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PHARMACOLOGY AND PHARMACOKINETICS OF EZETIMIBE AND SIMVASTATIN FOR DYSLIPIDEMIA

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ABSTRACT

Cardiovascular disease involves cardiovascular systems: heart, blood vessels, and blood circulation system. One of the main risks of cardiovascular disease is arteriosclerosis resulted from dyslipidemia in which LDL cholesterol increases. Simvastatin is one of the derivatives of Statins also known as 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase used to reduce cholesterol. Ezetimibe reduces cholesterol by working in the brush border located in the small intestine to block the reabsorption of cholesterol. As a result, less cholesterol is taken to the liver. The combination of ezetimibe (10mg) and simvastatin (10, 20, 40 mg) is effective in reducing the level of LDL-C, so it can be used to cure dyslipidemia suffered by patients with an increased cardiovascular disease risk.

KEYWORDS: Ezetimibe, Simvastatin, Dyslipidemia.

I. INTRODUCTION

Cardiovascular disease involves cardiovascular systems: heart, blood vessels, and blood circulation.[1] From 2004 to 2014, even though mortality rate caused by heart coronary disease had been reduced by 35%, the risk factor was still high.[2] One of the main risks of cardiovascular disease is arteriosclerosis resulted from increased LDL cholesterol.[3]

Dyslipidemia is a metabolic disorder increasing plasmatic concentration of cholesterol and triglycerides and a common global cause of morbidity. Hypercholesterolemia is its common form where the total cholesterol level is above 5.0 mmol/L or 190 mg/L. One third of ischemic heart diseases in the world is a secondary result of hypercholesterolemia.[3]

The use of statins is the initial therapy recommended to manage patients with high lipid risk.[4] Ezetimibe serves to block the reabsorption of cholesterol in the intestine and bail. The combination of low-dose ezetimibe and statins is effective in inhibiting the production of endogenous and exogenous cholesterol, reducing the level of plasma LDL cholesterol.[5]

II. DISCUSSION

A. Chemical Definition and Information of Ezetimibe and Simvastatin

1. Ezetimibe

The chemical name of Ezetimibe is 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4hydroxyphenyl)-2-azetidinone. It is available in a 10-mg dose. Ezetimibe was firstly developed as a potential inhibitor of Acyl-coenzyme: A cholesterol acyltransferase (ACAT) intracellular. Ezetimibe is also abundantly expressed in the human liver. If it is given as monotherapy or combined with statins, it can reduce low density lipoprotein (LDL) by 18% by increasing LDL catabolism.[6]

2. Simvastatin

Simvastatin is one of the statin derivatives also known as 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors used to reduce cholesterol. It is also reportedly effective for atherosclerosis. Simvastatin is a rate-limiting enzyme involved in the cholesterol biosynthesis mainly expressed in the liver. Simvastatin is a type-1 statin binding HMG-CoA reductase through decalin ring structure.[6,7]

B. PHARMACOLOGY

Simvastatin is hydroxy-methylglutaryl Coenzyme A (HMG-CoA) reductase inhibitors. The general pharmacology activity of statins depends on the strong inhibition from the endogenous mevalonate pathway, directly leading to cholesterol biosynthesis and isoprenoid, that in turn binding the micromolar concentration.[8] HMG-CoA inhibition decreased cell cholesterol, increasing LDL receptor expression in the liver and decreasing LDL-C serum level.[9]

Ezetimibe is a cholesterol absorption inhibitor that is primarily defined as a drug to change the lipid and potential to inhibit cholesterol absorption in the bile and small intestine without affecting vitamin absorption. Ezetimibe works in the enterocyte brush border located in the small intestine and reduces the reabsorption of cholesterol to the enterosit.[10]

There are specific synergy effects from the combining ezetimibe with simvastatin. An in vivo kinetic study on lipoprotein using stable isotope in human beings argues that compared to monotheraphy, the combination of ezetimibe and simvastatin gradually increasing lipoprotein catabolism containing apolipoprotein (apo) B, including LDL, is more effective in increasing LDL catabolism. Besides, the regulation of liver LDL receptor expression is also more effective. The combination of 10mg-dose ezetimibe and low-dose (10-20mg) simvastatin increases LDL-C that is proportional with or more effective than 80-mg dose simvastatin or the highest-dose of statins.[6]

