UCP Supplement 194
March 2003

What future for combination therapies?

John KASTELEIN, Academic Medical Center, Amsterdam, The Netherlands.

Abstract *For most patients who require lipid-lowering treatment, statin monotherapy is the appropriate treatment. However, in those patients where statin monotherapy does not produce optimal lipid levels, the combination of a statin with niacin, a bile acid sequestrant, a fibric acid derivative, a cholesterol absorption inhibitor or a fish oil preparation may provide improved control. The choice of combination therapy depends upon the patient's lipid profile and tolerability of the medication. Combination of a statin with niacin, a bile acid sequestrant or ezetimibe, a cholesterol absorption inhibitor, should be considered for patients with very high low-density lipoprotein cholesterol (LDL-C) levels, while combination with either a fibric acid derivative or a fish oil should be considered for patients with high LDL-C and high triglyceride levels.*

A number of new lipid-lowering agents are currently in development, including cholesteryl ester transfer protein (CETP) inhibitors, acyl coenzyme A: cholesterol acyltransferase (ACAT) inhibitors, ileal bile acid transport (IBAT) inhibitors, microsomal triglyceride transfer protein (MTP) inhibitors and dual peroxisome proliferator-activated receptor (PPAR) α and γ agonists. Introduction of these novel therapies will provide opportunities for developing different combination strategies that may help to optimise lipid profiles in patients who are currently difficult to treat. The introduction of new combinations will require careful study to ensure that the risks of drug interactions and adverse events are minimised.

Introduction

For the great majority of patients who require lipid-lowering therapy, either for primary hypercholesterolaemia or for secondary prevention of vascular events, statin monotherapy is the most appropriate treatment. Newer statins such as atorvastatin and rosuvastatin can reduce low-density lipoprotein cholesterol (LDL-C) levels by more than 50%[1–3] and, in most cases, this will provide the required lowering of lipid levels to reduce the risk of vascular events. In fact, monotherapy with the newer, more efficacious statins can provide a degree of lipid-lowering previously observed only when older statins were used in combination with other lipid-lowering agents. However, in some patients statin monotherapy is insufficient to optimise circulating lipid levels. These patients include individuals with very high LDL-C levels, especially those with familial hypercholesterolaemia, and individuals that have accompanying dyslipidaemias in addition to high LDL-C levels.[4]

A number of combination regimens are available for the treatment of individuals for whom monotherapy is unsatisfactory. These include combinations of statins with niacin, bile acid sequestrants, fibric acid derivatives and fish oils. Each combination has its advantages and disadvantages, and different combinations are appropriate for different blood lipid profiles. Furthermore, newer lipid-lowering therapies are constantly being developed and the scope for combination therapy will increase.

The availability of different lipid-lowering drugs presents the clinician with a bewildering array of potential therapeutic options. This article will review the use of combination therapy from a practical, clinical, perspective and address ways in which the efficacy and safety of combinations of lipid-lowering therapies can be maximised. The use of combinations of both currently available drugs and those that are likely to become available in the near future will be discussed. In addition, the future of combination therapy for dyslipidaemia will be considered in the light of newly emerging therapeutic modalities.

Why consider combination therapy?

Over the last 20 years many patients have derived substantial benefit from statin therapy.

Indeed, the more recently developed statins such as rosuvastatin are so effective that low-dose statin monotherapy is probably all that is necessary for up to 80–90% of patients. Nevertheless, clinical trial results and epidemiological data suggest that, for some patients, there is room for improvement.

The recently published results of the Heart Protection Study (HPS)[5] provide incontrovertible evidence not only that lowering lipid levels is beneficial in the secondary prevention of vascular events but also that statin therapy is beneficial in patients with relatively normal lipid profiles. Whether this is due purely to the antihyperlipidaemic effects of treatment or to other pleiotropic effects of statin therapy remains to be determined. What is clear is that active management by the clinician to optimise circulating levels of LDL-C and high-density lipoprotein cholesterol (HDL-C) and triglycerides will significantly reduce the risk of vascular events. However, the results of the EUROASPIRE I and II studies[6,7] indicate that many patients with coronary heart disease (CHD) do not achieve recommended blood cholesterol levels.

