Management of mixed hyperlipidaemia

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This editorial refers to 'Efficacy and safety of the coadministration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia† by M. Farnier et al., on page 897

The introduction of the HMG-CoA reductase inhibitors (statins) about 15 years ago has influenced the daily practice of cardiologists and other physicians enormously with respect to preventive strategies of first and second cardiovascular events. These drugs can lower the concentration of LDL-cholesterol by 30–60% and are generally well tolerated. In the last decade, randomized trials with statins have involved more than 90 000 patients, in which the overall safety and efficacy of the statins has been firmly established. The use of statins has, therefore, become the cornerstone of drug therapy in reducing the concentration of LDL-cholesterol and thereby the risk of cardiovascular disease and stroke, even in subjects without high serum cholesterol levels. Despite the success of statins in reducing cardiovascular morbidity and mortality, a substantial number of patients continue to have clinical events, which can partly be explained by the fact that other lipoprotein particles in addition to LDL contribute to the risk of cardiovascular disease, such as abnormalities in triglyceride-rich lipoproteins (very low-density lipoproteins, chylomicrons, or their remnants) and HDL. This is especially the case in subjects with mixed hyperlipidaemia, in whom statins are less effective in correcting lipoprotein abnormalities other than LDL ones. Mixed or combined hyperlipidaemia is a frequent lipid disorder, which can be genetically determined. A similar lipoprotein phenotype can occur in diabetes mellitus type 2 and can be induced by certain drugs such as immunosuppressive agents and protease inhibitors. The genetic form, familial combined hyperlipidaemia (FCH), is the most common form of heritable lipid disorder with an estimated prevalence of 1–2% in the general population and 10–20% in the survivors of myocardial infarction below age 60. The hyperlipidaemia is characterized by elevated plasma total cholesterol and/or triglyceride concentrations and is therefore also known as 'multiple type hyperlipidaemia'. The lipoprotein phenotype is frequently associated with an unfavourable decrease in HDL-cholesterol concentration, an elevated apolipoprotein B concentration, and a preponderance of small, dense LDL particles. These small, dense LDL particles are more atherogenic because they have a higher affinity to proteoglycans of vascular cells and are more prone to oxidative modification.

Although statins lower serum triglycerides to some extent (up to 20%), fibrates are the drugs of choice to reduce triglyceride-rich lipoproteins (up to 50% depending on the baseline levels). In addition, fibrates increase the buoyancy of the LDL particles, making them less prone to oxidative modification, and increase HDL-cholesterol. In the case of severe hypertriglyceridaemia, fibrates are useful in reducing the risk of acute pancreatitis. In this condition, the metabolic conversion of triglyceride-rich lipoprotein particles to LDL is impaired, and consequently LDL concentration is very low. However, upon treatment with fibrates, this conversion is improved, and LDL-cholesterol concentration increases. The combination of statins with fibrates is therefore a powerful strategy because multiple lipoprotein abnormalities are corrected, but deserves more careful monitoring because of the increased potential of adverse effects. This is especially the case in patients with concomitant medications, hepatic and renal insufficiency, hypothyroidism, and older age. Cerivastatin was withdrawn in 2001 after the drug was related to approximately 100 deaths as a result of rhabdomyolysis, a relatively very high reporting rate when compared with other statins. Concomitant medications, especially the fibrates, can alter the metabolism of
statins and increase the plasma concentrations of statins. In the label of rosvastatin, its combination with gemfibrozil is therefore discouraged. The reporting rates of rhabdomyolysis with statins (other than cerivastatin) plus fenofibrate are much lower than those for statins plus gemfibrozil (fenofibrate 0.58 vs. gemfibrozil 8.6 per million prescriptions dispensed). Therefore, some authors discourage the use of gemfibrozil in combination with any statin. Other possible, but less used in Europe strategies, for the treatment of mixed hyperlipidaemia are the combination of statins with niacin or statins with omega-3 fatty acids.

Farnier et al. report another combination therapy as a therapeutic option, namely, fenofibrate plus ezetimibe, for patients with mixed hyperlipidaemia. Ezetimibe reduces intestinal cholesterol absorption by blocking a specific transporter in humans by ~50% and thereby lowers LDL cholesterol by ~20%. In this multicentre study, the efficacy and safety of ezetimibe co-administered with fenofibrate was compared with that of fenofibrate alone and placebo during 12 weeks in a 3:3:3:1 ratio. Over 600 patients with serum triglycerides between 2.3 and 5.7 mmol/L and LDL-cholesterol between 3.4 and 5.7 mmol/L [2.6–4.7 mmol/L in patients with diabetes (16%)] were randomized to receive one of four daily treatments: placebo, ezetimibe 10 mg, fenofibrate 160 mg, and fenofibrate 160 mg + ezetimibe 10 mg. The effects of fenofibrate plus ezetimibe induced an additional ~10–15% reduction in total cholesterol, LDL-cholesterol, non-HDL-cholesterol, and apolipoprotein B-100 compared with that of fenofibrate alone, whereas on other study variables, addition of ezetimibe to fenofibrate had little or no additional effects (serum triglycerides, HDL-cholesterol, apolipoprotein A-1, high sensitivity C-reactive protein (hsCRP), LDL subclass pattern). In the subgroup of patients with serum triglycerides levels above the median (> 3.1 mmol/L) and thus low LDL-cholesterol levels at baseline, the combination was not more efficacious in lowering LDL-cholesterol than ezetimibe alone (approximately ~13%). There was no difference in incidence of adverse effects in the treatment groups. This study confirms a smaller study. The latter study also investigated the pharmacokinetic interaction between the two drugs: ezetimibe did not affect the plasma concentrations of fenofibrate, but the mean concentration and area under curve were increased by ~50%, which was not considered to be clinically significant.

The study by Farnier et al. is the first large short-term study on the effects of the combination of fenofibrate with ezetimibe in patients with mixed hyperlipidaemia. Long-term studies are needed to show its safety and additional clinical benefit, but the combination of a fibrate with ezetimibe offers an additional alternative approach to combination of fibrates with statins, which seems to be useful in selected patients with mixed hyperlipidaemia, at least in those with baseline triglycerides levels < 3.4 mmol/L.

References

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