



Combination therapy for dyslipidemia

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In the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines, the emphasis of lipid-lowering therapy is placed on reaching target plasma low-density lipoprotein cholesterol (LDL-C) levels in order to reduce the risk for coronary heart disease (CHD). Although therapeutic lifestyle changes can have a positive effect on LDL-C levels, the ATP III recognizes that a majority of patients with dyslipidemia will also require drug therapy to achieve lipid targets. Currently, only a small percentage of patients, including those with CHD, are reaching goal.

Early aggressive use of the effective lipid-lowering agents currently available is critical to achieve target lipid levels in a greater number of patients. Use of drug combinations further enhances the likelihood of achieving target lipid levels. Ideally, the combination of therapeutic modalities used both the endogenous and exogenous pathways of cholesterol synthesis to reduce the amount produced in the body, as well as the amount absorbed from the diet.

This article reviews the pharmacotherapeutic effects of combination therapy, summarizes the strengths and weaknesses of current lipid-lowering drug combinations, and identifies the potential impact of the novel cholesterol absorption inhibitor ezetimibe on the LDL-C treatment algorithm.

(Key words: cholesterol, combination therapy, dyslipidemia, low-density lipoprotein cholesterol [LDL-C])

Combination therapeutic modalities are often required for optimal lipid management. Combining agents from different classes can be effective, well tolerated, and safe in most patients; however, many primary care physicians

are reluctant to prescribe combination modes of therapy for patients who do not achieve lipid goals with starting doses of lipid-lowering agents. This reluctance is unfortunate because for these patients, combination therapy offers a potentially attractive therapeutic option. The proper combination of two drugs has proven effective in achieving lipid reductions that exceed those of monotherapy.

By having an impact on lipid homeostasis with use of complementary mechanisms of action, combinations of low-dose drugs have a greater lipid-lowering effect compared with an increased dose of single-agent therapy. This effect is especially true when the combination involves augmenting a 3-hydroxy-3-methylglutaryl coenzyme A reductase

inhibitor (statin) with a drug from another class. Some combinations may prove to be better tolerated than high-dose monotherapy, particularly when the lipid-lowering capacity of the add-on drug allows for reduction in the dose of the original therapy and offers a favorable side effect profile. Examples of currently available combination modes of therapy are described here.

Currently available combination modes of therapy

Statins are considered by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) to be first-line agents for all but a few patients. Consequently, the most common combination strategy is to add a drug from another class to a statin (*Figure*). Combination therapy with statins has some distinct advantages. In general, lower doses of each drug can be used, minimizing the risk of side effects. Additionally, combining a drug with a mechanism of action different from that of a statin typically achieves an additional 10% reduction in low-density lipoprotein cholesterol (LDL-C), whereas doubling the dose of a statin will result in about a 6% additional lowering of LDL-C.¹ Bile acid resins and niacin are common add-on therapy to a statin. Other statin combinations, though effective in favorably modifying lipid profiles, must be used with caution because of an increased possibility of side effects.

Statins and bile acid resins are a commonly used and well-tolerated combination of lipid-lowering agents. Adding a statin to bile acid resin monotherapy overcomes the compensatory response that minimizes the LDL-C-lowering effectiveness of bile acids when administered alone. This combination has been shown to reduce LDL-C by as much as 50% or equal to the reduction that occurs with a high-dose statin alone¹ and offers a favorable side effect profile. Unlike the older bile acid resins that require multiple daily dosing to be effective and are poorly tolerated, newer resins such as colestevlam hydrochloride are usually taken as a once-a-day dose and have a more favorable side effect profile. Thus, use of a newer resin either in monotherapy or in combination with

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Figure. Currently available agents used in lipid-lowering combination therapy and their advantages and disadvantages. ►

statins can overcome many of the obstacles to achieving success with this combination.

The combination of statins and fibrates appears to have complementary effects on triglyceride concentrations and LDL-C levels and prove to be especially attractive for patients with mixed hyperlipidemia characterized by elevated triglyceride and LDL-C levels. In particular, statins and fenofibrate appear to be a safe and effective combination to use in these hard-to-treat patients. By substituting fenofibrate for gemfibrozil, the risk of myopathy frequently reported when statins and gemfibrozil are used together can be minimized.² When the choice is made to use statins and gemfibrozil in combination, these drugs should be used only in the lowest effective doses and only used in patients who have normal liver and kidney function.

The combination of statin and niacin offers an alternative to the fibrate-statin therapy for patients with mixed hyperlipidemia as well as for patients with only elevated LDL-C. The addition of 2 g of niacin to a stable dose of statin was recently reported to add an additional 31% LDL-C lowering³; however, an increased chance of myopathy is associated with this combination, and the vasodilatory effects of niacin are difficult to tolerate for many patients.