Furthermore, some specific dyslipidaemias — e.g. monogenic familial hypercholesterolaemia, familial defective apolipoprotein B, and polygenic hypercholesterolaemia — that can result in highly elevated LDL-C levels can be especially difficult to treat with monotherapy.[4] The current US National Cholesterol Education Program (NCEP) guidelines recommend a range of combination therapies for use in these circumstances, depending upon the particular needs of the patient.

Currently available antihyperlipidaemic therapies encompass a wide range of biochemical mechanisms by which lipid-lowering may be achieved. Furthermore, the spectrum of effects on LDL-C, HDL-C and triglycerides differs according to the mechanism of action (Table 1). By utilising combinations of drugs with different mechanisms it becomes possible to produce additive effects that can be tailored to the specific needs of the patient. While many combinations are theoretically possible, statins are likely to remain the baseline therapy around which combinations will be designed. This is due not only to their proven efficacy both in purely antihyperlipidaemic terms and in the primary and secondary prevention of vascular events but also, and more importantly, to their very good and well studied long-term safety profile.

Initial diagnosis

Identification of patients who require combination therapy requires a careful initial diagnosis. A detailed medical history should be taken and an assessment made of their risk status. All patients with increased risk should be given advice on lifestyle modification, receive initial treatment with a statin and have their fasting blood lipoprotein profile determined.

Table 1. Mechanism of action of lipid-lowering drugs.

Drug class	Mechanism of action
Statins	Inhibit HMG-CoA reductase, a key step in cholesterol biosynthesis,[8] causing upregulation of the LDL-receptor and reduction of circulating cholesterol levels
Niacin	Appears to inhibit free fatty acid mobilisation from peripheral tissues, reducing hepatic synthesis of triglycerides[9]
Bile acid sequestrants	Bind bile acids in intestine and interrupt bile acid enterohepatic recirculation, increasing conversion of cholesterol into bile acids in liver and reducing circulating cholesterol levels[9]
Fibrates	Activate PPARα (peroxisome proliferator-activated receptor α) and act at the level of transcription to affect numerous genes involved in the metabolism of lipoproteins[10]
Cholesterol absorption inhibitors	Selectively inhibit the intestinal absorption of cholesterol and related phytosterols[11]

A decision to commence combination treatment should be based on the patient's absolute lipid levels, the lipid profile with respect to the relative levels of LDL-C, HDL-C and triglycerides, and on issues such as the patient's concurrent medical conditions and concomitant therapy.

Combination therapy in patients with very high LDL-C levels

Very high LDL-C levels are most often seen in patients with familial hypercholesterolaemia. Patients with markedly elevated LDL-C levels should initially receive statin monotherapy and have their response monitored. If statin monotherapy is insufficient to achieve optimum lipid levels, combination with either niacin or bile acid sequestrants is indicated.

The combination of a statin with niacin can prove successful in the patient with very high LDL-C levels. Studies have shown that the combination of a statin with niacin can reduce LDL-C levels by a further 16%, compared with the statin alone.[12] In general, adverse event rates are low with niacin treatment — although flushing, the most common adverse event, while not clinically deleterious, has been shown to lead to discontinuation of treatment by up to 10% of patients.[13] In addition, niacin treatment worsens glycaemic control in patients with diabetes and should be avoided in these individuals. Niacin can also exacerbate gout.