C. MECHANISM OF ACTION

1. Ezetimibe

Ezetimibe reduces cholesterol by working in the brush border located in the small intestine to block the reabsorption of cholesterol, lessening cholesterol taken to the liver. it reduces hepatic cholesterol and increases cholesterol cleansing from blood.[11]

Ezetimibe inhibits cholesterol absorption by small intestines by inhibiting Niemann-Pick C1-Like 1 (NPC1L1) in the brush border located in the small intestine. Therefore, sterol and biliary are inhibited, leading to up-regulated LDL receptor and increased LDL-C serum absorption (9). When the concentration of extracellular cholesterol is high, cholesterol will be inserted into cell membrane and NPC1L1 on the cell surface and internalized together through endocytosis mediated by clathrin adaptor protein. Next, it is transported along the microfilament to Endocytic Recycling Compartment (ERC) in the vesicle where cholesterol is stored. When the level of intracellular cholesterol is low, NPC1L1 localized by ERC moves back to PM along the microfilament to absorb cholesterol. Ezetimibe inhibits complex interaction of NPC1L1/cholesterol with complex AP2-clathrin.[12]

2. Simvastatin

Simvastatin is hydrolyzed in vivo to produce beta, delta-dihydroxy acid, active metabolites that are structurally similar to HMG-CoA (hydroxymethylglutaryl CoA). In the first hydrolysis, simvastatin competes with HMG-CoA for reductase HMG-CoA, the liver microsomic enzyme. By the enzyme activity, the amount of mevalonic acid, cholesterol precursor, is reduced. Simvastatin is 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors.[13] The beneficial effect of simvastatin is that it can reduce cholesterol biosynthesis, especially in the liver, where it is distributed selectively. In addition to that, it

also can modulate lipid metabolism that originally comes from their inhibition effect on the HMG-CoA reductase.[14]

D. PHARMACOKINETICS

Pharmacokinetic study shows that ezetimibe – simvastatin is a combined tablet whose component is bioequivalent simultaneously given. A non-active lactone proactive medicine, simvastatin is quickly absorbed and hydrolyzed into active beta-hydroxyacid having bioavailabity by 5% because it is processed through first-pass hepatic metabolism. The binding of the protein is more than 95%. From many entities involved in the elimination of simvastatin, cytochrome P450 (CYP) 3A4 is the central of oxidation and transportation to the liver. Its most eliminations are fecal through the bile excretion. Due to its small component, it can be eliminated in the kidney for two-five hours after administration of 10-mg dose.[6]

After oral administration, ezetimibe is absorbed in the form of glucuronidated and changed into a single active metabolite. The affinity of NPC1L1 binding is higher than ezetimibe. Drug and metabolite are closely bound with protein. Around 80% of ezetimibe administered orally is excreted in the stool; while the rest contained in the urine is mainly in the form of glucuronide.[6] Ezetimibe reaches peak plasma concentration at 4-12 hours with half-life of 22 hours. 10-20% of ezetimibe is found in the blood circulation; while 80-90% of it is in the form of active metabolite, which is glucuronide. Ezetimibe and its metabolite are closely bound with plasma protein. Ezetimibe and ezetimibe-glucuronide are found in the intestinal epithelium, especially in the brush border cell, where cholesterol is inhibited and phytosteroid is absorbed. 80% of the drug is excreted in the stool, while ezetimibe-glucoronide is excreted in the urine in a small amount.[15]

Simvastatin is found in the form of inactive lactone prodrug and quickly absorbed in the gastrointestinal and hydrolyzed in the liver in the form of beta-hydroxyacid active metabolite. It reaches the peak plasma concentration in two-four hours with half-life of five hours. 95% of the drug is circulated and bound with plasma protein. The enzyme involved in the metabolism and elimination of simvastatin is cytochrome P450 (CYP) 3A4 involved in the process of intrahepatic oxidation and transportation. Simvastatin is generally eliminated though the stool by biliary excretion and excreted though the kidney in a small amount.[15]

1. Effect of Ingested Food

The level of ezetimibe absorption is not affected by all types of food ingested, but high-fat food may increase the maximum plasma concentration (Cmax) by 38%. Profile of simvastatin pharmacokinetics is not affected by foods when it is given.[15]

2. Effect of Age, Gender, and Race

In the literature, age, gender and race provide significant effects to ezetimibe and simvastatin pharmacokinetics. However, the latest pharmacokinetic study has been identified by using more than 40 of gene variations that are able to modify statin pharmacokinetics, especially parameter such as AUC0-last and half-life.[15]

3. Effect of Liver Dysfunction

For mild liver impairment, 10-mg dose ezetimibe therapy does not require dose adjustment. However, the administration must be stopped when moderate or severe hepatic insufficiency occurs because it can increase the drug exposure. The significant effects of statin pharmacokinetics in the mild hepatic impairment condition; such as increased plasma concentration (peak concentration) and steady state in patients with severe hepatic insufficiency[15] are not stated in the literature.

