Clin. Cardiol. 29, 52–55 (2006)

Review

Ezetimibe: Rationale and Role in the Management of Hypercholesterolemia

LEONID YATSKAR, M.D.,* EDWARD A. FISHER, M.D., PH.D.,*† ARTHUR SCHWARTZBARD, M.D.*†‡

*Cardiology Division, NYU School of Medicine; †Vascular Biology and Disease Program, NYU Medical Center; ‡Non-Invasive Cardiology, Manhattan VAMC, New York, New York, USA

Summary: Elevated low-density lipoprotein (LDL) cholesterol plays an important role in the development of atherosclerosis. In part, plasma LDL levels are dependent on cholesterol absorption in the intestine and the rate of intrinsic cholesterol synthesis. Therapy with 3-hydroxy-3-methylglutaryl coenzyme A-reductase inhibitors has often proven to be successful in reducing plasma LDL levels. However, a significant number of patients do not reach their target LDL levels despite statin therapy. As is reviewed, drugs that inhibit cholesterol absorption are a useful adjunct to lipid-lowering therapy by statins. This review discusses the mechanisms involved in intestinal absorption of cholesterol and its transport as potential targets of newer agents that affect cholesterol absorption. The use of bile acid sequestrants and esters of plant stanols, as well as other intestinally active agents for reducing plasma LDL levels, has been limited by side effects and difficulties in patient compliance. In contrast, the new selective cholesterol transporter inhibitor ezetimibe has been demonstrated to reduce plasma LDL alone or in combination with statins without significant adverse effects. In spite of the robust lipid-lowering data with ezetimibe, questions about clinical outcomes, safety, and efficacy in various combinations remain.

Key words: ezetimibe, cholesterol absorption, lipoproteins, hypercholesterolemia

Address for reprints:
Arthur Schwartzbard, M.D.
Cardiology Section
VA NY Harbor Healthcare System
New York Campus, 12th Floor
423 East 23rd Street
New York, New York 10010, USA
e-mail: Arthur.Schwartzbard@med.va.gov

Received: December 21, 2004
Accepted: June 20, 2005

Importance of Low-Density Lipoprotein Lowering

Epidemiologic studies consistently demonstrate a direct correlation between levels of total cholesterol (TC) and the incidence of coronary artery disease (CAD). Epidemiologic studies have also established specific lipid parameters as important risk factors for CAD. For example, in the Münster Heart Study, the incidence of CAD correlated positively with increasing serum levels of low-density-lipoprotein cholesterol (LDL-C) and triglycerides (TG) and correlated negatively with increasing high-density-lipoprotein cholesterol (HDL-C) concentrations.[1] From the many outcome studies so far reported, it has been firmly established that for every 1% reduction in plasma LDL, independent of mode of therapy, there was at least a 1% reduction in events achieved.

Adult Treatment Panel (ATP) III guidelines have established LDL lowering as a primary goal in cholesterol treatment. These guidelines also recognize diabetes as a coronary heart disease (CHD) equivalent and the metabolic syndrome as a potent risk factor for CAD. It lowered optimal parameters for LDL-C (< 100 and < 70 mg/dl in the highest-risk patients), defined low HDL (< 40 mg/dl) as a major risk factor, and set a new secondary goal of lowering non-HDL-C (LDL-C + very low-density lipoprotein [VLDL]-C) in patients with metabolic syndrome.[2]

Unfortunately, many patients are not reaching their LDL-C goal. The Lipid Treatment Assessment Project (L-TAP) survey results demonstrated that hypercholesterolemia treatment is suboptimal, particularly among patients in higher-risk groups. Retrospective analysis showed that only about 40% of patients with two or more risk factors who were receiving various lipid-lowering drugs and only about 18% of patients with CHD were meeting their National Cholesterol Education Program (NCEP) LDL-C goal.[3]

Overview of Cholesterol Metabolism

There are many determinants of the plasma LDL level. Here, we will focus on the fact that plasma LDL-C correlates positively with the amount of cholesterol absorbed in the in-

testine. For example, Kesäniemi and Miettinen showed that participants in the lower deciles based on serum cholesterol had lower cholesterol absorption than those in the highest deciles.[4] This supports the rationale for LDL-C-lowering therapy via inhibition of intestinal cholesterol absorption.

