

Statin therapy in the management of dyslipidaemia

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Introduction

Cardiovascular disease is the leading cause of mortality among men and women in Ireland, accounting for approximately 40% of all deaths. Between the 1940s and 1970s, epidemiological studies identified an association between elevated levels of cholesterol, particularly low-density lipoprotein cholesterol (LDL-C), and the development of coronary atherosclerosis.

Clinical studies performed over the past three decades have assessed the impact of lipid modification on the clinical manifestations of atherosclerosis. The development of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, or statins, represented a major advance in the pharmacological lowering of elevated LDL-C. Clinical trials using statins have clearly established the crucial role of LDL-C reduction in preventing cardiovascular disease. Moreover, the more recent clinical trials suggest that aggressive LDL-C lowering provides additional benefit.

Mechanism of action

HMG CoA reductase is the rate-limiting enzyme for cholesterol formation in the liver and other tissues. HMG CoA reductase responds to negative feedback regulation by both sterol and non-sterol products of mevalonate metabolism through decreased reductase gene expression. By inhibiting HMG CoA reductase, statins ultimately reduce the hepatocyte cholesterol content. When cells become depleted in cholesterol, an escort protein called sterol regulatory element binding protein (SREBP) cleavage-activating protein (SCAP) transports SREBPs from the endoplasmic reticulum to the Golgi apparatus where proteases modify the SREBPs. This allows the NH₂-terminal domain to translocate to the nucleus, where it binds to a sterol response element in the enhancer/promoter region of target genes, including the LDL receptor gene. Increased expression of LDL receptors mediates LDL cholesterol uptake via receptor-mediated endocytosis.

Pharmacology of statins

The statins differ in their absorption, plasma protein binding, excretion and solubility, and exhibit variable dose-related

efficacy in reducing LDL-C. In general, LDL-C is reduced by an additional 7% with each doubling of the statin dose.

In addition, in patients with hypertriglyceridaemia (but not in subjects with normal triglycerides), statins achieve a 22-45% reduction in triglyceride levels due to decreased hepatic secretion of very low-density lipoprotein cholesterol (VLDL-C).

Statin cause relatively minor increases in high-density lipoprotein (HDL) cholesterol (5-10%). Statin therapy does not reduce lipoprotein-a.

Drug interactions

Important drug interactions have been described that may increase serum levels of statins and increase the likelihood of side effects, particularly the incidence of muscle toxicity.

The cytochrome P (CYP) 450 superfamily is the most significant drug-metabolising pathway in the liver and other tissues. The most prevalent metabolising isoform is CYP3A4, which serves as the major pathway for metabolism of lovastatin, simvastatin, atorvastatin and cerivastatin. Inhibition of the activity of CYP3A4 can increase serum levels of these statins, raising the potential for side effects. Pravastatin does not undergo metabolism through the CYP450 system, but is metabolised by sulfation and conjugation. Fluvastatin is metabolised mainly by CYP2C9 and to a lesser extent by CYP3A4 and CYP2D6. Rosuvastatin is mainly metabolised by CYP2C9 and CYP2C19. Atorvastatin and fluvastatin have minimal renal excretion and dose adjustment of these statins in patients with renal insufficiency is therefore unnecessary.

Drugs that are metabolised by CYP3A4, which may interfere with the metabolism of statins, include antibiotics (erythromycin and other macrolides),azole antifungal drugs, cyclosporine, verapamil, diltiazem, amiodarone, antihistamines, benzodiazepines and protease inhibitors. Genetic variation in the activity of the CYP450 system may also contribute to susceptibility to drug interactions and toxicity.

Gemfibrozil is known to increase the myotoxic potential of statins. Although it was initially suspected that gemfibrozil increased statin levels by inhibiting CYP450 enzymes, it is now clear that a major effect of gemfibrozil is mediated through the

inhibition of glucuronidation of statins. Glucuronidation is now recognised as a major pathway for the elimination of the active hydroxy-acid metabolites of statins. There are differences among fibrates in their ability to affect glucuronidation, and fenofibrate appears not to interfere with the UGT1A1 and UGT1A3 enzymes that mediate statin glucuronidation. This suggests that statin-fenofibrate combinations may be safer than therapy with statins and gemfibrozil.

