration of LDL apheresis has been appropriate. Now these 2 new medications are a consideration as well.

Dr. Brown: Do you manage children in any different way? LDL-C in the 400 to 1000 mg/dL range is usually associated with atherosclerosis even in children younger than 5 years.

Dr. Goldberg: As stated by Dr Rader, I would initially treat with a high-dose statin and then a second and third drug, most commonly ezetimibe and a bile acid sequestrant. Starting apheresis depends on the age and size of the child. A port system is needed for vascular access. Before the availability of LDL apheresis, plasmapheresis was done in children, starting at about 9 years of age.

Dr. Brown: I find it both intriguing and rewarding to witness the growing prevalence of patients who started with these extremely high LDL-C values and are now living into their fifth and sixth decade of life. This was unheard of 40 years ago, before the statin era. So there may be some benefit from statin therapy even in persons without satisfactory LDL-C reduction. Statin-treated patients do seem to be living longer even though the cholesterol level may remain well above 300 to 400 mg/dL. Lipoprotein apheresis evidently extends life in combination with drug therapy, but this is costly and is not always available to a given patient.

What has been your customary combination of various therapeutic options in such patients? Do you always use statins plus ezetimibe plus bile acid sequestrants?

Dr. Rader: The data are that these 3 classes of drugs are additive in terms of their ability to lower LDL. Certainly, that is my experience, so I think if patients on high-dose statin and ezetimibe are still not at target levels, it would be perfectly appropriate to add a bile acid sequestrant as the next step.

Dr. Brown: In my practice, I had a 2-year-old present with a baseline LDL-C of 900 mg/dL. With titration, he tolerated maximum statin dosing, rosuvastatin 40 mg/day with ezetimibe (10 mg/day) and colesevelam (3.65 g/day), for several years with no adverse effects. However, he had only about a 15% reduction in LDL-C level, and he was placed on lipopheresis at 6 years of age. This child was small and was thought not to be a candidate for lipopheresis until he had grown physically and mentally to a sufficient level so this procedure could be tolerated.

Dr. Rader: We should at least mention that occasionally young children with severe homozygous FH are referred for liver transplantation.

Dr. Brown: The initial experience with liver transplantation was problematic in this condition. However, with much better immunosuppression, hepatic transplantation is now being done again in some cases. Severe homozygous FH is a lethal disease, and such heroic procedures can be justified in certain patients.

Dr. Rader: I want to remind physicians that the Food and Drug Administration (FDA) guidelines for LDL apheresis are for patients to be on the highest tolerated drug therapy and to have LDL-C $>$ 300 mg/dL. In the case of documented cardiovascular disease the patient should have LDL $>$ 200 mg/dL and be on maximally tolerated therapy. One of the questions is whether that LDL-C threshold should be lowered further in such patients. I have personally referred patients for LDL apheresis with LDL-C of approximately 170 mg/dL on maximally tolerated therapy and with progressive vascular disease; the LDL apheresis was reimbursed by insurance.

Dr. Brown: Coronary disease is not required to treat a patient with LDL-C $>$ 400 mg/dL. The patient deserves therapy; we know the consequences of failing to treat that condition.