Combination of a bile acid sequestrant with a statin can also improve lipid levels more than a statin alone. Knapp et al (2001)[14] demonstrated a 42% reduction in LDL-C levels in patients treated for six weeks with 2.3 g/day colesevelam and 20 mg/day simvastatin, compared with a 34% reduction in patients receiving 20 mg/day simvastatin alone. Although the side effect profile of bile acid sequestrants is good, compliance is often poor, as patients find the palatability of the large doses necessary for efficacy to be unacceptable. Triglyceride levels may be increased by bile acid sequestrant treatment and, for this reason, their use should be restricted to patients in whom dyslipidaemia is limited to elevations of LDL-C and avoided in patients with metabolic syndrome.

Recently a new lipid-lowering agent, ezetimibe, has been developed. Ezetimibe is a new type of cholesterol absorption inhibitor. It inhibits cholesterol absorption at the brush border of the intestine without affecting the absorption of triglycerides or fat-soluble vitamins. Studies in homozygous familial hypercholesterolaemic subjects have shown that addition of ezetimibe to therapy with statins alone results in up to an additional 20% reduction in both LDL-C and total cholesterol.[15] A similar LDL-C reduction is seen in subjects with polygenic hypercholesterolaemia.[16] In addition to reducing LDL-C, studies conducted so far have indicated that ezetimibe is well tolerated and has a good safety profile, although long-term clinical usage is necessary before a definitive judgment can be made.

Combination therapy in patients with high LDL-C and triglyceride levels

In patients where high levels of LDL-C are accompanied by elevated levels of triglycerides, a different approach is necessary. In these patients the combination of a statin with either a fibrate or with a fish oil preparation should be considered.

The combination of a statin and a fibrate provides a therapeutic regimen that can significantly reduce both LDL-C and triglyceride levels.[17–19] For instance, Durrington and colleagues undertook a 24-week study, involving 213 type 2 diabetic patients, in which treatment with rosuvastatin 10 mg od and fenofibrate 67 mg tds reduced triglycerides by 47.1% and LDL-C by 42.2% from baseline. In comparison, monotherapy with rosuvastatin 40 mg od reduced triglycerides by 30.3% and LDL-C by 46.7%.[20]

However, there are a number of safety issues associated with the use of all statin–fibrate combinations. Recent evidence has suggested a possible association of this regimen with myopathy and rhabdomyolysis.[21] Blood levels of creatine kinase (CK) can be monitored and medication discontinued if elevations are seen. However, myopathy can occur in the absence of raised CK levels — thus, CK-level monitoring should not solely be relied upon to detect the presence of myopathy. Patient counselling on the risks and warning signs of myopathy is important, and combination

therapy should be discontinued if muscle symptoms develop. The risk of myopathy is increased by older age, compromised renal function and concurrent therapy with drugs that impair statin metabolism. Therefore, it is important for all patients that the lowest effective doses of fibrate and statin should be determined by titration.[22] In particular, if a patient presents with elevated triglycerides, consideration should be given to the early introduction of a fibrate before the statin dose is escalated. Of the fibrate class of drugs, for combination purposes, currently fenofibrate is the most preferred and gemfibrozil the least, as it is associated with more cases of myopathy when used in combination with statins.[21] This may be due to the fact that gemfibrozil significantly affects the metabolism of statins (although fenofibrate does not), possibly by inhibiting glucuronidation.[23]

Clearly, therapy with this regimen must be undertaken cautiously and only after careful risk:benefit analysis. Nevertheless, for patients with markedly elevated cholesterol and triglyceride levels, the benefit of achieving lipid goals probably outweighs the risk of myopathy. The occurrence of fatal rhabdomyolysis should always be preventable by the institution of careful patient monitoring. Rapid discontinuation of the medication and treatment by haemodialysis may be used in the rare event that signs of rhabdomyolysis are observed.

An alternative approach in patients with high LDL-C and triglyceride levels is the coadministration of a statin with a fish oil preparation. This combination is highly effective and can decrease triglyceride levels by up to 30%. It also has an excellent safety profile.[24] However, lack of tolerability is common and often leads to non-compliance and discontinuation of medication. Patients frequently report an unpleasant aftertaste and 'fishy breath'. Furthermore, fish oils do not have any beneficial effects on LDL-C or HDL-C.

