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**Review**

# Ezetimibe – a new approach in hypercholesterolemia management

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**Abstract:**
Ezetimibe is the first agent used in hypercholesterolemia treatment known to lower intestinal cholesterol uptake that is able to inhibit NPC1L1 transport proteins in the brush boarder of enterocytes and macrophages. Furthermore, it demonstrates anti-inflammatory and immunomodulatory properties and influences the expression of certain antigens. The drug is rapidly absorbed from the gastrointestinal tract and is then glucuronidated to form the active metabolite. It also undergoes extensive enterohepatic circulation. Various genetic polymorphisms seem to influence the pharmacokinetics of ezetimibe with different effects. The drug also presents a complex impact on cytochrome P450 enzymes, as it is a metabolism-dependent inhibitor of CYP3A4. Ezetimibe does not demonstrate any clinically significant interactions with statins, fibrates, mipomersen sodium, levothyroxine or lopinavir. However, its effect in conjunction with cyclosporine is not neutral. The use of this cholesterol absorption inhibitor has been shown to be safe and effective among patients after cardiac, renal and liver transplants, as well as in HIV patients.

**Key words:**
ezetimibe, hypercholesterolemia, pharmacokinetics, interactions

**Abbreviations:** ApoB-100 – apolipoprotein B-100, ApoE – apolipoprotein E, AUC – area under the curve, CHD – coronary heart disease, $C_{max}$ – peak plasma concentration (maximal concentration) , CPK – creatine phosphokinase, CRP – C-reactive protein, CYP – cytochrome P-450, CYT – cytochrome, F – bioavailability, HAART – highly active antiretroviral therapy, HDL – high-density lipoprotein, HIV – human immunodeficiency virus, HLM – human liver microsomes, HMG-CoA – 3-hydroxy-3-methylglutaryl-CoA, hsCRP – high-sensitivity CRP, $IC_{50}$ – half maximal inhibitory concentration, IDL – intermediate-density lipoprotein, LDL – low-density lipoprotein, MRP – multidrug resistance protein, NADPH – reduced nicotinamide adenine dinucleotide phosphate, NNRTI – non-nucleoside reverse transcriptase inhibitor, NPC1L1 – Niemann-Pick C1-Like 1 transporter, OATP – organic anion transporting polypeptide, ox-LDL – oxidized LDL, P-gp – P-glycoprotein, PI – proteinase inhibitor, RNA – ribonucleic acid, $T_{max}$ – time of maximal concentration, UDP – uridine diphosphate, UGT – uridine diphosphate glucuronosyltransferase, V – volume of distribution, VLDL – very low-density lipoprotein

## Introduction

Hypercholesterolemia, which manifests as an increased level of low-density lipoproteins (LDL), re-

sults in an elevation of the risk of coronary heart disease (CHD), leading to a rise in fatal cardiovascular events [16, 53]. Multiple investigations indicate that hypercholesterolemia is a crucial factor in atherosclerosis. The elevated cholesterol levels correlate with the increased risk of death from CHD [69], and determining the appropriate treatment remains essential given that this disease is becoming the major cause of morbidity in developed countries [53].

For the most part, the first choice drugs in hypercholesterolemia treatment are the 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase inhibitors – statins like simvastatin, atorvastatin, lovastatin, pravastatin, fluvastatin and rosuvastatin. Others are fibrates, including fenofibrate, clofibrate, and gemfibrozil, as well as bile acid sequestrants and niacin, which are used depending on the type of hyperlipidemia. Nonetheless, these drugs are often insufficient for lowering cholesterol levels [28]. High-dose statin therapy often results in hepatotoxicity and myopathy, and the risk/benefit ratio needs revision. The safety of both fibrate administration and coadministration with statins is also a point to consider [23]. In this view, an expansion of the effective ways of managing hypercholesterolemia appears crucial. The solution may be found in the cholesterol absorption inhibitor ezetimibe [28], 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone (Fig. 1), which has been applied in the combinatory treatment of familial and non-familial hypercholesterolemia and in the adjunctive monotherapy of homozygous familial sitosterolemia [31].

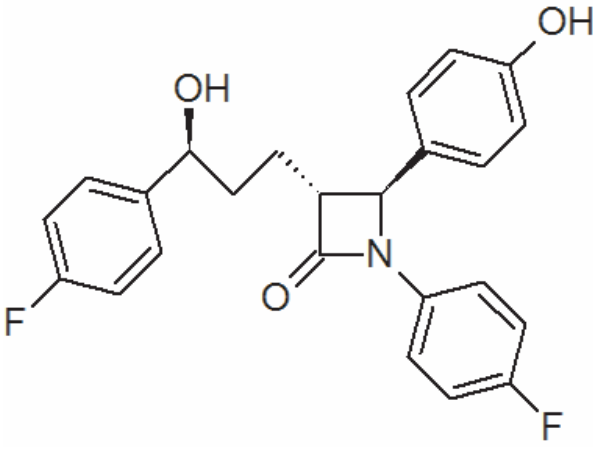


**Fig. 1.** Chemical structure of ezetimibe

## Main mechanism of action

Ezetimibe was discovered as an active and potent metabolite of Schering-Plough's SCH48461 substance after extensive structure-activity relationship research [53]. It is a strong inhibitor of cholesterol and phytosterol absorption [9], lowering plasma cholesterol in humans by 15–20% [22]. Nevertheless, for a long time the mechanism of ezetimibe action has remained vague. Radioligand binding investigations indicated that the direct target of ezetimibe is a Niemann-Pick C1-Like 1 transporter (NPC1L1) [22]. The NPC1L1, located in the brush border of enterocytes, is a critical protein in cholesterol transmembrane transport in the small intestine [3, 17]. Ezetimibe binds to its extracellular loop and blocks sterol absorption [17]. In comparison, bile acid sequestrants (BAS), which are positively charged indigestible resins, bind to negatively charged bile acids in the intestinal lumen and block their recirculation, followed by excretion in the feces and leading to the depletion of the endogenous cholesterol pool [30]. Consequently, the mechanism of lowering cholesterol absorption cannot be identified with the one presented by BAS.