Table 1: Pharmacokinetic Characteristics, Dose, and Parameter of Ezetimibe and Simvastatin.[10,15]

Description	Ezetimibe	Simvastatin
Solubility	Ethanol, methanol, and acetone soluble	Fat soluble
Absorption (%)	90	60-80
Bioavailability (%)	Not measurable	<5
Protein bind (%)	> 90	>95
Prodrug	Yes	Yes
Metabolic pathway	Glucuronide conjugation	CYP3A4
Active metabolite	Yes	Yes
Half-life	22	2-5
Transporters involved in liver	ATP-binding cassette transporter	QATP1B1
Unmodified urinary excretion (%)	Not significant	Not significant

4. Effect of Kidney Dysfunction

Ezetimibe (10mg) treatment can also be tolerated properly by the subject with kidney dysfunction, so that no dosage adjustment is required.

Kidney insufficiency does not affect simvastatin pharmacokinetics. However, even though the administration does not have contraindication, it is suggested giving low-dose (10mg) simvastatin lower than 30ml/minute for patients with Gromerular Filtration Rate (GFR).[15]

E. PHARMACODYNAMICS

Ezetimibe is an effective cholesterol inhibitor. It absorbs phytosterols in the intestine, but does not absorb triglycerides and vitamins dissolved in fat. It selectively blocks Niemann-Pick C1 Like 1 (NPC1L1) protein in the brush border, allowing sterol biliary absorption by up-regulating LDL receptor and increasing LDL absorption in the liver. Genetic variant of NPC1L1 protein appears to affect the level of LDL-C plasma, but the effect on ezetimibe efficacy is still unclear, so it requires further research.[15]

Simvastatin, produced from the lovastatin methylation process is very effective. It is a reversible 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase inhibitors and the main microsomal enzyme involved in the cholesterol biosynthesis in the liver. It reduces the production of mevalonic acid, cholesterol precursors, leading to up-regulated LDL receptors expressed in the liver by decreasing the level of LDL cholesterol and cardiovascular risks. Working mechanism of the two lipid reductions above is substantially different, but complementary and perfects each other. Some gene polymorphisms appear to significantly affect the effectiveness of lipid reduction from simvastatin.[15]

F. DRUG INTERACTION

Simvastatin is a substrate of cytochrome p4503A4, and as a consequence of its co-administration, potent inhibitors of cytochrome p4503A4 is increased. Simvastatin serves as a HMG-CoA reductase inhibitor in plasma and may have myopathy and rhabdomyolysis effects. This also happens when simvastatin is administered along with ketoconazole, itraconazole, posaconazole, clarithromycin, telithromycin, erythromycin, and human immunodeficiency virus protease inhibitor (such as nelfinavir). Cyclosporine inhibits CYP3A4 and OATP1B1 transporters and when administered with simvastatin, it may bring myopathy and rhabdomyolysis effects. The administration of simvastatin with fusidic acid or colchicine may also increase rhabdomyolysis effects, especially in patients with kidney dysfunction. Potent CYP3A4 induction such as rifampicin can reduce simvastatin effectiveness.[9]

Table 2: Drugs Potentially Interacting with Ezetimibe/Simvastatin.[9,11]

Description	Inhibitor	Inducer
CYP3A4 Substrates	Azole antifungals, erythromycin, clarithromycin, tricyclic antidepressants, nefazodone, venlafaxine, fluvoxamine, fluoxetine, sertraline, cyclosporine A, tacrolimus, amiodarone, danazol, diltiazem, verapamil, protease inhibitors, midazolam, corticosteroids, tamoxifen	Phenytoin, phenobarbital, rifampin, dexamethasone, cyclophosphamide, carbamazepine, omeprazole, St. John's-wort
MDR/ P-glycoprotein	Ritonavir, cyclosporine, verapamil, erythromycin, Ketoconazole, itraconazole, quinidine	Rifampicin, St. John's-wort