Future approaches

A number of new lipid-lowering agents are currently in development, some of which are developments of existing therapeutic approaches, while others explore totally novel approaches (Table 2).

CETP inhibitors are a new class of agent that can effect an increase in circulating HDL-C and a reduction of LDL-C.[25] Increasing HDL-C levels is gradually being recognised as an important therapeutic target, and drugs that affect HDL levels are likely to play a significant role in optimising lipid levels in future. As CETP inhibitors appear principally to affect HDL-C levels, it is probable that they will need to be used in combination with LDL-C-lowering therapies such as statins.

Inhibition of the enzyme ACAT, which is present in the arterial wall, may prevent excess accumulation of cholesteryl esters in macrophages and reduce the development of atherosclerosis. Studies in animals have shown that inhibitors of ACAT can reduce the development of atherosclerotic lesions.[26,27] Avasimibe is one ACAT inhibitor currently in Phase III trials.[28] In addition to use as a monotherapy, combination of a statin with an ACAT inhibitor may be a promising approach to further prevent the progression of atherosclerosis.

Table 2. Mechanism of action of potential future lipid-lowering drugs.

Drug class	Postulated mechanism of action
CETP inhibitors	Inhibit cholesteryl ester transfer protein (CETP) and increase circulating HDL-C
ACAT inhibitors	Inhibit acyl coenzyme A: cholesterol acyltransferase (ACAT), preventing excess accumulation of cholesteryl esters in macrophages
IBAT inhibitors	Inhibit ileal bile acid transport (IBAT)
MTP inhibitors	Inhibit microsomal triglyceride transfer protein (MTP), blocking the hepatic secretion of very-low-density lipoproteins (VLDL) and the intestinal secretion of chylomicrons
Dual PPARα and PPARγ agonists	Activate PPARα and PPARγ to affect numerous genes involved in glucose and lipid metabolism

Other targets for therapy currently being studied include the inhibition of IBAT, the inhibition of MTP (which blocks the hepatic secretion of VLDL and the intestinal secretion of chylomicrons) and the development of dual PPARα/γ agonists that simultaneously influence lipid and glucose metabolism and will have particular application in subjects with the metabolic syndrome and type 2 diabetes.

The use of all of these new agents opens up exciting possibilities for new therapeutic strategies. The combination of drugs with different mechanisms may help to achieve optimum lipid profiles in patients that are currently difficult to treat. The availability of new drugs may help to improve the side effect profiles of therapeutic regimens and new combinations may be able to address multiple, related therapeutic targets — such as concurrent lipid and glycaemic control in patients with the metabolic syndrome and type 2 diabetes.

However, the emergence of new therapeutic strategies will not be without its problems. The recent events surrounding the use of cerivastatin with gemfibrozil should bring a note of caution into the introduction of new combination therapies. The efficacy and safety of all new therapies must be well established, first, in monotherapy and, subsequently, in combination regimens. Each potential combination must be studied to ensure that efficacy is maximised with respect to both lipid-lowering and, more importantly, cardiovascular risk reduction, while the risk of adverse events is minimised. Particular attention should be paid to studying the pharmacokinetics of combinations, as this is frequently the area in which drug interactions occur. Finally, care needs to be taken to ensure that the value of new therapies is not diminished by complex regimens that lead to poor patient compliance.

Conclusions

For patients who require antihyperlipidaemic medication, therapy should always be initiated with a statin, unless specifically contraindicated. Some patients, as a result of their specific dyslipidaemic profile, will require combination therapy to provide optimal lipid levels.

Combination therapy should be selected according to patient need, based on both clinical considerations — such as absolute risk for a primary or secondary vascular event, blood lipid profiles and requirements for concomitant medication — and on patient preference so as to ensure good compliance with the medication regimen, which is long term in most cases.

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