The total body cholesterol pool consists of two sources: dietary and cholesterol synthesized by the tissues of the body. The liver synthesizes a considerable quantity of cholesterol, which leaves either in the form of VLDL (some of which is converted to LDL) or as biliary cholesterol. Liver also takes up lipoprotein cholesterol (LDL, chylomicron and VLDL remnants; chylomicron cholesterol originally comes from dietary sources) through its LDL and LRP receptors. Approximately 60% of the body's total LDL-receptor activity resides in the liver. In addition, the liver converts some cholesterol to bile salts, which are also secreted into the bile.

Dietary cholesterol comprises about a quarter of the total intestinal cholesterol pool; the remainder (~ 800 mg daily) is comprised of biliary cholesterol. Cholesterol entering the small intestine is emulsified by bile salts into micelles and transferred from the micelles into duodenal and jejunal enterocytes via a putative sterol transporter, tentatively identified as a member of the Niemann-Pick family of proteins (NPC1L1).[5] In the enterocyte, absorbed cholesterol is esterified and packaged into chylomicrons, which are released into the lymphatic circulation. During their brief circulation through lymph and blood, chylomicrons are converted to cholesterol-enriched chylomicron remnants, which are taken up by the liver.[6]

Pathophysiologic Rationale for Cholesterol Absorption Inhibitors

As explained above, intestinal absorption of cholesterol from diet and bile, and intestinal reabsorption of cholesterol-derived bile salts are important targets for cholesterol-lowering therapy. Bile acid sequestrants inhibit intestinal reabsorption of bile acids.[7] This stimulates the liver to produce more bile salts from cholesterol, thereby depleting the hepatic cholesterol pool, which upregulates the LDL receptor and increases LDL clearance by the liver.

Bile acid sequestrants reduce LDL-C by 15–30%, raise HDL-C by 3–5%, but may increase TG in patients, particularly those with preexisting hypertriglyceridemia.[7] Side effects associated with some bile acid sequestrants include gastrointestinal distress or constipation, which may lead to decreased compliance.[8] In addition, first-generation agents (such as cholestyramine and colestipol) reduce absorption of other drugs.

Plant sterol and stanol esters have a low degree of intestinal absorption and block cholesterol absorption by inhibiting the incorporation of dietary and biliary cholesterol into micelles.[9] When 2–3 g of phytosterols are incorporated in the diet, they produce LDL-C reductions of 10–15%.[10] Because of the high caloric content of the phytosterol-enriched products, significant weight gain may be observed in some patients. Due to their nonselective action, there is a theoretical concern that the small reductions in plasma soluble vitamin levels reported with use of plant sterol and stanol esters may become clinically significant with long-term treatment.[11] Despite these concerns, the NCEP ATP III guidelines note the potential benefits in selected patients of the dietary incorporation of plant sterol and stanol esters in order to reduce plasma levels of LDL-C.[2] The American Heart Association (AHA) however, in its scientific advisory statement, offered the following recommendation: "Although their [plant sterol and stanol esters] uses as a dietary adjunct in moderate to severely hypercholesterolemic children can be considered, fat-soluble vitamin status should be monitored…more information is required before their routine ingestion is recommended."[12]

The limitations of the above agents suggest an improved approach would be a valuable treatment option.

Effect of Ezetimibe on Cholesterol Absorption

Ezetimibe is a novel agent that selectively inhibits cholesterol absorption.[13] It is believed to block selectively the above-noted putative cholesterol transporter in the brush border membrane of intestinal epithelial cells.[14] Because of its mechanism of action, it does not interfere with intestinal absorption of nutrients (i.e., lipid-soluble vitamins[15]) and drugs.[16]

Ezetimibe decreases the intestinal absorption of dietary and biliary cholesterol by > 50% (from 49.8 to 22.7%).[13] The amounts of cholesterol transported through the plasma compartment via chylomicron and chylomicron remnants are dramatically reduced. In addition, the reduced cholesterol delivery to the liver induces a compensatory increase in LDL receptors and, thus, increased clearance of LDL and chylomicron-remnant particles from the circulation. This net decrease in circulating levels of LDL (and chylomicrons/chylomicron remnants) effectively reduces their availability to peripheral tissues and the contribution of these particles to atherosclerosis.