Ezetimibe metabolism does not count on the conversion and has activities to inhibit some CYP P450 isozymes. Ezetimibe does not give significant effect to bioavailability of digoxin, warfarin, statins, ethinyl estradiol, or glipizide. Ezetimibe does not give significant effect to bioavailability of gemfibrozil or fenofibrate, yet the drug may increase the bioavailability of the ezetimibe. The increase does not give significant effect to the clinical effectiveness of the ezetimibe. The administration of cholestyramine can reduce area under the curve (AUC) of the ezetimibe by 80%. Cholestyramine can increase bioavailability of the ezetimibe.[9]

G. CONTRAINDICATION

Ezetimibe is not recommended for patients with moderate-severe hepatic insufficiency. There is no dose adjustment for patients with hepatic and kidney impairment.[9]

Simvastatin is contraindicated for use during pregnancy or pregnancy program. It is because cholesterol and its derivatives are needed for normal fetal growth. Grapefruit juice is an inhibitor component of CYP3A4 and can increase plasma level metabolized by CYP3A4 enzyme. The combination of statin and ezetimibe is able to be excreted in breast milk and not recommended to be administered to breast-feeding women.[11]

H. DOSAGE

Ezetimibe should administered by 10mg-dose once a day; while simvastatin should be administered by 10 mg, 20 mg, 40 mg, 80 mg-dose once a day. Meanwhile, the combination of ezetimibe/simvastatin in a single tablet that has a fixed dose of 10 mg ezetimibe and variable doses of (10/20/40mg) simvastatin can cure primary and secondary hypercholesterolemia.[15]

1. ***Familial Hypercholesterolemia – Homozygous***

10mg-dose ezetimibe/40mg-dose simvastatin are orally administered once a day in the evening. They should be given every day for 12 months or more without muscle toxicity.[11]

2. ***Hyperlipidemia, Primary***

Dosis awal, ezetimibe 10 mg / simvastatin 10 mg atau ezetimibe 10 mg / simvastatin 20 mg sekali sehari per oral di malam hari; kisaran dosis keduanya dapat mengurangi LDL-C lebih besar dari 55%.[11]

3. ***Mixed hyperlipidemia***

The initial dosage is 10mg of ezetimibe/10 mg of simvastatin or 10 mg of ezetimibe/20 mg of simvastatin orally administered once a day at night; the range of both dosages is able to reduce LDL-C that is higher than 55%.[11]

I. SIDE EFFECTS

The most frequently reported side effects in ezetimibe clinical research are upper respiratory tract infection, headache, myalgia, and back pain. In the post-marketing surveillance, the most terrible and serious effects are rarely or very rarely reported, regardless the causality, hypersensitive reaction, pancreatitis, and myopathy/rhabdomyolys.[16] Ezetimibe experiences extensive glucuronidation on the wall of the small intestine and liver, so that the form of ezetimibe changes into active metabolite, which is glucuronide toxic for hepatocyte cell.[17] Therefore, it increases the level of mild ATL and leads to also autoimmune hepatitis.[18] Ezetimibe generally can be properly tolerated by most patients.[19] The side effect of ezetimibe is considered latent because appearing around two to ten months after the administration. Meanwhile, based on the severity of side effects, it is mild and requires therapy changing. The side effect is reportedly disappeared when the administration is stopped or changed.[20]

Simvastatin is categorized as statins whose the most frequently reported side effects are muscular pain, fatigue, and weakness, as well as rhabdomyolysis. In the Randomized Controlled Trial (RCT), it shows that the side effect attacks the muscle; while meta-analysis of randomized double-blind, placebo-controlled trials shows that myositis increases in patients with statin administration on placebo, with myositis defined as creatine kinase (CK) > 10 times of normal upper limit with myalgia. Muscular pain as a result of statin administration cannot be simply relieved even though the administration is stopped. 155

biopsy crossover studies show mitochondrial myopathy that is reversible on patients suffering from continuous muscular pain as a result of statin administration. Rhabdomyolysis is one of the most known and feared statin complications because it may cause severe muscle damage and increase CK (for example, more than ten times of normal upper limit) and also often lead to kidney dysfunction or even kidney failure or death.[21]