## Further pharmacodynamic properties of ezetimibe

### Inhibition of oxidized LDL absorption and foam cell formation in macrophages

According to recent data, ezetimibe interacts with annexin-2 and caveolin-1, components of an intestinal sterol transport system, to form a heterocomplex, thus leading to the inhibition of micellar cholesterol uptake into enterocytes [64, 67]. The same mechanism has been observed in human macrophages, which also express annexin-2, caveolin-1 and NPC1L1. However, in this type of cell, the expression of NPC1L1 is about 0.3–0.5% of that seen in enterocytes [64]. The drug molecules specifically bind to the surface receptors, which are then endocytosed through the classical pathway. In macrophages loaded with oxidized low density lipoproteins (ox-LDL), ezetimibe subsequently represses LXR/RXR gene lipid induction and inhibits the expression of apolipoprotein E (ApoE)

and LXR. Ezetimibe dose-dependently decreases ox-LDL absorption by 50%, specifically and effectively reducing the formation of foam cells [64].

### Anti-inflammatory features

Presently, atherogenesis is regarded not only as a process of passive lipid deposition in the vascular wall but also as an inflammatory process [48, 71]. Inflammation, which involves all of the cellular elements of the vascular wall, i.e., endothelial cells, myometrial cells and immune cells, is extensively perceived to be the major factor in the etiopathology of atherosclerosis [76].

Numerous trials have demonstrated that ezetimibe, used as monotherapy or in combination with statins, significantly influences the level of blood inflammation markers; e.g., it reduces the C-reactive protein (CRP) level [1, 15, 34, 44, 46, 54, 65]. Considering this property, ezetimibe administered in a standard dose of 10 mg per day combined with a low dose of pravastatin (10 mg) is more effective than a high dose of pravastatin (40 mg) alone [15]. Nevertheless, there is no significant difference between therapies using 80 mg of simvastatin and 10 mg of simvastatin coadministered with 10 mg of ezetimibe [65]. Despite this, it has been demonstrated that ezetimibe reduces CRP levels by 6% compared with placebo, but when added to statin treatment, it causes a 10% reduction [54]. Comparing daily treatment with 20 mg of simvastatin to treatment with 10 mg of ezetimibe, the latter proves to be more effective in reducing the level of CRP. Ezetimibe and simvastatin improve the Disease Activity Score of rheumatoid arthritis, which is a chronic inflammatory condition resulting in an increased cardiovascular risk [46].

Overall, it is still unclear whether the reduction of the CRP level in blood by treatment with ezetimibe is an important pleiotropic effect itself or if it is related to the concurrent LDL level decrease [46, 54]. Investigations suggest a weak positive correlation between changes in CRP and LDL levels, but only in the case of the addition of ezetimibe to statin therapy [46]. This may demonstrate that the anti-inflammatory action may derive from a reduction in LDL.

Ezetimibe also exerts an effect on the endothelium [1, 44, 46, 65]. The drug was proven to enhance brachial artery flow-mediated vasodilatation (FMD), which is a metric used to describe endothelial function [46, 65]. Ezetimibe has also been evaluated in comparison with another endothelial parameter, the Rho-associated coiled-coil containing protein kinase (ROCK), which is increased in vascular inflammation and endothelial dysfunction. These reports, however, indicated that high doses of statins have a better effect than ezetimibe and low doses of statins in combination. Only high-dose statin monotherapy (40 mg), not simvastatin (10 mg) plus ezetimibe (10 mg), significantly reduced ROCK activity and increased FMD [44]. In summary, ezetimibe seems to reduce inflammation in combined therapy with statins, but the effect exerted on endothelial function appears mixed or unclear [1].

### Immunomodulative properties

Cardiac allograft vasculopathy (CAV) is considered to be the primary cause of mortality in patients living more than 5 years after cardiac transplantation [72]. CAV, an effect of the development of atherosclerosis, is a result of hyperlipidemia [35], and thus it is treated with lipid-lowering agents such as statins. CAV, moreover, appears to be dependent on T lymphocyte activity [74]. In particular, it has been demonstrated that CD4+ lymphocytes infiltrate the vascular walls of the allografts arteries at a significantly higher rate [75]. T lymphocytes also play a crucial role in the progress of atherosclerosis and acute coronary incidents [63].

Having considered these facts, one group investigated the influence of ezetimibe on the immune system. After incubating peripheral blood mononuclear cells with ezetimibe, a significant linear reduction in the CD3+CD4+ T helper subpopulation as well as in CD3+CD4+CD45ro+ T memory cells was observed. Expressed in median values, a 10 mg simulated dose of ezetimibe diminished the CD3+CD4+ T cell count from 469 to 358, and a 100 mg simulated dose of ezetimibe diminished the count to 303 [66]. However, no significant changes were noticed in either the CD3+CD8+ T cytotoxic cell count or in the amount of CD107a, a highly sensitive marker of cytotoxic T cell degranulation, in comparison with placebo [66].

The above information regarding the decrease in helper and memory T cells may be of great importance in transplant patients, as CD4+ lymphocytes play a critical role in the process of acute graft rejection. Nevertheless, the *in vivo* reproducibility of these *in vitro* findings might be affected by the differences in absorption and biotransformation of the drug. Also, the assump-

tion that 1 kg of body weight equals 1 liter of volume of distribution may create a significant error profile. The *in vitro* conditions cannot be easily translated into equivalent conditions in an organism [66].