Clinical Pharmacology of Ezetimibe

Ezetimibe localizes in the intestinal wall, primarily as a glucuronidated metabolite. After being absorbed in the intestine, it undergoes enterohepatic circulation and reenters the intestinal lumen via bile.[17] This minimizes systemic exposure and the potential for adverse effects. The half-life of ezetimibe is 22 h, making once a day dosing possible. It can be taken with or without food and at any time of the day. Experimental data from clinical trials have been compiled on safety and efficacy of ezetimibe in more than 4,700 patients as monotherapy[18, 19] and in combination with a statin.[20, 21] Generally, ezetimibe was well tolerated, and the overall incidence of adverse events was similar to that reported with placebo. Of importance is the fact that ezetimibe appeared to have no clinically significant pharmacokinetic interactions with other drugs, including those known to be metabolized by the cytochrome CYP450 system.[16] In clinical trials, coadministration of ezetimibe with a statin resulted in a three times higher incidence of consecutive elevations in serum transaminases ($\geq 3 \times$ ULN) than that of

statins alone. Absolute incidence, however, was still very low (1.3 vs. 0.4%), and generally these elevations were asymptomatic and returned to baseline regardless of whether treatment was discontinued.[21] Safety monitoring for ezetimibe monotherapy is not required; when used with a statin, the recommendations for the statin apply.

Potential Role of Ezetimibe in Cholesterol-Lowering Therapy

In response to the decreased hepatic cholesterol pool, the liver responds by upregulating LDL receptors and increasing de novo cholesterol synthesis; the net result is a modest decrease in plasma LDL. Therefore, although plasma cholesterol can be effectively lowered by intestinal cholesterol absorption inhibitors, their efficacy is decreased by the adaptive increase of hepatic cholesterol synthesis, which can go up by as much as 89%.[13] In the presence of a HMG CoA reductase inhibitor, this compensatory increase in cholesterol synthesis is markedly diminished, resulting in the substantially greater decrease in LDL cholesterol that can be achieved from administration of intestinal-acting agents alone.

Therapy with ezetimibe provides a modest LDL reduction of 17% as well as having a favorable effect on HDL cholesterol and TG.[20, 21] Monotherapy with this agent will most likely benefit the select group of patients with only mild LDL elevations in the absence of other risk factors; those who had previous adverse reaction to other first line agents, particularly statins; and a small group of patients who are found to have increased absorption of cholesterol.

Given the modest reduction of LDL-C with ezetimibe monotherapy, its greatest value is likely to be found as a combination agent with statins. In clinical trials, ezetimibe was used in combination with a statin, as well as added to an ongoing therapy with a statin. On average, combination therapy resulted in the incremental decrease in LDL-C by 15%, and add-on therapy gave an additional 20% LDL lowering from post-statin values, compared with statin therapy alone.[21–23] Recently, a combination therapy pill of simvastatin and ezetimibe became available in the U.S. Compared with atorvastatin, the combination of simvastatin and ezetimibe was superior in percent LDL cholesterol decrease and HDL cholesterol increase at equal doses.[24]

The addition of ezetimibe to a starting dose of statin is therefore a therapeutic alternative to a three-step statin titration because, with only an average of 6% further lowering of LDL-C with each doubling of the starting dose of a statin, these strategies have similar incremental LDL-C-lowering effects (15–18%). In addition, statin titration is associated with increased incidence of adverse effects, the most serious of which being rhabdomyolisis.[25] Overall, combination therapy effectively increases the likelihood of reaching LDL-C goals and allows the use of lower statin doses in order to achieve target LDL-C levels, thereby reducing the potential for adverse effects.

Recently, C-reactive protein (CRP), which is believed to reflect the inflammatory state, was shown to be a powerful risk marker for cardiac events in patients in all risk categories and across a wide range of LDL-C levels.[26] New evidence continually emerges that implicates CRP as a potent etiologic factor in the development of atherosclerosis.[27, 28] Therapy with statin results in significant lowering of CRP and this may play a role in its ability to retard progression of atherosclerosis and plaque passivation.[29] Ezetimibe may also have an anti-inflammatory effect. In two recent trials, addition of ezetimibe to statin therapy resulted in greater hs-CRP reduction than with statin therapy alone.[21, 30] No change in hs-CRP, however, was noted in the ezetimibe alone group.