Recent clinical trials

The classic statin trials were completed in the 1990s and form the backbone for contemporary lipid-lowering practice. These trials clearly demonstrated the efficacy and safety of statins in both the primary and secondary prevention of cardiovascular events in patients with both elevated and average cholesterol values.

Since then, a number of additional trials have been published that extend the observations of the classic statin trials and widen the population of patients that will benefit from lipid-lowering therapy.

During this time, an important blurring of the boundary between the traditional concepts of primary and secondary prevention has also taken place. It is now clear that many patients, such as diabetics who do not have an overt history of a vascular event, are at high risk of myocardial infarction (MI) and stroke. Hence the concept of 'high-risk primary prevention'.

Novel combination therapy with statins

Statin may be combined with a number of other lipid-modifying drugs, including bile acid binding resins, niacin and fibrates. There is an increased risk of myotoxicity when statins are combined with either niacin or fibrates, but particularly with fibrates, as discussed above. Patients receiving combination therapy should be carefully monitored for evidence of side effects, especially muscle-related symptoms.

Statin and niacin

Low HDL-C is increasingly recognised as a major risk factor in the development of coronary artery disease (CAD). Nicotinic acid (niacin) is currently the most efficacious agent available to raise HDL-C. Niacin increases HDL-C by 15-35%. The Coronary Drug Project suggested that niacin reduces coronary events. Niacin is now often combined safely with statins in patients with low HDL-C.

This strategy was studied in the HDL-Atherosclerosis Treatment Study (HATS), which was a three-year, double-blind trial of 160 patients with CAD, low HDL-C levels and 'normal' LDL-C levels. Patients were randomly assigned to receive one of four regimens: simvastatin plus niacin, antioxidant vitamins (vitamin E, vitamin C, beta-carotene and selenium), simvastatin-niacin plus antioxidants or placebo. The end points were arteriographic evidence of a change in coronary stenosis and the occurrence of a first cardiovascular event (death, MI, stroke, or revascularisation).

In the simvastatin-niacin group, mean levels of LDL-C decreased by 42% and HDL-C increased by 26%. The rate of coronary stenosis progression was significantly attenuated by simvastatin-niacin combination. Notably, the frequency of the clinical events was significantly less with the simvastatin-niacin combination. The protective increase in HDL-C with simvastatin plus niacin was attenuated by concurrent therapy with antioxidant vitamins, indicating that these should not be prescribed.

Patients commencing niacin therapy should be advised to take the drug with food, avoid alcohol or spicy food, and take concomitant low-dose aspirin therapy, which attenuates the tendency to flush. By carefully counselling patients about the potential benefit of niacin and manoeuvres to prevent flushing, long-term compliance can be greatly enhanced.

Statin and ezetimibe

Statin may also be combined with the novel cholesterol absorption inhibitor, ezetimibe. Ezetimibe is indicated for use alone or with a statin to reduce elevated total cholesterol and LDL-C in patients with hypercholesterolaemia.

In clinical practice, ezetimibe is prescribed chiefly to reduce serum LDL-cholesterol concentrations. The addition of ezetimibe to a statin provides an additional 14-17% reduction in LDL-C. Notably, the administration of ezetimibe in combination with low-dose statin therapy provides an LDL-C reduction similar to that achieved with statin monotherapy at intermediate or maximum doses.

The combination of ezetimibe plus maximum-dose statin may produce LDL-C reductions of up to 60% from baseline, and can lower triglyceride concentrations by up to 40%.

Ezetimibe is also effective when added to statin therapy in homozygous familial hypercholesterolaemia. Treatment with ezetimibe in combination with statins is generally well tolerated.

Statin in acute coronary syndrome (ACS)

Over the past three years there has been a growing body of literature suggesting that statin therapy is beneficial when administered early to patients presenting with an ACS. This is primarily based on observational studies that have exploited pre-existing ACS databases to compare outcomes among patients receiving statins to those not on lipid-lowering therapies. Taken together, the data from these observational studies suggest, but do not prove, benefit with early initiation of statins. One prospective, randomised, placebo-controlled trial has investigated the early use of statin therapy in patients presenting with an ACS. The Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study randomised patients to atorvastatin 80mg or placebo within 24-96 hours of admission with unstable angina or non-ST elevation MI. The primary endpoint was a composite of death, non-fatal MI, cardiac arrest with resuscitation, or recurrent symptomatic ischaemia requiring emergent re-hospitalisation.