### The influence of ezetimibe on raft-associated antigens

It has been previously determined that CD13 (aminopeptidase N), a raft-associated antigen, is a molecular target of ezetimibe in the enterocytic brush border membranes [42]. CD13 is also constitutively expressed in the lipid rafts of monocytes and macrophages [49]. Further investigations revealed a significant decrease in the expression of the surface raft-associated antigens CD13, CD16, CD36 and CD64 in monocyte-derived macrophages cultured with ezetimibe *in vitro*. Ezetimibe is also likely to cause a redistribution of CD13 from the cell membrane to cytoplasmatic vesicles, leading to a major shift in the localization of CD13 to these structures. In addition to this effect, the drug was found to reduce the total cellular CD13 concentration [49]. Nonetheless, no significant changes regarding CD11b and CD14 expression were observed [49]. Because the raft-associated antigens scavenger receptor CD36 and Fcγ receptors CD16 and CD64 are in charge of modified lipoprotein uptake and phagocytosis, in addition to associating with CD13, ezetimibe may impair macrophage differentiation and lipid absorption in these cells [49].

### Ezetimibe and atherosclerosis

Despite its anti-inflammatory and immunomodulatory actions, the effect of ezetimibe on carotid artery atherosclerosis has not been documented. In the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, Kastelein et al. did not observe any differences between the primary end points as measured by changes in the carotid intima-media thickness (CIMT) between familial hypercholesterolemic subjects who were randomly assigned a high dose of simvastatin (80 mg daily) plus ezetimibe (10 mg daily) or the same dose of simvastatin plus placebo [33]. Nevertheless, this observation, in contrast with the finding of a significant difference between both groups in the degree of reduction of plasma LDL cholesterol and hsCRP, which was more pronounced in the former group of patients, may be attributed to a small initial value of CIMT (0.70 mm) [33].

In the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study, which was a randomized, double-blind trial involving 1873 patients with mild-to-moderate, asymptomatic aortic stenosis, the patients who received 40 mg of simvastatin plus 10 mg of ezetimibe did not show any significant effect on the composite end point of death from cardiovascular causes, aortic valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention and nonhemorrhagic stroke [62]. Although there was a trend toward a reduction of ischemic cardiovascular events through a median follow-up of 52 months, it remains uncertain whether this trend is associated with the action of ezetimibe or simvastatin [62].

Moreover, in patients with type 2 diabetes and no prior cardiovascular events who participated in the Stop Atherosclerosis in Native Diabetics Study (SANDS), reducing LDL cholesterol levels to aggressive targets (less than 70 mg/dL) resulted in a regression of CIMT similar to patients who achieved equivalent LDL cholesterol reductions from a statin alone or statin plus ezetimibe [20].

### Potential for carcinogenicity

The SEAS study reported surprising results considering the possible carcinogenicity of ezetimibe. It indicated a statistically significant increase in the occurrence of cancer in the statin-ezetimibe group compared with placebo at 9.9% *vs.* 7.0%, respectively, as well as an increase in cancer deaths at 4.1% *vs.* 2.5%, respectively [27]. Prostate and skin cancer were found to occur most frequently [27]. Nonetheless, despite the significance of the differences, the percentages were small, and the causal relationship with the drug administration does not appear credible. In the proposed carcinogenic mechanism of action, ezetimibe was supposed to interfere unselectively with the gastrointestinal absorption of cholesterol, influencing the absorption of molecules affecting cancer cell growth [18, 27].

The larger trials following SEAS, such as the Study of Heart and Renal Protection (SHARP) and the Improved Reduction of Outcomes Vytorin Efficacy International Trial (IMPROVE-IT), refuted the hypothesis of that ezetimibe has carcinogenic properties.

Both trials demonstrated no increase in cancer incidence in the group treated with ezetimibe and simvastatin [18, 27, 55]. No connection between exposure to these drugs and an elevation of carcinogenicity was observed, which suggests the lack of a causal relationship [27]. Nonclinical studies also supported the findings of SHARP and IMPROVE-IT, verifying that therapeutically used ezetimibe does not present any carcinogenic hazards to humans [26]. Additionally, recent findings may even suggest opposite properties of ezetimibe. In addition to lowering the cholesterol concentration, ezetimibe was found to increase levels of the angiogenesis inhibitor thrombospondin-1 in human prostate cancer xenografts in mice, suppressing prostate cancer growth by inhibiting tumor angiogenesis [68].

## Pharmacokinetics of ezetimibe

### Absorption

The absolute bioavailability of ezetimibe has not been determined, as the substance is virtually insoluble in aqueous solvents suitable for intravenous administration [21]. Ezetimibe is rapidly absorbed from the gastrointestinal tract [53] and efficiently biotransformed into ezetimibe glucuronide [19, 53]. The absorption of the substance from the intestine was demonstrated to be a first-order process, described by an absorption half-life with a range of 0.5 and 0.8 h in a population model [19]. Because food does not demonstrate any impact on the extent of absorption of ezetimibe, it can be administered with or without meals [11, 21]. However, other investigations revealed that high fat meals may increase the total bioavailability of ezetimibe by 25–35% [11]. High fat meals were also observed to increase the peak plasma concentration ($C_{max}$) by 38% after oral ingestion of 10 mg of ezetimibe [21].

