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Ezetimibe: A Novel Cholesterol-lowering Agent that Highlights Novel Physiologic Pathways

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Abstract

Ezetimibe is a US Food and Drug Administration-approved novel drug that targets the absorption of cholesterol in the intestine. The identification of this drug has also led to the elucidation of the dietary cholesterol receptor. Ezetimibe is efficacious as a plasma cholesterol-lowering agent as monotherapy, but its greatest utility seems to be as a combination with a low-dose statin, where it results in cholesterol lowering that is equivalent to using maximum-dose statins. It has a very favorable side-effect profile, as well as a lack of drug-drug interactions. In addition, it prevents the absorption of noncholesterol sterols, such as plant sterols. In clinical studies, it has been shown to be highly efficacious in lowering plant sterols in a rare genetic disorder, sitosterolemia. Both the disease, as well as this therapeutic agent, have led to the concept that ezetimibe may be also useful in dissecting the role of these noncholesterol sterols in the pathogenesis of atherosclerosis.

Introduction

Plasma cholesterol is arguably the single cardiovascular risk factor most recognizable by a layperson. Drugs that therefore target this risk factor have been relatively successful, with agents (commonly known as statins) that inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase (the rate-limiting step in cholesterol synthesis) as the most widely prescribed agents. Despite evidence that the use of these agents, in almost any setting for cardiovascular risk factor management, can reduce morbidity and mortality, compliance and goal attainment (as judged by the National Cholesterol Education Panel) remain below acceptable standards [1•]. There are several reasons for this; some of these are the need to use higher or more potent doses of statins, the increased dose-related side-effect profiles that accompany this (*eg*, myalgia, myositis, drug-drug interactions) and the layperson's worry that these agents may damage the liver (despite the lack of proven cases of statin-induced liver toxicity for the currently marketed statins). Although a number of other cholesterol lowering agents that are not systemic is available, these agents have a very small market share. Resins, such as cholestyramine and colestevam, bind bile acids and prevent absorption of intestinal cholesterol by preventing its solubilization into micelles. In addition, they cause loss of bile acids, each molecule of bile acid having been generated from a molecule of cholesterol by the liver, and thus cause a drain on the body pools of cholesterol. Their use is limited, as they can cause considerable gastroenterologic distress, as well as reduce the bioavailability of any other drug that is co-administered at the same time. Natural fiber is also known to lower cholesterol, in part by increasing the loss of bile acids in the stool. More recently, the fortification of margarines with plant sterols or their metabolites that compete with cholesterol for solubilization into micelles have also been available for lowering plasma cholesterol [2]. In general, all of these agents that operate to lower cholesterol absorption or increased fecal loss are moderately effective and need to be used in gram doses that act via a mass-action effect.

The newest agent, ezetimibe, now available for management of plasma lipids and also acts in the intestine has revolutionized this aspect [3]. Ezetimibe belongs to a class of chemicals termed

the *azetidinones*, identified as part of a screen for agents that acted in the intestine to specifically block intestinal cholesterol absorption [4]. Ezetimibe is active in micromolar amounts and kinetic and binding studies suggest that it specifically bound to a cell surface receptor that was deemed to be the dietary cholesterol receptor [5,6•]. Indeed, until the identification of this class of compounds that specifically blocked intestinal cholesterol absorption in this manner, this pathway had not been characterized, although a receptor for cholesterol absorption (such as a receptor for docking micelles, or a molecule that specifically extracted cholesterol from micelles) had been hypothesized.

Following ingestion, the drug is glucuronidated and the intestinal enzyme that carries out this step has recently been identified [7,8]. The glucuronidated compound is thought to be more active than the parent at blocking cholesterol absorption. Both the parent compound and the glucuronidated compound are absorbed, and recirculated via hepatobiliary excretion [9]. Because no organ within the body seems to be a store of these compounds or have any direct biologic response to them, aside from the intestine, these agents are described as nonsystemic. The estimated half-life of ezetimibe is about 22 hours and thus the agent is dosed as a once a day agent and can be taken at bedtime for convenience. Ezetimibe can block intestinal cholesterol absorption by more than 50% in both humans and animals, with no effect on absorption of dietary triglyceride, fat-soluble vitamins, or any drugs. In human studies, bioavailability and kinetics of commonly used drugs is also not affected, because ezetimibe does not appear to be metabolized or interact with the cytochrome P450 pathway. In humans, about 10% to 15% of the drug is excreted in the urine, and the rest in the feces.

