International Congress Series 1303 (2007) 121 – 128

www.ics-elsevier.com

Inhibition of synthesis and absorption of cholesterol: A new option in managing hypercholesterolemia

Liliana Grigore [b], Giuseppe Danilo Norata [a,b], Alberico L. Catapano [a,b,*]

[a] *Department of Pharmacological Sciences, University of Milan, Milan, Italy*
[b] *Center for the Study of Atherosclerosis, Bassini Hospital, Cinisello B, Italy*

Abstract. Although widely used in lipid lowering therapy, HMG CoA reductase inhibitors or statins (even when administered at high doses) are frequently insufficient to achieve guideline-recommended LDL-C goals for many patients with hypercholesterolemia in everyday clinical practice. Often over half of patients do not achieve LDL-C goal on the initial dose of statin and most of these patients do not reach goal neither after 6 months. Thus, a wide therapeutic gap exists between target LDL-C levels and those typically achieved in clinical practice. A recent and more effective therapeutic strategy, therefore, is to treat the two main sources of cholesterol simultaneously (production of cholesterol, mainly in the liver, and absorption of cholesterol in the intestine) with a complementary mechanism of action, by co-administering ezetimibe, a novel agent inhibiting cholesterol absorption, together with a statin, which inhibits cholesterol production in the liver. Ezetimibe can be effectively co-administered with any dose of any statin and, compared with single inhibition of cholesterol production, afforded by statins alone, provides consistently greater reductions in LDL-C through Dual Inhibition of both cholesterol production and absorption. Here we summarize the pivotal role of both the liver and intestine in the overall balance of cholesterol in the body and describe the clinical impact and relevance of inhibiting both sources of cholesterol either by using ezetimibe/simvastatin as a single tablet or co-administering ezetimibe together with any dose of any statin. © 2007 Published by Elsevier B.V.

Keywords: Hypercholesterolemia; Cholesterol absorption; Cholesterol biosynthesis; Ezetimibe; HMG-CoA reductase inhibitors; LDL-C

* Corresponding author. Center for the Study of Atherosclerosis, Department of Pharmacological Sciences, University of Milan, Via Balzaretti 9, 20133 Milan, Italy. Tel.: +39 02 50318302; fax: +39 20 50318386.
E-mail address: alberico.catapano@unimi.it (A.L. Catapano).

0531-5131/ © 2007 Published by Elsevier B.V.
doi:10.1016/j.ics.2007.04.004

1. Introduction

Hypercholesterolemia plays a key role in the development and progression of atherosclerosis and is a proven risk factor for coronary heart disease (CHD) [1–4]. Pharmacologic interventions to lower cholesterol levels both in primary and secondary prevention trials show a clear reduction in the incidence of CHD as well as stroke [5–11].

Although widely used in lipid lowering therapy, HMG CoA reductase inhibitors or statins (even when administered at high doses) are frequently insufficient to achieve guideline-recommended LDL-C goals for many patients with hypercholesterolemia in every day clinical practice [12]. According to a recent study, a large proportion of high-risk hyperlipidemic patients receiving statins alone were not at goal even when physicians were free to use any statin and titrate according to their professional judgment [13]. Over half (52%) of patients did not achieve LDL-C goal on the initial dose of statin, and 86% of these patients had still not reached goal after 6 months [13]. Thus, a wide therapeutic gap exists between target LDL-C levels and those typically achieved in clinical practice [14].

The therapeutic gap will undoubtedly increase in light of the recent amendments of the National Cholesterol Education Program Adult Treatment Program III (NCEP ATP III) guidelines, which recommend even more aggressive reductions in lipid levels for patients at high risk of CHD [15]. The more aggressive cholesterol treatment goals proposed by the revised guidelines call for a more advanced approach to maximize the cardiovascular benefits associated with lower LDL-C levels.

There are two main sources of cholesterol, which are similar in size: production of cholesterol, mainly in the liver, and absorption of cholesterol in the intestine [16,17]. Approximately 50% of the cholesterol pool is absorbed and recirculated through the intestine, while the remainder is excreted through the feces [16,17]. The intestinal pool is composed of both dietary, and the majority, from biliary excretion. A recent and more effective therapeutic strategy, therefore, is to treat both sources of cholesterol simultaneously with a complementary mechanism of action, by co-administering ezetimibe, a novel agent inhibiting cholesterol absorption, together with a statin, which inhibits cholesterol production in the liver [16,18,19]. This results in Dual Inhibition of both sources of cholesterol provides significantly greater LDL-C reduction and subsequent goal attainment.

Ezetimibe can be effectively co-administered with any dose of any statin and, compared with single inhibition of cholesterol production, afforded by statins alone, provides consistently greater reductions in LDL-C through Dual Inhibition of both cholesterol production and absorption [20–23]. The single product of ezetimibe/simvastatin is the first and only product to treat both sources of cholesterol through Dual Inhibition. As with ezetimibe co-administered with any dose of any statin, the single tablet of ezetimibe/simvastatin provides superior LDL-C lowering efficacy with improved LDL-C goal attainment [24–26].

Here we summarize the pivotal role of both the liver and intestine in the overall balance of cholesterol in the body and describe the clinical impact and relevance of inhibiting both sources of cholesterol either by using ezetimibe/simvastatin as a single tablet or co-administering ezetimibe together with any dose of any statin.