Ezetimibe glucuronide accounts for the majority of the total drug concentration in human blood plasma, including glucuronide conjugated and unconjugated ezetimibe, reaching 80–90% [53]. A meta-analysis including 154 healthy volunteers who were given 10 mg of ezetimibe orally showed that the $C_{max}$ of total ezetimibe was 83 ng/ml and that the area under the plasma concentration-time curve (AUC) was 773 ng × h/ml, while the relevant values for unconjugated ezetimibe were 6.0 and 84.0, respectively [36]. The time of maximal concentration ($T_{max}$) of conjugated ezetimibe in plasma was found to be, on average, 2–3 h after administration. Soon after, the concentration of both conjugated and unconjugated ezetimibe rapidly declined, followed by an increase, demonstrating the occurrence of multiple peaks due to enterohepatic recycling [19, 53]. The $T_{max}$ of unconjugated ezetimibe was found to be between 4–8 h in the above investigations by Ezzet et al. [19] and about 10 h in the study by Patrick et al., in which ezetimibe was administered in a single 20 mg oral dose [53]. In the studies by Courntey et al. [11] and Reyderman et al. [58] with 10 mg of ezetimibe administered orally, the time of maximal concentration of total ezetimibe occurred 1–2 h after ingestion [11, 58].

In the population model developed by Ezzet et al. [19] for single and multiple-dose administration, the $C_{max}$ of ezetimibe was estimated to occur at 1.3 and 1.4 h, reaching 74 and 131 ng/ml, respectively. The analysis of the steady-state pharmacokinetics revealed rapid absorption, with multiple peaks due to enterohepatic recycling and its slow elimination given its estimated terminal elimination half-life of 16–31 h. These investigations demonstrated that, after once-daily dosing, the steady-state concentrations of ezetimibe and total ezetimibe in plasma are reached after approximately 10 days [39].

### Distribution

The pharmacokinetic profile of ezetimibe is described as a two-compartment model [19]. Because it appeared that the volume of distribution (V) in the central compartment could not be treated independently from the parameter of bioavailability (F) in the given model, a relative volume of distribution (V/F) was used. For the estimations, F was fixed at 1, resulting in a V/F of 107.5 and 105.3 l for single- and multiple-dose administration, respectively [19].

In the given population model, the estimated amount of ezetimibe recycled from the intestine to the central compartment was found to be 17–20% of the total amount absorbed, independent of the volume of distribution [19]. The model revealed that ezetimibe and its glucuronide derivative are released with bile from the gallbladder during meals [19]. Other investigations revealed that the plasma peaks corresponding to enterohepatic recycling were found at about 4–6 h and 10–12 h, confirming a correlation with meal times [53].

Following ingestion and intestinal absorption, ezetimibe is glucuronidated, enters portal plasma, passes through the liver and is returned to the lumen of the intestine with bile. At this point, ezetimibe glucuronide binds to the intestinal wall, with more than 95% of the total drug accumulating there [36].

A high level of ezetimibe and its glucuronide metabolite were observed to bind to human plasma proteins. In the *in vitro* experiments, the mean protein binding was 99.5–99.8% and 87.8–92.0% for ezetimibe and ezetimibe glucuronide, respectively [39]. Additionally, the *in vivo* investigations revealed that the total ezetimibe protein binding ranged from 93.9 to 94.5% [60].

### Biotransformation

In the human organism, ezetimibe undergoes intensive biotransformation (Fig. 2), mainly of phase II, through which it is transformed into two glucuronides [24, 53]. The process takes place in the jejunum and liver, carried out by different isoforms of UDP-glucuronosyltransferase (UGT) [24]. The main metabolite circulating in human plasma is a phenolic glucuronide, formed by 4-hydroxyphenyl group glucuronidation, while the second conjugate – a benzylic glucuronide – constitutes a trace metabolite. The phenolic conjugate was found to be produced *in vitro* by liver microsomes supplemented with UDP-glucuronic

