**LECTURE 7: DRUGS USED IN DYSLIPIDEMIA**

The decision to use drug therapy for hyperlipidemia is based on the specific metabolic defect and its potential for causing atherosclerosis or pancreatitis.

**COMPETITIVE INHIBITORS OF HMG-COA REDUCTASE (REDUCTASE INHIBITORS: “STATINS”)**

These compounds are structural analogs of HMG-CoA (3-hydroxy3-methylglutaryl-coenzyme A). Lovastatin, atorvastatin, fluvastatin, pravastatin, simvastatin, rosuvastatin, and pitavastatin belong to this class. They are most effective in reducing LDL. Other effects include decreased oxidative stress and vascular inflammation with increased stability of atherosclerotic lesions. It has become standard practice to initiate reductase inhibitor therapy immediately after acute coronary syndromes, regardless of lipid levels.

**Mechanism of Action**

HMG-CoA reductase mediates the first committed step in sterol biosynthesis. The active forms of the reductase inhibitors are structural analogs of the HMG-CoA intermediate that is formed by HMG-CoA reductase in the synthesis of mevalonate. These analogs cause partial inhibition of the enzyme and thus may impair the synthesis of isoprenoids such as ubiquinone and dolichol and the prenylation of proteins. It is not known whether this has biologic significance. However, the reductase inhibitors clearly induce an increase in high-affinity LDL receptors. This effect increases both the fractional catabolic rate of LDL and the liver’s extraction of LDL precursors (VLDL remnants) from the blood, thus reducing LDL. Because of marked first-pass hepatic extraction, the major effect is on the liver. Preferential activity in liver of some congeners appears to be attributable to tissue-specific differences in uptake. Modest decreases in plasma triglycerides and small increases in HDL also occur. Clinical trials involving many of the statins have demonstrated significant reduction of new coronary events and atherothrombotic stroke. Mechanisms other than reduction of lipoprotein levels appear to be involved. The availability of isoprenyl groups from the HMG-CoA pathway for prenylation of proteins is reduced by statins, resulting in reduced prenylation of Rho and Rab proteins. Prenylated Rho activates Rho kinase, which mediates a number of mechanisms in vascular biology. The observation that reduction in new coronary events occurs more rapidly than changes in morphology of arterial plaques suggests that these pleiotropic effects may be important. Likewise, decreased prenylation of Rab reduces the accumulation of Aβ protein in neurons, possibly mitigating the manifestations of Alzheimer’s disease.

**FIBRIC ACID DERIVATIVES (FIBRATES)**

Mechanism of Action Fibrates function primarily as ligands for the nuclear transcription receptor PPAR-α. They transcriptionally upregulate LPL, apo A-I, and apo A-II, and they downregulate apo C-III, an inhibitor of lipolysis. A major effect is an increase in oxidation of fatty acids in liver and striated muscle (Figure 35–4). They increase lipolysis of lipoprotein triglyceride via LPL. Intracellular lipolysis in adipose tissue is decreased. Levels of VLDL decrease, in part as a result of decreased secretion by the liver. Only modest reductions of LDL occur in most patients. In others, especially those with combined hyperlipidemia, LDL often increases as triglycerides are reduced. HDL cholesterol increases moderately. Part of this apparent increase is a consequence of lower triglyceride in plasma, resulting in reduction in the exchange of triglycerides into HDL in place of cholesteryl esters.

**Therapeutic Uses & Dosage**

Fibrates are useful drugs in hypertriglyceridemias in which VLDL predominate and in dysbetalipoproteinemia. They also may be of benefit in treating the hypertriglyceridemia that results from treatment with antiviral protease inhibitors. The usual dose of gemfibrozil is 600 mg orally once or twice daily. The dosage of fenofibrate as Tricor is one to three 48-mg tablets (or a single 145-mg tablet) daily. Dosages of other preparations vary. Absorption of gemfibrozil is improved when the drug is taken with food.

**NIACIN (NICOTINIC ACID)**

Niacin (but not niacinamide) decreases triglycerides and LDL levels, and Lp(a) in most patients. It often increases HDL levels significantly. Historically, combination therapy including niacin has been associated with regression of atherosclerotic coronary lesions in three angiographic trials and with extension of lifespan in one large trial in which patients received niacin alone.

**Mechanism of Action**

Niacin inhibits VLDL secretion, in turn decreasing production of LDL. Increased clearance of VLDL via the LPL pathway contributes to reduction of triglycerides. Excretion of neutral sterols in the stool is increased acutely as cholesterol is mobilized from tissue pools and a new steady state is reached. The catabolic rate for HDL is decreased. Fibrinogen levels are reduced, and levels of tissue plasminogen activator appear to increase. Niacin inhibits the intracellular lipase of adipose tissue via receptor-mediated signaling, possibly reducing VLDL production by decreasing the flux of free fatty acids to the liver. Sustained inhibition of lipolysis has not been established, however.

