Lipid Therapy

Lipid management: past, present, and future.

BY EMILE R. MOHLER III, MD

In the past, lipid therapy utilized medications for which the exact mechanisms of action were not known.The significant breakthrough in lipid therapy came with the discovery of HMG CoA reductase, which is the rate-limiting enzyme in cholesterol biosynthesis and is situated in hepatocytes. Cholesterol is made in other parts of the body as well, of course, but the control of cholesterol levels is mainly orchestrated by the liver (Figure 1). HMG CoA reductase works through control by a low-density lipoprotein (LDL) receptor on the hepatocyte surface. The result is that the LDL receptor, when cholesterol is bound to it, actually downregulates HMG CoA reductase, essentially creating a negative feedback loop.

If there is an abundance of cholesterol, the liver does not need to create as much. Patients who have mutations in this LDL receptor can have a high LDL cholesterol level (familial hypercholesterolemia). These patients do not have the negative feedback because the LDL cholesterol does not bind very well to the abnormal LDL receptor. The HMG CoA reductase continues to work so that cholesterol is made by the cells to a high degree, and the LDL receptor does not work to remove cholesterol. The net effect is higher circulating levels of LDL cholesterol, which then can deposit in the vascular wall and cause the development of atherosclerosis.

Statins (HMG CoA reductase inhibitors) were developed to block cholesterol biosynthesis, which can lead to a dramatic reduction of LDL cholesterol (40% to 50% or more). Once it was known that statins worked to lower cholesterol, they began to be tested in larger populations to determine if there was a reduction of cardiovascular events.

Several angiographically based coronary artery trials were initiated in which patients were administered a statin to determine whether there was a reduced amount of plaque in the coronary arteries. The results were not as encouraging as was hoped because the plaque size at 1-year follow-up had not changed significantly. However, those patients who were randomized in the statin treatment group did better than those in the placebo group. There was a reduction of cardiovascular events in the statin treatment group even after only a year of treatment. It appeared that statin therapy did not shrink the plaque significantly, at least on angiography, but probably stabilized the plaque and reduced cardiovascular events in that manner. However, we do know now from intravascular ultrasound studies that the plaque morphology changes with statins. Some recent trials have been released that have shown that effect.

ANTI-INFLAMMATORY EFFECTS

Although statins were initially developed to lower cholesterol, it turns out they seem to have what is termed *pleiotrophic* effects, whereby they do more than simply lower cholesterol—they may actually provide an anti-inflammatory effect. It is also believed that the anti-inflammatory effect may be responsible for statins' plaque stability. One of the mechanisms by which we measure inflammation is with a protein called *C-reactive protein* (CRP). An elevated high-sensitivity CRP level indicates a higher risk of cardiovascular events. It is unknown, however, if patients with an elevated CRP are treated with statins in a prospective fashion, whether they will have reduced cardiovascular events. The JUPITER trial evaluates whether patients who

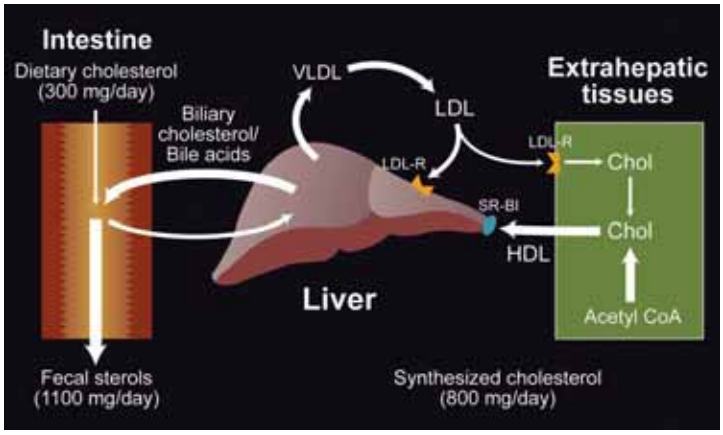

Figure 1. Diagrammatic representation of the liver control of cholesterol metabolism.

have relatively low cholesterol (LDL <130) with high sensitivity CRP >2 mg/L and are randomized to placebo or a statin, will have a reduction in cardiovascular events, despite having a higher CRP level.