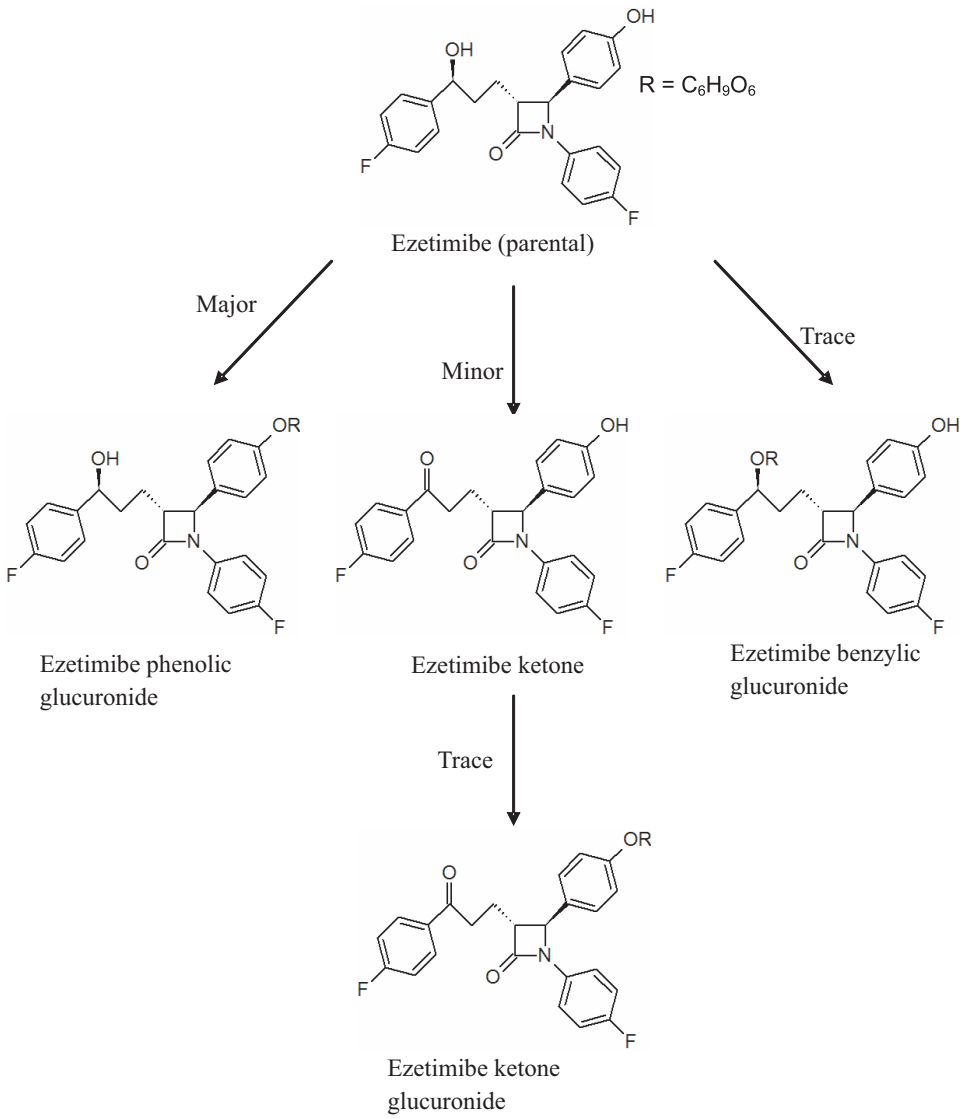


**Fig. 2.** Ezetimibe biotransformation scheme

acid. In contrast, the benzylic derivative was formed in jejunum microsome cultures [24]. The experiments revealed that the phenolic glucuronide was conjugated by the UGT1A1, UGT1A3 and UGT2B15 isoforms, while the benzylic glucuronide is conjugated by the UGT2B7 isozyme [24].

The cholesterol lowering activity of the phenolic glucuronide was found to be comparable with the parent compound [53]. This derivative accounts for about 90% of the total ezetimibe [19]. The quantity of the benzylic conjugate is marginal, reaching about 1% [39].

Other minor metabolites are a ketone derivative, the oxidative product of phase I biotransformation, and the 4-hydroxyphenyl glucuronide, which account for a total of 4.1% of the administered dose. The glucuronide of the ezetimibe ketone analogue comprises about 0.9% of the dose [53].

## Excretion

Ezetimibe and its metabolites are excreted mainly with feces (78%), and only small amounts are found in urine [53]. In the experiment with radiolabeled ezetimibe, the amount detected in urine consisted of approximately 11% of the administered dose [53]. Hypothetically, ezetimibe glucuronide undergoes hydrolysis during intestinal transit and biliar secretion [19, 53]. Due to that process and probable incomplete ezetimibe absorption, approximately 68.6% of the dose is excreted as the parent drug *via* feces after 96 h [53]. After the 72 h collection, it was found that the main metabolite detected in urine was ezetimibe glucuronide, consisting of approximately 9% of the dose. A glucuronide ketone derivative of ezetimibe accounted for less than 1% of the dose and was the minor metabolite excreted in urine [53]. In total, the occurrence of the ezetimibe ketone and its glucuronide amounted to 4.1% in feces and urine together [53]. Altogether, after 240 h, approximately 89% of the dose was excreted *via* both mechanisms [53]. Based on the cumulative amount of the excreted radiocarbon, the estimated half-life of ezetimibe was determined to be approximately 24 h, the same as the plasma half-life for ezetimibe glucuronide [53]. The investigations of repeated dose administration revealed that the terminal elimination half-life of ezetimibe was estimated to be from 16 to 31 h [39]. In the population model, the estimated terminal elimination half-life was 30 h [19].

## Genetic aspects

### Influence of cellular transporters

There is ample evidence supporting the idea that the hepatic extraction of multiple endogenous substances as well as many drugs (e.g., pravastatin [77]) from the sinusoidal blood depends on specific protein carriers such as the organic anion transporting polypeptide (OATP) [8]. In that light, the influence of OATP polymorphisms on ezetimibe pharmacokinetics was investigated as they relate to the extensive enterohepatic recycling [51]. Experiments with OATP1B3-, OATP2B1-, and OATP1B1-transfected HEK cells, including the OATP1B1 variants OATP1B1*1b, OATP1B1*5 and *15, were carried out to reveal the impact of genetic polymorphisms on ezetimibe and its glucuronide disposition [51]. It was found that ezetimibe glucuronide inhibited the uptake of bromosulfophthalein, a common OATP substrate, in all the OATP-transfected cells investigated, whereas the potency of the parent ezetimibe was 30–100 times smaller regarding that process. While ezetimibe glucuronide significantly accumulated in the cells expressing OATP1B1 and OATP2B1, diminished accumulation was observed in OATP1B1 variants *1b and *5 [51].

In the *in vivo* experiments with single-dose administration of 20 mg of ezetimibe in participants with OATP1B1*1b (*1a/*1b, *1b/*1b), a reduction in the AUC of the drug and a tendency for increased glucuronide exposure was noticed. In *1b/*1b carriers, the fecal excretion of ezetimibe was significantly lowered, while the renal excretion of ezetimibe glucuronide was increased. Similarly, fecal excretion was decreased in the OATP1B1*5 and *15 variants [51]. In the homozygous *1b variant, hepatocyte extraction of glucuronide from sinusoidal blood was weaker. Nevertheless, this led to only a marginal increase in serum levels due to the compensatory increase of glomerular glucuronide filtration in the kidneys [51]. The described OATP1B1 polymorphisms were not of significance regarding the sterol-lowering effect of ezetimibe [51].