The primary endpoint occurred in 17.4% of the placebo

group and in 14.8% of the atorvastatin group, yielding a relative risk reduction of 16%. The only statistically significant reduction seen was in recurrent ischaemia (6.2 versus 8.4%, $P=0.02$). Importantly, in MIRACL, the rate of serious side effects was similar ($<1\%$) in both groups. Statin users did have an increased rate of liver enzyme elevation (2.5 versus 0.6%). This is important when considering the safety of high dose statin therapy as this trial used the maximum dose of the most potent statin available at that time.

Starting a statin during the acute hospitalisation phase may have the additional benefit of improving long-term compliance with therapy.

Recent data also indicate that statins are beneficial in patients undergoing coronary intervention by increasing short- and long-term survival as well as reducing peri-procedural cardiac enzyme elevation. One study showed that initiation of statin therapy immediately after successful intervention significantly benefited patients with unstable angina at six months, but not patients who had presented with ST elevation MI.

Finally, data from one case-controlled study indicate that mortality is lower among patients undergoing major non-cardiac vascular surgery who are on statins.

Statins and stroke reduction

Although LDL-C is an established risk factor in the pathogenesis of coronary artery disease, clear epidemiologic evidence is lacking for a relationship between the risk of stroke and an elevated serum cholesterol level.

However, clinical studies indicate that statin therapy significantly reduces ischaemic stroke among patients with established vascular disease. For example, in the Cholesterol and Recurrent Events (CARE) study, pravastatin significantly reduced the pre-specified endpoint of stroke by 31%, without increased haemorrhagic stroke.

The Heart Protection Study (HPS) provides further strong evidence that statin therapy represents a powerful means of reducing stroke. In the HPS, stroke was also significantly reduced by 25% – 444 strokes in the simvastatin group (4.3%) versus 585 strokes in the placebo group (5.5%).

The reduction in stroke was mainly due to a reduction in ischaemic stroke, and similar numbers in each treatment group suffered a haemorrhagic stroke. This finding helps negate prior concerns that cholesterol lowering might increase haemorrhagic stroke. There was also a significant reduction in transient ischemic attacks in HPS. Although the absolute stroke rate in these clinical trials was small, these studies did show that statin therapy decreases ischemic stroke without increasing haemorrhagic stroke.

The Anglo Saxon Cardiac Outcomes Trial (ASCOT) study also demonstrated a reduction in fatal and non-fatal stroke (89 strokes in atorvastatin group versus 121 stroke in placebo, HR 0.73 [0.56-0.96], $P=0.024$).

Statin use in MIRACL was also associated with a 50% decrease

in stroke rate ($P=0.05$). The PROSPER study, however, remains an exception and failed to show a reduction in stroke. The precise reason for this is not clear, but may reflect the age of the population studied and the trial duration.

Conclusion

Evolving clinical evidence clearly supports the use of statins in the majority of patients with vascular disease and elevated, average or even below-average cholesterol levels. Recent clinical trials have broadened the population of patients who will benefit from statin therapy and the HPS strongly supports the use of statins to lower LDL-C levels beyond those recommended in current NCEP III guidelines.

Even though the safety of statin therapy was called into question following the withdrawal of cerivastatin, contemporary data on statin safety indicate that these drugs are very safe. Although the mechanisms responsible for muscle toxicity with statins are unknown, a number of promising avenues for research have been highlighted in recent years.

There is a maturing appreciation of the therapeutic potential of combination therapy with statins and niacin, fibrates, and more recently ezetimibe and the need for closer attention and monitoring for adverse effects in such patients. Moreover, we now have a heightened respect for the potential of drug interactions with statins and a greater understanding of recently elucidated metabolic pathways for statin metabolism.

There is a growing body of data showing that statin therapy reduces stroke and an evolving literature base on the benefit of statins in patients with ACS and in those undergoing coronary intervention.

Ongoing trials will address new therapeutic targets and dictate future guidelines.