Despite the robust LDL lowering data with ezetimibe, it is important to realize that our knowledge of this drug is far from complete. Thus far, no clinical outcome trials of ezetimibe with the endpoint of morbidity and mortality are available. Although low-dose statin plus ezetimibe may achieve LDL reduction similar to high-dose statins, no outcome data compare these two treatment approaches. No large series have examined the effect of ezetimibe in diabetics. Little is known of efficacy of ezetimibe in combination with a fibrate, and no data are presently available on combinations with niacin, resins, and plant stanol esters. Also, the increased cost of ezetimibe must be considered. Despite these limitations, LDL lowering remains a primary objective of cholesterol treatment. A recent trial has demonstrated that high-risk patients with LDL cholesterol < 100 mg/dl prior to treatment still benefited from cholesterol lowering treatment.[31] Recent trials, such as Treating to New Targets (TNT),[32] Study of Effectiveness of Additional Reductions of Cholesterol and Homocysteine (SEARCH), Incremental Decrease in Endpoints through Aggressive Lipid lowering (IDEAL),[33] confirm further event reduction with LDL cholesterol far below 100 mg/dl, so it is expected that the need for drugs like ezetimibe will only increase.

Conclusions

Ezetimibe is a novel selective cholesterol absorption inhibitor that reduces the delivery of cholesterol to the liver. The distinct mechanism of ezetimibe appears to be complementary to that of statins and other hypolipidemic agents. Ezetimibe has a potential clinical role both as monotherapy and in combination with other lipid-lowering therapies. As monotherapy, ezetimibe may be useful in individuals requiring only modest LDL-C reductions, ineligible for or intolerant to other agents, or those with high intestinal cholesterol absorption. In combination with other lipid-lowering agents, ezetimibe may be useful in individuals who do not reach their LDL-C goal with statin therapy alone, or as an alternative to increasing statin dose. Further studies that assess long-term outcome are needed for a more clear definition of its role in reducing the risk of coronary artery disease.

References

1. Assmann G, Cullen P, Schulte H: The Munster Heart Study (PROCAM). Results of follow-up at 8 years. *Eur Heart J* 1998;19(suppl A):A2–11
2. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ: Coordinating Committee of the