J. THE USE FOR SPECIAL POPULATION

Simvastatin is contraindicated for use during pregnancy or pregnancy program. It is because cholesterol and its derivatives are needed for normal fetal growth.[22] It is still unclear whether or not ezetimibe simvastatin is excreted in breast milk. The administration of ezetimibe/simvastatin of more than 40mg dose a day to adolescents has not yet obtained further research. Also, the combination of both drugs administered to patients under ten years old or menarche girls has not been studied. Based on the total of ezetimibe (ezetimibe + ezetimibe-glucuronide), there is no pharmacokinetic difference between adolescents and adults.[22]

The use of statin on the statin pediatric is proved to be effective in decreasing LDL level and total cholesterol. Besides, it can also be properly tolerated for short-term period.[23] There is no difference on the security or effectiveness observed between elderly and adult subjects, and the other clinical experiences reported have not identified different responses from elderly and adult subjects, but higher sensitivity developed on some elderly subjects cannot be ruled out.[22]

According to meta-analysis of 28 RCT, statin therapy provides significant effects in decreasing vascular symptoms regardless of age differences.[24] Cautions must be exercised, when ezetimibe/simvastatin is administered to patients with severe kidney dysfunction even though 10mg dose of it can be tolerated properly. Ezetimibe is contraindicated and not recommended for patients with active liver disease or persistent increase in hepatic transaminases, either medium or severe liver disorder.[22]

K. THE USE OF COMBINATION OF EZETIMIBE AND SIMVASTATIN

In the clinical practice, if the statin dosage is doubled, it can decrease LDL-C level by 6% and increase side effects; such as liver dysfunction, myalgia, and rhabdomyolysis. Ezetimibe improves the therapeutic effect of statin. Furthermore, the administration of low-dose ezetimibe is proved to be able to reduce LDL-L level by 5-27%. The combination therapy

gives more beneficial effects to other lipid parameter and higher sensitivity of C-reactive protein (hsCRP) if compared to statin administration to patients with hypercholesterolemia, mixed hyperlipidemia, type-2 diabetes, metabolic syndrome, and elderly patients for 6-12 weeks of therapy. Ezetimibe combined with statin will improve the effectiveness in controlling LDL-C, nin-HDL-C and apoB.[25]

The combination of ezetimibe and simvastatin (or other statins) effectively decreases LDL-C that is better than the administration of statin monotherapy. Ezetimibe is an agent used to decrease lipid that is not categorized as statins. The evidence of previous clinical trial doubts ezetimibe aggressive role in decreasing LDL-C as non-statin agent and even the use of target LDL-C. The previous research is designed and supported based on primary replacement endpoints; such as the decrease in lipid or noninvasive on the measurement of cIMT. In contrast, IMPROVE-IT is designed around clinically meaningful primary composite and shows the benefit of simple combination, and simvastatin monoteraphy. Patients administered the combination of 80mg-dose simvastation are potential for having an increased long-term security.[6]

The combination of ezetimibe/simvastatin is effective for patients with hyperlipidemia. The combination of 10mg-dose ezetimibe and low dose (10 or 20mg) simvastatin results decreases LDL-C by or higher than 80mg dose simvastatin or other highest dose statin. The recent IMPROVE-IT trial shows that high-risk of LDL-C in patient decreases after the use of combination of ezetimibe/simvastatin related to the significantly decreased cardiovascular occurrence if compared to that when the patient is given simvastatin only. The most important thing given by the clinical research is the benefit observed where the combination has less side effects than monotherapy simvastatin.[9]

The combination of ezetimibe and low dose statin can inhibit endogenous and exogenous cholesterol production, hence decreasing LDL level of plasma cholesterol. Therefore, it is suitable for dyslipidemia patients.[26] Phase II and III studies on ezetimibe show that combining cholesterol absorption inhibition with statin is an effective strategy to optimize the effect of cholesterol decrease. 10mg-dose simvastatin administered to hypercholesterolemia patients for 14 days decreased LDL-C by 35%; while 10mg dose simvastatin and 10mg-dose ezetimibe simultaneously administrated to patients decreased LDL-C by 52% that is expected to be achieved by 80mg dose simvastatin. Besides, ezetimibe almost does not affect statin pharmacokinetics.[5]

III. CONCLUSION

The combination of ezetimibe/simvastatin in a single tablet with fixed dosage of ezetimibe (10mg) and variable dosages of simvastatin (10/20/40 mg) is approved to heal primary and secondary hypercholesterolemia. It is also effective in decreasing LDL-C level, so it is suitable to overcome dyslipidemia on patients with increased cardiovascular disease risk.

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