The identification of this drug has also led to the identification of the putative intestinal cholesterol receptor, NPC1L1 [10•,11•]. This protein is homologous to the protein defective in Niemann-Pick C disease, although no human disease is known to be caused by defects in NPC1L1. In a mouse deficient of Npc1l1, intestinal cholesterol absorption was reduced to a minimal amount and administration of ezetimibe failed to lower this any further, compared with the result in wild-type mice [10•]. Thus, ezetimibe works through a NPC1L1-sensitive pathway. This protein seems to be expressed only in the apical cells of the intestinal villi and may be restricted to the proximal small intestine. This correlates with the notion that almost all cholesterol absorption also takes place in this segment of the small intestine.

Animal Studies

Although a number of pharmacokinetic and efficacy studies have been carried out in animal model studies that demonstrate that ezetimibe is effective in inhibiting intestinal cholesterol absorption, I highlight one study that may indicate its potential future utility. In a mouse model of atherosclerosis, the apolipoprotein (Apo) E knockout mouse, the administration of ezetimibe led to a significant reduction of lipid-laden plaques in the aortas of these animals compared with controls [6•]. Thus, blocking dietary cholesterol in this animal model had significant benefits on atherosclerotic plaque formation. There are no similar outcome studies in humans at present, but the expectation would be that its use may beneficially modify the atherosclerotic pathway.

Clinical Studies

Ezetimibe is US Food and Drug Administration (FDA)-approved for both monotherapy, as well as in combination with a statin for management of cholesterol lowering. Monotherapy is effective in lowering plasma low-density lipoprotein (LDL) cholesterol by about 18% and results in modest, but statistically significant, increases in high-density lipoprotein (HDL) cholesterol and decreases in triglycerides [12,13]. Based upon its mode of action, ezetimibe is likely to be most effective in those individuals who are hyperabsorbers of dietary cholesterol, compared with those individuals who are hypoabsorbers. Presumably, these individuals are

likely to be most and least diet responsive, respectively, though there are no formal studies to confirm this. The average percentage of cholesterol absorbed by normal healthy individuals is about 55%, with a Gaussian distribution about this mean [14]. Reducing the pool of cholesterol absorbed from the diet results in a reduced pool of cholesterol available to the liver and it is hypothesized that the liver in turn will upregulate the LDL receptor, trapping more LDL particles from the blood and result in a fall in measured LDL cholesterol (Fig. 1) [15•]. Because ezetimibe reduces cholesterol absorption by 40% to 50%, those individuals who absorb less intestinal cholesterol (note the pool of cholesterol consists of ingested cholesterol, as well as that secreted by the hepatobiliary system into bile) will have less of a therapeutic effect than those who absorb much more efficiently [16•].

Its greatest effectiveness results from its use in combination with statin drugs [17,18•,19–21]. In placebo-controlled studies, the combination of 10 mg of ezetimibe with a starting dose of a statin resulted in an LDL cholesterol lowering that was the equivalent of using the maximum dose of the statin alone. This combination seems to result in a statin-sparing effect, though the basis for this synergistic effect is likely to be a greater clearance of LDL cholesterol particles by the liver (Fig. 1). This synergistic effect is seen with all of the statins (simvastatin, atorvastatin, lovastatin pravastatin) and in general leads to a further 21% to 23% LDL cholesterol lowering.

