EZETIMIBE AND CHOLESTEROL ABSORPTION

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1 INTRODUCTION

Coronary heart disease (CHD) remains the leading cause of morbidity and mortality in the western world. More than the half of atherosclerosis-associated deaths were due to CHD (in the United States: ~450,000 in 2004), which is responsible for 83% of deaths in individuals over 65 years of age [1]. There is convincing evidence from many large epidemiological studies that elevated serum low-density lipoprotein cholesterol (LDL-C) concentrations are associated with an increased risk for the development of atherosclerosis and CHD leading to such potential life-threatening events as myocardial infraction and stroke [2–5].

The pathophysiological mechanisms behind these observations are complex and currently explained with LDL-C oxidation, incorporation of these lipids into macrophages, their conversion to foam cells, and subsequent development of atherosclerotic lesions in the vessel wall, which results in manifold dysfunctions of the endothelium [6].

Recent treatment guidelines such as the Third National Cholesterol Education Program (NCEP) emphasize the need for aggressive LDL-C-lowering therapy in individuals at substantial risk or patients with cardiovascular diseases [7].

For pharmacological intervention several classes of lipid-lowering drugs have been approved in the last two decades, such as hydroxy-methylglutary-coenzyme A (HMG-CoA) reductase inhibitors (statins), fibrates, nicotinic acids, and bile-acid-binding resins. In particular for statins, the most potential and most frequently prescribed of the cholesterol lowering drugs, the benefits of lipid-lowering therapy have been clearly demonstrated in several clinical trials for primary and secondary prevention [8–10]. However, many hypercholesterolemic patients fail to reach the recommended LDL-C target concentrations on statin therapy [11, 12]. Potential reasons include poor patient compliance, insufficient drug response, drug intolerability, as well as inadequate stain dose caused by concerns about safety risks at higher satin doses. With regard to the latter, the relatively high doses of statins required to enhance their cholesterol-lowering effects are connected with the incidence of serious adverse side effects (e.g., myopathy, rhabdomyolysis) [13]. However, even at maximum statin dose titration up to 80 mg, approximately one-third of patients did not achieve the recommended LDL-C levels [14]. Compared to the high LDL-C-lowering potency of 30–40% by low-dose satins (10–20 mg/day), doubling the daily dose only results in an additional cholesterol-lowering benefit of about 5%. Although combining lipid-lowering drugs that act via complementary pathways may provide more pronounced reduction of LDL-C, comedication with available agents may increase the risk for drug interactions or side effects [15]. Specifically, the combination therapy with fibrates was shown to increase the risk of myotoxicity, which caused the worldwide withdrawal of cerivastatin in August 2001 due to numerous deaths [16]. Thus, there was the urgent need for other compounds and principles that would offer supportive strategies.

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