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REVIEW ARTICLE

Setting a new standard in achieving superior efficacy: ezetimibe + simvastatin

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ABSTRACT

Ezetimibe with simvastatin in combination inhibits both the absorption and production of cholesterol. This dual mechanism of inhibition substantially increases the capacity to decrease levels of atherogenic low-density lipoproteins, compared with that observed when either drug is used alone. Ezetimibe/simvastatin is more effective than atorvastatin or rosuvastatin monotherapy treatments in low-density lipoprotein cholesterol lowering and getting more patients to goals. Ezetimibe/simvastatin offers an important treatment alternative to patients who respond inadequately even to high-dose statin therapy.

Dyslipidaemia is a pivotal risk factor for the development of atherosclerotic cardiovascular disease. Multiple clinical trials demonstrated that the reduction of low density lipoprotein-cholesterol (LDL-C) reduces cardiovascular morbidity and mortality. Despite the promulgation of clearly defined guidelines for the management of lipid disorders, a large proportion of patients at risk for cardiovascular disease do not achieved their recommended LDL-C goals with statin monotherapy, and many of these patients require combinations of drugs to reach their LDL-C goals.

Cholesterol homeostasis is regulated by both intestinal absorption and cellular synthesis. Ezetimibe is a specific inhibitor of the absorption of dietary and biliary cholesterol. The best LDL-C lowering can be achieved by inhibiting cholesterol absorption with ezetimibe and cholesterol production with a statin. Ezetimibe plus simvastatin has recently been combined as a fixed-dose therapy, which offers the possibility of simultaneously inhibiting the two key pathways in cholesterol metabolism: hepatic cholesterol synthesis and intestinal cholesterol absorption.

The combination of ezetimibe and simvastatin in a single tablet is a drug which combines a fixed dose of ezetimibe (10 mg) with increasing doses of simvastatin (10, 20, 40 and 80 mg). In a randomized, double-blind, placebo-controlled trial [1], the co-administration of ezetimibe and simvastatin was significantly more effective than simvastatin alone in reducing LDL-C levels for the pooled ezetimibe plus simvastatin vs. pooled simvastatin analysis and at each specific dose comparisons.

After this preliminary trial, the efficacy of the four single tablets ezetimibe/simvastatin 10/10, 10/20, 10/40 and 10/80 mg was compared to the most efficacious available statins in several randomized studies. The VYVA study [2] compared atorvastatin 10, 20, 40 and 80 mg to ezetimibe/simvastatin 10/10, 10/20, 10/40

and 10/80 mg in patients with primary hypercholesterolemia. Ezetimibe/simvastatin led to greater LDL-C reductions (47–59%) than atorvastatin (36–53%) and more patients received combination therapy to achieve their LDL-C goals. There was no difference in the change in hs-CRP levels between groups. A second head-to-head comparison between ezetimibe/simvastatin and atorvastatin was conducted in patients with type 2 diabetes and hypercholesterolaemia, the VYTAL study [3]. The objectives of this study were to compare the efficacy and safety of the recommended usual starting and next highest doses of ezetimibe/simvastatin and atorvastatin. Significantly greater mean reductions were found in LDL-C levels with ezetimibe/simvastatin 10/20 mg than with atorvastatin 10 or 20 mg, and with ezetimibe/simvastatin 10/40 mg than with atorvastatin 40 mg. Ezetimibe/simvastatin was also superior to atorvastatin for attaining LDL-C levels <70 mg/dL. Another study [4] evaluated the efficacy of switching from atorvastatin 10 mg to ezetimibe/simvastatin (10/20 or 10/40 mg), or doubling the dose of atorvastatin in patients with type 2 diabetes. Greater complementary reductions in LDL-C were achieved by switching to ezetimibe/simvastatin 10/20 mg (26.2%) or 10/40 mg (30.1%) than by doubling the dose of atorvastatin to 20 mg (8.5%).

The efficacy of ezetimibe/simvastatin 10/20, 10/40 or 10/80 mg single tablets has also been compared with rosuvastatin 10, 20 or 40 mg in 2959 hypercholesterolaemic patients [5]. Ezetimibe/simvastatin was more effective than rosuvastatin in LDL-C lowering and provided greater or comparable improvements in other lipid measures and high sensitivity-C-reactive protein, at the usual starting, next highest and maximum doses. In all these studies comparing ezetimibe/simvastatin and atorvastatin or rosuvastatin, treatments were generally well tolerated.

As clinical trials usually do not reflect clinical practice-based conditions, the efficacy of the single tablet ezetimibe/simvastatin has also been examined in two large open-label, prospective, observational cohort studies conducted in high-risk patients with either coronary heart disease (study 1, 19 194 patients) or type 2 diabetes (study 2, 19 484 patients) not adequately controlled on statin monotherapy [6]. Compared with baseline values on statin monotherapy, mean LDL-C was reduced by 27–28%. The effects on LDL-C and other lipid parameters were comparable with those seen in randomized clinical studies. In both studies, the rate of clinical adverse events were low.

In conclusion, ezetimibe/simvastatin as a single tablet inhibits both the absorption and production of cholesterol and thus consistently enables more patients to reach their LDL-C goals. This combination therapy also improves other lipoprotein parameters, with a safety and tolerability profile compared with that of statin monotherapy. In clinical practice, the ezetimibe/simvastatin single tablet represents a therapeutic approach of choice to achieve LDL-C targets and to optimize the potential synergistic benefits of these pharmacological agents.

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