CALCIFICATION

Vascular calcification is a complex area of study. There are questions regarding the impact of calcification in the arteries and whether it contributes to plaque problems. Interventional specialists deplore calcium because it makes it difficult to perform angioplasty and stenting, especially in ostial lesions, but it is unclear if calcium is good, bad, or just ugly in plaques. There are some data to suggest that if there is a high degree of calcium but very little lipid, the plaque is actually more stable than if there were a high degree of lipid and inflammatory cells with very little calcium.[1] The question then becomes, is it important to reduce calcification? We believe it is important in heart valves, but it is unclear whether reducing calcification is useful in atherosclerotic arteries. Calcium, however, appears to be a sentinel, so if you administer a statin and reduce the amount of calcium, it may reduce the amount of plaque in the system.

The pathology of calcification is now being elucidated, and we are currently learning more about the effects of statins on calcification.

INDICATIONS

The PREVENT Trial and TNT indicate that lower LDL cholesterol is better. The question now is, how low do we need to go in reducing LDL before we really halt the progression of disease? The most recent data suggest that patients with known atherosclerosis or a risk equivalent, such as diabetes or peripheral arterial disease, really benefit by having the LDL closer to 70 mg/dL rather than 100 mg/dL. That means choosing more aggressive therapy by giving patients a higher dose of statin. For example, instead of using 10 mg of atorvastatin, you might use 40 mg or 80 mg, or start with a potent statin such as rosuvastatin. In addition, in order to attain this goal, you will have to add another agent, such as ezetimibe, to the medical regimen. This drug blocks cholesterol absorption via a receptor on the enterocyte rather than in the liver.

The non-HDL cholesterol level, simply calculated by subtracting the HDL from total cholesterol, should always be measured when triglycerides are >150 mg/dL. This number, usually 30 mg/dL greater than the LDL cholesterol, assesses the amount of circulating cholesterol in lipoproteins other than LDL, such as very low-density lipoprotein. A non-HDL cholesterol number of 100 mg/dL is analogous to an LDL of 70 mg/dL and is the goal for those with metabolic syndrome or diabetes mellitus and elevated triglycerides. Always consider the non-HDL cholesterol when determining therapeutic effectiveness of lipid-modifying drugs, especially when triglycerides are elevated. After LDL is treated, the HDL and triglyceride should not be forgotten as they are also targets for therapy as identified on NCEP III guidelines. Niacin is considered the most efficacious in raising HDL whereas fibrates such as fenofibrate are most efficacious for lowering triglycerides.

CONTRAINDICATIONS

There are two concerns with using statin therapy. The first is liver-enzyme elevation, but this is usually relatively mild and reversible by stopping the statin. The second problem is muscle ache, which may be just an annoyance, or in rare cases, may develop into a condition called rhabdomyolysis. It may result when statin drugs are used with other drugs that are predisposed to that problem.

Physicians should be aware of drugs that interact with statins. For example, certain antibiotics in the mycin group (eg, erythromycin) interact with some of the statins. However, some of them do not interact with the statins, as not all statins have the same pharmacodynamics.

FUTURE THERAPIES

I believe the future of lipid therapy will involve answering whether we can regress plaque rapidly using statins. The REVERSAL trial indicates that it might be possible to enhance reverse cholesterol transport. The Framingham study taught us that low HDL indicates a high risk of a heart attack. The question now is, can HDL-like proteins, or *HDL mimetics*, or other molecules that enhance cholesterol efflux be used to regress plaque over a short period of time (ie, within a year or two) by either intravenous or oral administration.

CONCLUSION

The lipid hypothesis has been proven: reduction in LDL cholesterol results in a reduction of cardiovascular events. The recent data suggest that the LDL goal should be closer to 70 mg/dL for patients with known atherosclerotic diseases that is already manifest, or in risk equivalence, such as patients with diabetes mellitus or peripheral arterial disease. On the horizon is the manipulation of HDL in order to regress cholesterol plaques. It certainly is important to aggressively modify lipids in patients who have undergone a percutaneous or surgical procedure for atherosclerosis. ■

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1. Mohler ER III. Vascular calcification: good, bad, or ugly. Vasc Med. 2002;7:161-162.