Although ezetimibe has not been approved for use in combination with a fibrate, pharmacokinetic studies suggest no potential deleterious side-effect profiles (Merck-Schering Plough, Whitehouse Station, NJ, and Kenilworth, NJ; data on file). In addition, synergism is expected because both of these agents target separate pathways (peroxisome proliferator-activated receptor- α -mediated gene expression changes for fibrates versus intestinal cholesterol absorption for ezetimibe). In a retrospective clinic-based survey of patients taking lipid-lowering agents, the addition of ezetimibe to on-going fibrate therapy led to an approximate 21% LDL cholesterol reduction, similar to that observed for a statin-ezetimibe combination [22]. No side effects with this combination were reported, but some caution must be expressed until formal prospective studies with much larger numbers have been reported. In general, no significant side effects have been reported, although there is one report of angioedema, and two cases of mild elevations in creatine kinase (< fourfold elevations), all of which resolved upon stopping ezetimibe [23]. The overall side-effect profile, either as monotherapy or as a statin combination, is very favorable, and in controlled clinical studies, no significant adverse events have been reported. Because this is a new drug, clearly continued monitoring and surveillance will be necessary before this drug can be fully evaluated for safety.

Special Circumstances

Ezetimibe has been approved by the FDA for treatment of a rare human genetic disorder, sitosterolemia. In this condition, dietary plant and shellfish sterols accumulate in the bodies of affected individuals [24•]. Humans have an ability to prevent accumulation of such sterols in their plasma levels are normally very low to undetectable. In a randomized placebo-controlled study of affected individuals, 10 mg of ezetimibe led to a progressive fall in their very elevated plasma plant sterol levels [25•]. Interestingly, ezetimibe also lowers plant sterol levels in normal individuals, even though the levels of these are very low to start with [16•]. In a few limited studies, the levels of these plant sterols has been proposed as being a marker cardiovascular risk [26•]. It is not possible to determine whether these plant sterols are directly involved in the atherosclerotic process, or are an indirect marker. Additionally, although ezetimibe is very effective in lowering these plant sterols in both the genetic disease of sitosterolemia, as well as in normal individuals, there are no studies to demonstrate that lowering these plant sterols will lead to an improved cardiovascular outcome. Potentially, this may be the most interesting aspect of this drug, beyond the cholesterol-lowering effect. We

have proposed that the link between diet and atherosclerosis may be such noncholesterol sterols (and in this category are included oxidized sterols) and this ezetimibe-sensitive pathway may also be very important in preventing such toxic sterol-like molecules from entering our bodies [26•].

Conclusions

The newest cholesterol-lowering agent on the market is an agent that inhibits dietary cholesterol absorption and to date seems to have a very beneficial side-effect profile with no adverse drug-drug interactions. Its greatest clinical utility is when it is used in combination with a low-dose statin that results in LDL cholesterol lowering that is equivalent to using high-dose statins, but without the dose-related side effects of using high-dose statins. Additionally, it is indicated for lowering plant sterols in a rare genetic disorder, sitosterolemia. The implication, based upon the increased cardiovascular disease in sitosterolemia, is that these noncholesterol sterols may be implicated in the atherosclerotic process and thus the use of ezetimibe may also be effective in normal, healthy individuals. The identification of this drug has improved our understanding of how dietary cholesterol is absorbed and regulated and may yet lead to an improved understanding of the role of diet in atherosclerosis.

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Figure 1.

The basis for action of ezetimibe and ezetimibe/statin combination. **A**, Upon treatment with the cholesterol inhibitor (and in general any modality that reduces dietary cholesterol absorption), less dietary cholesterol is delivered to the pool of cholesterol to the liver. This may result in the liver sensing this reduced delivery and will upregulate mechanisms to maintain its pools; synthesis and low-density lipoprotein (LDL) receptors will be upregulated and the latter will result in a modest fall in plasma LDL cholesterol. **B**, In contrast, if a statin is co-administered, the ability to upregulate cholesterol synthesis is impaired by the statin drug, resulting in the liver increasing further upregulation of both the receptors, as well as synthetic enzymes. The latter may restore the cholesterol balance in the liver, but the former will result in an enhanced clearance of LDL cholesterol particles from the blood. Only a small amount of statin is needed to greatly up-regulate these mechanisms and thus the greater efficacy and lower side-effect profiles. (*Adapted from Dietschy [15••].*)