The *in vivo* studies with healthy volunteers revealed that other transporters, such as the intestinal uridine diphosphate-glucuronosyltransferases (UGTs) and the efflux transporters P-glycoprotein (P-gp) (ABCB1) and multidrug resistance associated protein 2 (MRP2) (ABCC2), are also of great importance regarding ezetimibe pharmacokinetics and therapeutic

effects [50]. In the subjects given rifampin to upregulate the previously mentioned transport proteins in the intestine, markedly decreased AUC values for ezetimibe and its glucuronide derivative were observed (116 ± 78.1 ng × h/ml *vs.* 49.9 ± 31 ng × h/ml and 635 ± 302 ng × h/ml *vs.* 225 ± 86.4 ng × h/ml, respectively). The upregulation of the transporters also resulted in increased intestinal clearance of both ezetimibe and ezetimibe glucuronide (2,400 ± 1,560 ml/min *vs.* 5,500 ± 4,610 ml/min and 76.6 ± 113 ml/min *vs.* 316 ± 457 ml/min, respectively) [50]. In effect, the sterol-lowering action of ezetimibe was almost abolished [50].

The *in vitro* studies also demonstrated high affinity of ezetimibe glucuronide for MRP2 and low affinity for P-gp, while the parent compound ezetimibe is a high-affinity substrate for both transporters [50].

#### CYP3A4 inhibition ambiguity

The lack of effect of ezetimibe on cytochrome CYP3A4, a common enzyme that metabolizes many substances including most lipid-lowering statins [52, 82], has been demonstrated. However, recent findings seem to indicate a greater complexity of the problem [52].

In human liver microsomes (HLM), ezetimibe was found to act as an irreversible, metabolism-dependent inhibitor of CYP3A4 [52]. After 0.5 h of preincubation of NADPH-fortified HLM with ezetimibe, an approximately 100-fold shift of the $IC_{50}$ value for CYP3A4 inhibition (from 31 to 0.34 μM) was noticed, comparable to the effect caused by mibefradil, an antihypertensive drug, which was withdrawn from the US market due to its strong and prolonged inhibitory action against CYP3A4 [52]. It was also noticed that in hepatocytes, in the presence of UDP-glucuronic acid, both the direct and metabolism-dependent inhibition of CYP3A4 was decreased. Regarding the direct effect, the $IC_{50}$ was about 3-fold higher, changing from 12 to 37 μM, whereas in the experiments with preincubation to account for the metabolism-dependent effect, the $IC_{50}$ increased about 9-fold, from 0.24 to 2.1 μM [52].

Considering the above facts, it was concluded that the system-dependent inhibition of CYP3A4 by ezetimibe is reduced because of the protection emerging from glucuronidation, which occurs in hepatocytes but not in NADPH-fortified HLM [52]. To summarize this data, it can be deduced that hepatocytes are responsible for the clinical outcome because, for several drugs, no significant pharmacokinetic effects resulting from CYP3A4 inhibition, such as changes in $C_{max}$ or AUC, are observed [52].

## Pharmacokinetic drug interactions

### Statins

No clinically significant pharmacokinetic interactions between ezetimibe and simvastatin [37], atorvastatin [81], lovastatin [56], fluvastatin [57], rosuvastatin [13, 41] or pravastatin [39] have been observed. The $C_{max}$ and AUC values did not present any significant alternations for the parental drugs or for their metabolites, such as β-hydroxysimvastatin, *ortho*-hydroxyatorvastatin and β-hydroxylovastatin for ezetimibe or total ezetimibe [37, 41, 56, 57, 81].

However, in case of lovastatin coadministered with ezetimibe, a decrease in the plasma concentrations of lovastatin and β-hydroxylovastatin was observed. These findings, which were unaffected by the dose of ezetimibe, were not considered clinically significant [40]. A similar phenomenon was noticed in the investigation with fluvastatin, but the deteriorated average AUC of the drug was explained by the small sample size (n = 8) and high intersubject variability of fluvastatin pharmacokinetics. Therefore, the difference was evaluated as insignificant [57].

### Fenofibrate

The investigations by Kosoglou et al. [38] with 200 mg of fenofibrate and 10 mg of ezetimibe applied daily revealed that fibrate pharmacokinetics are not significantly affected by the cholesterol absorption inhibitor. Conversely, the parallel administration of these two drugs produced a significant increase in the bioavailability of ezetimibe, showing a 64% and 48% elevation of the $C_{max}$ and AUC of the drug, respectively. However, the effect was not considered clinically significant due to the flat-dose response and established safety profile of ezetimibe [38].

Later investigations by Gustavson et al. [25] with 145 mg of fenofibrate and 10 mg of ezetimibe confirmed the lack of influence of ezetimibe on the pharmacokinetics of fenofibrate. Nevertheless, that study

also indicated that fenofibrate significantly increases the AUC of both total and conjugated ezetimibe by 43% and 49%, respectively [25].

### Gemfibrozil

The experiments with 600 mg of gemfibrozil applied twice daily and 10 mg of ezetimibe applied once daily indicated no pharmacokinetic influence on gemfibrozil regarding its bioavailability as measured by AUC. However, gemfibrozil was found to increase the AUC of ezetimibe and total ezetimibe 1.4- and 1.7-fold, respectively [59]. Nonetheless, these findings were not considered of clinical significance [59].