Combinations of bile acid resins and nicotinic acids can achieve LDL-C reductions of 32% to 43% and high-density lipoprotein cholesterol (HDL-C) increases of 37% to 43% in patients with coronary heart disease (CHD) who have elevated lipid levels. Lowering the dose of each drug can reduce the side effects and achieve reasonably good improvement in LDL-C and HDL-C levels, though improvement is not as significant as with higher doses.⁴

Although used infrequently, the fibrate-niacin combination may have some synergy with respect to the individual effects of the drugs on triglyceride and HDL-C levels and may prove useful

Checklist

■ Statins and bile acid resins

- ☐ As great as a 50% reduction in low-density lipoprotein (LDL-C) or reduction equal to that occurring with a high-dose statin alone
- ☐ Favorable side effect profile

■ Statins and fibrates

- ☐ Complementary effects on triglyceride concentrations and LDL-C levels
- ☐ Effectiveness (especially statin-and-fenofibrate combination) for patients with mixed hyperlipidemia (elevated triglyceride and LDL-C levels)
- ☐ Restriction in use of statins and gemfibrozil only in lowest effective doses and only in patients with normal liver and kidney function

■ Statin and niacin

- ☐ Usefulness in patients with mixed hyperlipidemia and patients with elevated cholesterol alone
- ☐ Increased chance of myopathy
- ☐ Reduced tolerability due to vasodilatory effects of niacin

■ Bile acid resins and nicotinic acids

- ☐ Reductions of 32% to 43% in LDL-C
- ☐ Increases of 37% to 43% in high-density lipoprotein cholesterol (HDL-C) in patients with coronary heart disease (CHD)

■ Fibrate and niacin

- ☐ Synergistic effects on triglyceride and HDL-C levels
- ☐ Usefulness in patients with very high triglyceride concentrations

■ Cholesterol absorption inhibitors and low-dose statin

- ☐ Reduction in intestinal absorption of both dietary and biliary cholesterol from intestine
- ☐ Inhibition of both endogenous and exogenous production of cholesterol
- ☐ Possible reduction of plasma LDL-C levels, with subsequent decreased potential for development of CHD

in patients with very high triglyceride concentrations.⁵

Contribution of cholesterol absorption inhibitors to combination therapy

There exist several alternatives to currently available combination drug therapy. Novel selective cholesterol absorption inhibitors, such as ezetimibe, offer a mechanism of action distinct from statins and other agents. Cholesterol absorption inhibitors significantly reduce intestinal absorption of both dietary and biliary cholesterol from the intestine. The combination of ezetimibe and a low-dose statin inhibits both the endogenous and exogenous production of cholesterol and holds the promise for reducing plasma LDL-C levels and subsequently decreasing the potential of development of CHD.

Phase II and III studies from the ezetimibe development program have demonstrated that combining selective cholesterol absorption inhibition with statins is an effective strategy for optimizing cholesterol-lowering effects. For example, subjects with hypercholesterolemia treated with simvastatin, 10 mg/d for 14 days, achieved a 35% reduction in LDL-C, whereas those treated with simvastatin, 10 mg, plus ezetimibe, 10 mg, achieved a reduction of 52%⁶—a decrease in LDL-C expected from a simvastatin dose of 80 mg. Additionally, ezetimibe has virtually no effect on statin pharmacokinetics. Thus, combining ezetimibe with a statin may reduce the dose of the latter drug required to achieve target levels, or, in patients who respond poorly to statins, may improve the lipid-lowering effect.

A similar phase II coadministration study found that the decrease in LDL-C was 40.0% for 10 mg of atorvastatin calcium alone, 22.7% for 10 mg of ezetimibe alone, and 55.7% for both drugs given together. Consistent with the findings of the simvastatin coadministration studies, the additional reduction in LDL-C levels seen with the combination of ezetimibe, 10 mg/d, and atorvastatin calcium, 10 mg/d, was equivalent to the reduction expected with atorvastatin calcium monotherapy at high doses.⁷

Comment

For many dyslipidemic patients, statins represent the treatment of choice; however, evidence from many clinical trials and clinical practice shows that a majority of dyslipidemic patients do not achieve target LDL-C levels. This failure is especially true for high-risk patients. Multiple factors contribute to the failure to achieve lipid goals with drug therapy. Many patients receive no more than a starting dose that is often less than the dose identified in clinical trials as clinically effective. For most patients, statins prove to be exceptionally safe drugs; however, some patients clearly have side effects such as myositis and elevated liver enzyme levels, which tend to be associated with higher doses.

If high doses of statins are poorly tolerated or do not achieve appropriate LDL-C reduction, niacin and bile acid resins are typical add-on agents. However, the vasodilatory side effects of niacin are not tolerated by many patients,

and adding a bile acid resin may not be sufficient to lower LDL-C to therapeutic goals. A promising new alternative, the cholesterol absorption inhibitor ezetimibe, is now available and holds the potential to become a viable agent as either monotherapy or as an add-on to a statin.

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