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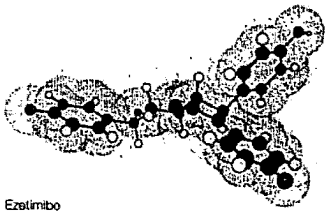
FRESH FROM THE PIPELINE

Ezetimibe

John Earl and Peter Kirkpatrick



Ezetimibe

Ezetimibe (Zetia), the first in a new class of agents that inhibit cholesterol absorption in the intestine, was approved by the FDA in October 2002 for the reduction of cholesterol levels in patients with hypercholesterolaemia. What impact is it likely to have on the multi-billion-dollar market for cholesterol-lowering drugs?

Many clinical trials and extensive epidemiological studies have clearly established the benefits of reducing serum levels of low-density lipoprotein cholesterol (LDL-C) and total cholesterol (TC) on coronary heart disease, a leading cause of death and morbidity in the developed world[1]. Although the statin class of drugs, which lower LDL-C and TC by inhibiting cholesterol biosynthesis, have proved highly effective in general, many patients taking statins continue to have higher-than-recommended LDL-C and TC levels. Consequently, several approaches have been pursued to develop novel cholesterol-lowering drugs, with one such program leading to the discovery and development of the small-molecule drug ezetimibe (Zetia; Schering Plough/Merck).

Therapeutic hypothesis

Serum cholesterol is primarily regulated by two organs: the liver, which produces cholesterol for use in digestion, and the intestine, which absorbs cholesterol from food and from bile. Statins inhibit cholesterol biosynthesis in the liver, and so agents that inhibit cholesterol absorption in the intestine might be expected to have additive effects when used in combination with statins.

Acyl coenzyme A: cholesterol acyltransferase (ACAT), an enzyme involved in cholesterol absorption in the intestine, was initially chosen as a target, and a class of compounds that inhibited cholesterol absorption in a cholesterol-fed hamster model was identified[2]. However, comparison of *in vivo* potency with *in vitro* ACAT inhibitory activity in structurally related compounds showed no correlation, indicating that these compounds inhibit cholesterol absorption by a different mechanism[3], which is still unknown.

Drug composition

The original compound series[2] was based on an azetidinone nucleus, which is crucial for *in vivo* activity. Extensive structure–activity studies[3] and rational considerations of metabolic properties[4,5] led to the discovery of SCH 58235, subsequently named ezetimibe (FIG. 1), which showed high efficacy as an inhibitor of cholesterol absorption in the cholesterol-fed hamster model[5] and a range of other cholesterol-fed animal models of human cholesterol metabolism[6], and which was thus chosen as the clinical development candidate.

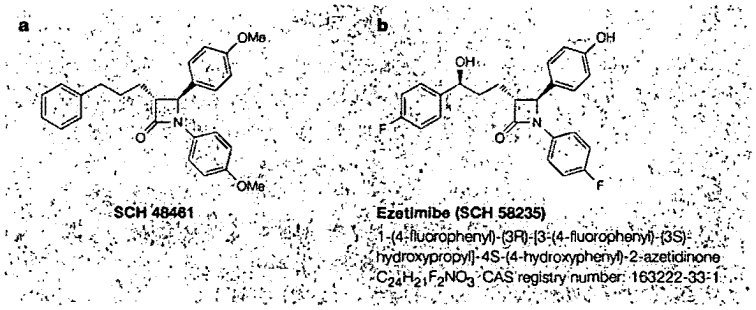


Figure 1 | **Structure of ezetimibe.** Structure–activity studies around the 2-azetidinone core showed that the key elements for the inhibition of cholesterol absorption are an N-1-aryl group, a 4S-alkoxyaryl substituent and a C-3 arylalkyl substituent[2,3]; these studies led to the compound SCH 48461. Further structure–activity studies that considered putative metabolites of SCH 48461, with the aim of blocking 'non-productive' metabolism (introducing fluorine at potential metabolic sites on the N-1 and C-3 aromatic rings) and pre-activating 'productive' metabolism (stereospecific benzylic hydroxylation of the C-3 side chain), resulted in SCH 58235 (ezetimibe), which had a 50-fold increase in *in vivo* potency over SCH 48461 in the cholesterol-fed hamster model[4,5]. A scalable stereoselective synthesis has been reported[7].

Trial data

In patients with hypercholesterolaemia, ezetimibe (10 mg orally, once-daily) reduces levels of LDL-C, TC, apolipoprotein B (the major protein constituent of LDL) and triglycerides (increased levels of which can promote atherosclerosis), and increases levels of high-density lipoprotein cholesterol (decreased levels of which are associated with the development of atherosclerosis)[6]. Maximal responses are typically reached within two weeks and are maintained during chronic therapy. Ezetimibe was generally well tolerated, with the overall incidence of adverse events reported with ezetimibe being similar to that reported with placebo.

In two 12-week studies in 1,719 hypercholesterolaemic patients, ezetimibe as a monotherapy reduced LDL-C by 18% compared with a 1% increase with placebo[6]. Adding ezetimibe to ongoing statin therapy in an 8-week study with 769 hypercholesterolaemic patients who had not reached their National Cholesterol Education Program (NCEP) II LDL-C goal reduced LDL-C by 25% compared with a 4% reduction with addition of placebo, with 72% of the patients receiving ezetimibe reaching their NCEP II goal compared with 19% of patients receiving placebo[6]. Finally, in four 12-week trials involving 2,382 previously untreated hypercholesterolaemic patients, ezetimibe in combination with various doses of one of four statins (including the most commonly used statins, atorvastatin and simvastatin) reduced LDL-C more than statin alone in each case.

Indications

Ezetimibe administered alone or in combination with a statin is indicated as adjunctive therapy to diet for the reduction of elevated TC, LDL-C and Apo B in patients with primary hypercholesterolaemia.

In addition, on the basis of small-scale trials, ezetimibe is also approved for use in two rare genetic disorders. The combination of ezetimibe and atorvastatin or simvastatin is indicated for the reduction of elevated TC and LDL-C levels in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments, and ezetimibe is indicated as an adjunctive therapy to diet for the reduction of elevated levels of the sterols sitosterol and campesterol in patients with homozygous sitosterolaemia. ▶