### Mipomersen sodium

Mipomersen sodium is a novel substance being evaluated in phase II/III clinical trials to assess its utility as an add-on drug to statin therapy for hypercholesterolemia. Considering its properties, it is an intravenously administered antisense oligonucleotide formed of 20mers complementary to human apolipoprotein B-100 (ApoB-100) messenger RNA, which subsequently reduces the translation of the ApoB-100 protein, the major apolipoprotein of very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL) [80]. With respect to AUC values, mipomersen sodium was not found to cause clinically significant pharmacokinetic interactions with ezetimibe and *vice versa* [80].

### Levothyroxine sodium

In the simultaneous administration of levothyroxine sodium and ezetimibe, the latter did not decrease the hormone's AUC value. There is no need for separate application, as ezetimibe was not found to cause pharmacokinetic interactions with levothyroxine sodium [32].

### Cyclosporine

Cyclosporine possesses an evidence-based capacity to raise LDL levels. Many specialists suggest early prophylaxis for hyperlipidemia in patients after transplantation to prevent atherosclerosis and coronary incidents [7]. One of the potential drugs is ezetimibe. Nonetheless, previous data indicate that the level of the drug may be 12-fold higher in cardiac transplant patients receiving cyclosporine and therefore is not recommended [7]. Later studies brought new results. In two treatments in healthy subjects with 100 mg of cyclosporine applied alone (experiment 1) or 20 mg of ezetimibe administered for 7 days or with 100 mg of cyclosporine coadministered on day 7 followed by 20 mg of ezetimibe administered alone on the day 8 (experiment 2), the AUC(0-last) and $C_{max}$ geometric mean ratios were calculated. The values of the ratios for treatment 2 *vs.* 1 were 1.15 and 1.10, respectively. This indicated that the mean exposure to cyclosporine in patients chronically receiving ezetimibe was approximately 15% higher. $T_{max}$ for cyclosporine was found to be similar for both treatments [5]. This data suggests the necessity for monitoring of cyclosporine levels and caution with this treatment in patients concomitantly receiving both drugs [5].

Another experiment, intended to reveal the influence of the immunosuppressant on ezetimibe pharmacokinetics, was carried out on patients after renal transplantation who were set on steady-state cyclosporine by receiving 75–150 mg of cyclosporine twice a day and also were administered 10 mg of ezetimibe (experiment 1). The results obtained were then compared with previous data on ezetimibe pharmacokinetics in healthy volunteers (experiment 2). The values for the geometric mean ratios for AUC(0-last) and $C_{max}$ for experiments 1 and 2 were 3.41 and 3.91, respectively [6]. However, due to the lack of a long-term safety profile for high exposure to ezetimibe, the implication of this result is of unclear clinical significance [6].

### Lopinavir

In HIV patients receiving protease inhibitors (PIs), the increase of triglycerides and cholesterol levels is often observed, resulting in the of addition lipid-lowering therapy. In a study assessing potential interactions between lopinavir and ezetimibe, no alterations in the level of PIs were detected nor was an enhancement in side effects noticed [29].

## Ezetimibe use in specific populations

### Liver transplant patients

As hypercholesterolemia appears to be a common problem among transplant patients, the safety and effectiveness of ezetimibe in that group was tested [2].

The transplant patients were receiving cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil and oral predisone immunosuppressants. Their baseline total cholesterol and LDL values were 236 ± 46 mg/dl and 147 ± 35 mg/dl, respectively. Ten milligrams of ezetimibe daily was added to this regimen, excluding patients on predisone, who were given 5 mg ezetimibe. After 6 months of ezetimibe therapy, a reduction in total cholesterol and the LDL fraction was observed, reaching 208 ± 46 mg/dl and 120 ± 31 mg/dl, representing an 11% and 18% decrease, respectively. Furthermore, after 3 and 6 months of therapy with ezetimibe, 28% and 32% of liver transplant patients, respectively, achieved the target LDL level of ≤ 100 mg/dl. Moreover, neither variations in immunosuppressant levels nor a need to adjust their doses was observed [2]. In this group of patients ezetimibe has been shown to be safe and effective, with no interactions and minor side effects [2].

### Cardiac transplant patients

In an investigation among patients after heart transplantation who were given ezetimibe, the lipid parameters were evaluated after 1 and 12 months of use. After one year of treatment with 10 mg of ezetimibe daily, total cholesterol decreased from 235 ± 49 to 167 ± 32 mg/dl, the LDL fraction decreased from 137 ± 47 to 89 ± 29 mg/dl, the HDL fraction decreased from 54 ± 13 to 51 ± 10 mg/dl and the triglycerides decreased from 243 ± 187 to 143 ± 72 mg/dl. Ezetimibe was found to be effective, with no significant alteration in HDL cholesterol levels in long-term treatment. It did not demonstrate any renal or liver toxicity or significant changes in immunosuppressant pharmacokinetics [12].

However, in spite of the fact of good ezetimibe tolerance in cardiac transplant patients it has been advised to monitor creatine phosphokinase (CPK) levels [12]. Further experiments confirmed recent findings regarding the impact of ezetimibe on lipid levels and minutely evaluated the influence on CPK activity [43]. A significant asymptomatic elevation in the CPK level was reported. CPK levels increased by 31.4 ± 8.1 mM in the ezetimibe (10 mg daily) group in comparison with 1.5 ± 5.0 mM in the placebo group [43].

### Renal transplant patients

In a study in patients after kidney transplantation in which 10 mg of ezetimibe was coadministered with 10 mg of simvastatin daily for 6 months, there was a significant reduction in lipid levels. Total cholesterol decreased by 34.6%, triglycerides by 16% and LDL cholesterol by 47.6%, allowing 82.5% of the patients to reach the target level below 100 mg/dl. No significant changes in the trough calcineurin inhibitor levels or allograft functions were noticed [79]. Other investigations also indicated that ezetimibe significantly lowered total cholesterol, LDL cholesterol and triglycerides [45, 61, 73]. During the investigations, no significant changes in HDL cholesterol [61], proteinuria [61, 79], high sensitivity C-reactive protein level [79], CPK activity [45, 61], amylase level [61], lactose dehydrogenase level [45], body mass index [61] or liver and renal function [45, 61] were observed. No important alternations in drug levels and adverse effects were noticed [45, 61].