National Cholesterol Education Program. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation* 2004;110:227–239
3. Pearson TA, Laurora I, Chu H, Kafonek S: The lipid treatment assessment project (L-TAP): A multicenter survey to evaluate the percentages of dyslipidemic patients receiving lipid-lowering therapy and achieving low-density lipoprotein cholesterol goals. *Arch Intern Med* 2000;160(4):459–467
4. Kesäniemi YA, Miettinen TA: Cholesterol absorption efficiency regulates plasma cholesterol level in the Finnish population. *Eur J Clin Invest* 1987; 17:391–395
5. Altmann SW, Davis HR Jr, Zhu LJ, Yao X, Hoos LM, Tetzloff G, Iyer SP, Maguire M, Golovko A, Zeng M, Wang L, Murgolo N, Graziano MP: Niemann-Pick C1 like 1 protein is critical for intestinal cholesterol absorption. *Science* 2004;303:1201–1204
6. Turley SD, Dietschy JM: The intestinal absorption of biliary and dietary cholesterol as a drug target for lowering the plasma cholesterol level. *Prevent Cardiol* 2003;6(1):29–33
7. Einarsson K, Ericsson S, Ewerth S, Reihner E, Rudling M, Stahlberg D, Angelin B: Bile acid sequestrants: Mechanisms of action on bile acid and cholesterol metabolism. *Eur J Clin Pharmacol* 1991;40(suppl 1):S53–S58
8. The Lipid Research Clinics Program: The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *J Am Med Assoc* 1984;251:351–364
9. Nguyen TT: The cholesterol-lowering action of plant stanol esters. *J Nutr* 1999;129(12):2109–2112
10. Miettinen TA, Puska P, Gylling H, Vanhanen H, Vartiainen E: Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. *N Engl J Med* 1995;333(20):1308–1312
11. Plat J, Kerckhoff DA, Mensink RP: Therapeutic potential of plant sterols and stanols. *Curr Opin Lipidol* 2000;11(6):571–576
12. Lichtenstein AH, Deckelbaum RJ: AHA Science Advisory: Stanol/sterol ester-containing foods and blood cholesterol levels. A statement for healthcare professionals from the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. *Circulation* 2001;103(8):1177–1179
13. Sudhop T, Lutjohann D, Kodal A, Igel M, Tribble DL, Shah S, Perevozskaya I, von Bergmann K: Inhibition of intestinal cholesterol absorption by ezetimibe in humans. *Circulation* 2002;106(15):1943–1948
14. van Heek M, Farley C, Compton DS, Hoos L, Davis HR: Ezetimibe selectively inhibits intestinal cholesterol absorption in rodents in the presence and absence of exocrine pancreatic function. *Br J Pharmacol* 2001;134(2):409–417
15. Knopp RH, Bays HE, Manion CV: Effect of ezetimibe on serum concentrations of lipid-soluble vitamins (abstr). *Atherosclerosis* 2001;2(suppl):90
16. Zetia (Ezetimibe): Prescribing information. Package insert. Merck/Schering-Plough Pharmaceuticals, 2001
17. Ezzet F, Krishna G, Wexler DB, Statkevich P, Kosoglou T, Batra VK: A population pharmacokinetic model that describes multiple peaks due to enterohepatic recirculation of ezetimibe. *Clin Ther* 2001;23(6):871–885
18. Dujovne CA, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, Yang B, Veltri EP: Esetimibe Study Group: Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90(10):1092–1097
20. Bays HE, Moore PB, Drehobl MA, Rosenblatt S, Toth PD, Dujovne CA, Knopp RH, Lipka LJ, Lebeaut AP, Yang B, Mellars LE, Cuffie-Jackson C, Veltri EP: Ezetimibe Study Group: Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: Pooled analysis of two phase II studies. *Clin Ther* 2001;23(8):1209–1230
21. Gagne C, Bays HE, Weiss SR, Mata P, Quinto K, Melino M, Cho M, Musliner TA, Gumbiner B: Ezetimibe Study Group: Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Cardiol* 2002;90(10):1084–1091
22. Gagne C, Gaudet D, Bruckert E, The Ezetimibe Study Group: Efficacy and safety of ezetimibe coadministered with atorvastatin or simvastatin in patients with homozygous familial hypercholesterolemia. *Circulation* 2002; 105(21):2469–2475
23. Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP, Suresh R, Sun S, Veltri EP: Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardiol* 2002;40(12): 2125–2134
24. Ballantyne CM, Blazing MA, King TR, Brady WE, Palmisano J: Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia. *Am J Cardiol* 2004;93: 1487–1494
25. Pasternak RC, Smith SC Jr, Bairey-Merz CN, Grundy SM, Cleeman JI, Lenfant C: The American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute: ACC/AHA/NHLBI Clinical advisory on the use and safety of statins. *Circulation* 2002;106(8):1024–1228
26. Ridker PM: Clinical application of C-reactive protein for cardiovascular disease detection and prevention. *Circulation* 2003;107(3):363–369
27. Pasceri V, Willerson JT, Yeh ET: Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation* 2000;102:2165–2168
28. Wang CH, Li SH, Weisel RD, Fedak PW, Dumont AS, Szmitko P, Li RK, Mickle DA, Verma S: C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. *Circulation* 2003;107(13):1783–1790
29. Ridker PM, Rifai N, Clearfield M, Downs JR, Weis SE, Miles JS, Gotto AM Jr: Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators: Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001;344 (26):1959–1965
30. Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, Sun S, LeBeaut AP, Sager PT, Veltri EP: Ezetimibe Study Group: Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: A prospective, randomized, double-blind trial. *Circulation* 2003;107(19):2409–2415
31. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 2002;360(9326):7–22
32. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart J-C, Gotto AM, Greten H, Kastelein JJP, Shepherd J, Wenger NK, for the Treating to New Targets (TNT) Investigators: Intensive lipid-lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005;352:1425–1435
33. Pedersen TR, Faergemann O, Kastelein JJP, Olsson AG, Tikkanen MJ, Holme I, Larsen ML, Bendiksen FS, Lindahl C, Szarek M, Tsai J, for the Incremental Decrease in End Point Through Aggressie Lipid Lowering (IDEAL) Study Group: High-dose atovastatin vs. usual-dose simvastatin for secondary prevention after myocardial infarction: The IDEAL Study: A randomized controlled trial. *J Am Med Assoc* 2005;294:2437–2445