**Therapeutic Uses & Dosage**

In combination with a resin or reductase inhibitor, niacin normalizes LDL in most patients with heterozygous familial hypercholesterolemia and other forms of hypercholesterolemia. These combinations are also indicated in some cases of nephrosis. In severe mixed lipemia that is incompletely responsive to diet, niacin often produces marked reduction of triglycerides, an effect enhanced by marine omega-3 fatty acids. It is useful in patients with combined hyperlipidemia and in those with dysbetalipoproteinemia. Niacin is clearly the most effective agent for increasing HDL and reduces Lp(a) in most patients. For treatment of heterozygous familial hypercholesterolemia, 2–6 g of niacin daily is usually required; more than this should not be given. For other types of hypercholesterolemia and for hypertriglyceridemia, 1.5–3.5 g daily is often sufficient. Crystalline niacin should be given in divided doses with meals, starting with 100 mg two or three times daily and increasing gradually.

**BILE ACID–BINDING RESINS**

Colestipol, cholestyramine, and colesevelam are useful only for isolated increases in LDL. In patients who also have hypertriglyceridemia, VLDL levels may be further increased during treatment with resins.

**Mechanism of Action**

Bile acids, metabolites of cholesterol, are normally efficiently reabsorbed in the jejunum and ileum. Excretion is increased up to tenfold when resins are given, resulting in enhanced conversion of cholesterol to bile acids in liver via 7α-hydroxylation, which is normally controlled by negative feedback by bile acids. Decreased activation of the FXR receptor by bile acids may result in a modest increase in plasma triglycerides but can also improve glucose metabolism in patients with diabetes. The latter effect is due to increased secretion of the incretin glucagon-like peptide-1 from the intestine, thus increasing insulin secretion. Increased uptake of LDL and IDL from plasma results from upregulation of LDL receptors, particularly in liver. Therefore, the resins are without effect in patients with homozygous familial hypercholesterolemia who have no functioning receptors but may be useful in those with some residual receptor function and in patients with receptor-defective combined heterozygous states.

**INHIBITORS OF INTESTINAL STEROL ABSORPTION**

Ezetimibe inhibits intestinal absorption of phytosterols and cholesterol. Added to statin therapy, it provides an additional effect, decreasing LDL levels and further reducing the dimensions of atherosclerotic plaques.

**Mechanism of Action**

Ezetimibe selectively inhibits intestinal absorption of cholesterol and phytosterols. A transport protein, NPC1L1, is the target of the drug. It is effective in the absence of dietary cholesterol because it also inhibits reabsorption of cholesterol excreted in the bile.

**TREATMENT WITH DRUG COMBINATIONS**

Combined drug therapy is useful (1) when VLDL levels are significantly increased during treatment of hypercholesterolemia with a resin; (2) when LDL and VLDL levels are both elevated initially; (3) when LDL or VLDL levels are not normalized with a single agent, or (4) when an elevated level of Lp(a) or an HDL deficiency coexists with other hyperlipidemias. The lowest effective doses should be used in combination therapy and the patient should be monitored more closely for evidence of toxicity. In combinations that include resins, the other agent (with the exception of niacin) should be separated temporally to ensure absorption.

FIBRIC ACID DERIVATIVES & BILE ACID-BINDING RESINS

This combination is sometimes useful in treating patients with familial combined hyperlipidemia who are intolerant of niacin or statins. However, it may increase the risk of cholelithiasis.

HMG-CoA REDUCTASE INHIBITORS & BILE ACID-BINDING RESINS

This synergistic combination is useful in the treatment of familial hypercholesterolemia but may not control levels of VLDL in some patients with familial combined hyperlipoproteinemia.

NIACIN & BILE ACID-BINDING RESINS

This combination effectively controls VLDL levels during resin therapy of familial combined hyperlipoproteinemia or other disorders involving both increased VLDL and LDL levels. When VLDL and LDL levels are both initially increased, doses of niacin as low as 1–3 g/d may be sufficient in combination with a resin. The niacin-resin combination is effective for treating heterozygous familial hypercholesterolemia.

NIACIN & REDUCTASE INHIBITORS

If the maximum tolerated statin dose fails to achieve the LDL cholesterol goal in a patient with hypercholesterolemia, niacin may be helpful. This combination may be useful in the treatment of familial combined hyperlipoproteinemia.

REDUCTASE INHIBITORS & EZETIMIBE

This combination is synergistic in treating primary hypercholesterolemia and may be of use in the treatment of patients with homozygous familial hypercholesterolemia who have some receptor function.

REDUCTASE INHIBITORS & FENOFIBRATE

Fenofibrate appears to be complementary with most statins in the treatment of familial combined hyperlipoproteinemia and other conditions involving elevations of both LDL and VLDL. The combination of fenofibrate with rosuvastatin appears to be especially well tolerated. Some other statins may interact unfavorably owing to effects on cytochrome P450 metabolism. In any case, particular vigilance for liver and muscle toxicity is indicated.

COMBINATIONS OF RESINS, EZETIMIBE, NIACIN, & REDUCTASE INHIBITORS

These agents act in a complementary fashion to normalize cholesterol in patients with severe disorders involving elevated LDL. The effects are sustained, and little compound toxicity has been observed. Effective doses of the individual drugs may be lower than when each is used alone; for example, as little as 1–2 g of niacin may substantially increase the effects of the other agents.

COMBINATIONS OF PCSK9 ANTIBODY WITH STATIN AND EZETIMIBE

These agents can be used together to achieve maximal reduction of LDL. Because of the need for parenteral administration of PCSK9 antibody and its expense, this therapy is reserved for patients with familial hypercholesterolemia or atherosclerotic vascular disease who do not respond adequately to other regimens.