It was also found that in patients after kidney transplantation, ezetimibe allows for the stabilization of mean creatinine clearance [73]. The study suggested that ezetimibe could ameliorate the decline of renal function [73].

Ezetimibe with small-dose statin treatment was found to be safe and effective in controlling dyslipidemia in renal transplant patients [45, 61, 79].

### HIV-infected patients

Since the introduction of highly active antiretroviral therapy (HAART), the life expectancy of HIV patients has extended notably, raising concerns about the impact of prolonged exposition to metabolic disorders on their long-term prognosis and outcome [14].

Ten milligrams of ezetimibe daily added to the maximally tolerated lipid-lowering therapy (defined as pravastatin, rosuvastatin, atorvastatin, fenofibrate, niacin and salmon oil) in HIV patients was found to reduce mean total cholesterol by 21%, mean LDL by 35%, mean triglycerides by 34% and mean apolipoprotein B-100 by 33%, and it increased mean HDL by 8% [4].

In a study with 10 mg of ezetimibe daily added to 20 mg pravastatin therapy, 61.5% patients reached the goal of LDL-cholesterol < 130 mg/dl after 24 weeks of treatment. The patients were simultaneously receiving antiretroviral proteinase inhibitors (PIs) or

non-nucleoside reverse transcriptase inhibitors (NNRTIs), and the decline was irrespective of the medication type taken. At the same time, the mean HDL-cholesterol and apolipoprotein A levels increased significantly [47].

In the study by Stebbing et al. [70], 10 mg of ezetimibe was used either alone or in combination with statins. The HIV patients were on PI or NNRTI HAART therapy. After 12 weeks of treatment, a statistically significant 18% reduction in serum total cholesterol and a 28.9% reduction in serum triglycerides was observed. There was no difference, regardless of the type of antiretroviral therapy the patient was receiving. In addition, the decline was independent of the presence of statins in the patient's treatment [70].

Ezetimibe was also investigated in comparative monotherapy in two HIV patient groups being given 10 mg of the drug or 80 mg of fluvastatin daily. Ezetimibe was observed to reduce the LDL-cholesterol level by 20%, which is similar to the fluvastatin group (24%) [10]. In a comparative study with placebo, where 10 mg of ezetimibe was used as monotherapy, after 6 weeks a 5.3% decline in LDL level in the ezetimibe group was observed in comparison with the placebo group, where a 5.5% increase was reported [78].

In all of the treatment schemes, ezetimibe was found to be effective, safe and well tolerated, due to the lack of influence on CYT P450, and it presented a lack of interactions while showing no risk of increasing the antiretroviral toxicity [4, 14, 47, 70]. In coadministration with other lipid lowering agents [4, 14, 47, 70] as well as in monotherapy, [10, 70, 78] ezetimibe was efficient in diminishing LDL levels.

## Conclusions

Ezetimibe is the first known drug that inhibits cholesterol absorption from the intestine through blocking its transport. Often, it is used concomitantly with statins or fibrates when the latter do not achieve satisfying lipid lowering results. The main mechanism of action includes blocking the transport protein NPC1L1 in the brush boarder of enterocytes. Based on the newest findings, ezetimibe inhibits NPC1L1 in the plasma membranes of macrophages and monocytes, thus lowering the uptake of oxidized LDL. Furthermore, it presents anti-inflammatory properties, which are crucial for atherosclerosis treatment as it influences immune cell functions and are also important among transplant patients. Ezetimibe decreases the expression of certain raft-associated antigens, causing an impact on macrophage differentiation and lipid absorption.

Ezetimibe is rapidly absorbed from the gastrointestinal tract with minor influence by food intake. After absorption, it is quickly metabolized, primarily into pharmacologically active glucuronide, which then undergoes extensive enterohepatic circulation, which seems to be correlated with meal time biliary excretion. Both ezetimibe and its glucuronide derivative are highly bound to plasma proteins. Ezetimibe glucuronide constitutes about 90% of the total ezetimibe circulating in blood. Ezetimibe is mainly excreted in the feces and is eliminated from the organism after about 10 days with an elimination half-life of approximately 1 day. Genetic polymorphisms have been proven to have an influence on ezetimibe pharmacokinetics. However, this is unrelated to the pharmacological sterol-lowering effect. In addition, the effect of ezetimibe is abolished when transport proteins were upregulated. Ezetimibe inhibits CYP3A4, but the effect is metabolism-dependent and is lowered by glucuronidation in hepatocytes; thus, it does not cause a significant impact on the pharmacokinetics of CYP3A4-metabolized drugs.

Ezetimibe does not present any clinically significant interactions with statins, fenofibrate or gemfibrozil. Furthermore, there is no significant interaction between ezetimibe and mipomersen sodium, levothyroxine or lopinavir. Ezetimibe raises the levels of cyclosporine, but the significance of this phenomenon remains unclear.

The drug is effective and safe in patients after heart, kidney or liver transplantation and well tolerated in the treatment of hypercholesterolemia in HIV-infected patients. It remains a good option in the case of statin intolerance or insufficiency of action.

Ezetimibe is an important drug in the development of hypercholesterolemia treatment. Its high effectiveness combined with a good tolerance among various groups of patients taking a wide variety of other drugs strengthens the argument for ezetimibe treatment.

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