IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
November 2020 Vol.:19, Issue:4

Clinical Approach of Pitavastatin for Treating Dyslipidemia

IJPPR
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ISSN 2349-7203
HUMAN

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Submission: 20 October 2020
Accepted: 27 October 2020
Published: 30 November 2020

Keywords: Dyslipidemia, Atherosclerotic cardiovascular disease, Low density lipoprotein, High density lipoprotein, Pitavastatin (LIVALO), Fredrickson classification, HMG CoA reductase

ABSTRACT

Dyslipidemia is considered a significant and most common predisposing issue for developing several cardiovascular diseases like ASCVD (Atherosclerotic cardiovascular disease) and a major health problem in across the world. The main cause of atherosclerotic cardiovascular disease is due to increasing level of LDL-C or decreasing level of HDL-C in the blood and also be dysfunction of lipid profile of apo B, IDL, apo A1, VLDL. Current therapy used for dyslipidemia/hyperlipidemia management involve HMG CoA reductase inhibitors, fibrates, bile acid sequestrants, nicotinic acid or ezetimibe but the treatment with statins is very operative and best option in dyslipidemia/hyperlipidemia or ASCVD consequence diminution. Though, in between the statins the drug Pitavastatin (HMG CoA reductase inhibitors) are better efficient for reducing serum level of LDL-C, apo B, triglyceride and increase level of HDL-C or also be promote plaque regression and improve plaque formation in patients with intense coronary disease shown in several clinical studies. Pitavastatin are well tolerated, satisfactory pharmacokinetic and safety profiles and provide a significant efficacy at low dose confirmed by large scale clinical studies and perspective post marketing surveillance. This review article we elaborated the Pitavastatin Pharmacology and their therapeutic impact on lipid outline (LDL-C, HDL-C, apo B etc.) or additionally be their alternative effect on body functions.

INTRODUCTION

Dyslipidemia is a crucial determinant condition for emerging atherosclerotic cardiovascular disease (ASCVD), stroke or a major health problem in globally [1,2]. Dyslipidemia is derived from two words, "Dys + lipid means Fat" and "Emia means in the blood" i.e. abnormal amount of lipids. Dyslipidemia are also called as Hyperlipidemia that is prolonged elevation of lipid, insulin and plasma cholesterol, triglyceride or low-density lipoprotein levels lead to expansion of atherosclerosis due to improper healthy diet and lifestyle [3]. The main cause of atherosclerotic cardiovascular diseases is due to increasing the LDL-C level or lower the HDL-C level in blood [4]. Low density lipoprotein (LDL) are also termed as a "bad cholesterol" since they are elevated and settle in higher amounts on the arteries walls lead to cause thickening, progressive hardening and formation of true plaques into the arteries that may completely block and altering in blood flow that this process called "Atherosclerosis" [5].

Lipid factor is a major central cause of developing of atherogenesis lead to contribute CVD risk and other factors. Hypertension, cigarette smoking, and diabetes impair endothelial dysfunction that accelerate or increasing lipid entrance in intimal layer or vascular reaction toward lipid retaining. Moreover, Plasma lipoproteins contains both sets of lipoproteins i.e. apolipoprotein B (apo B) contains chylomicrons, very-low-density lipoprotein (VLDL), intermediate-density lipoproteins (IDL), low-density lipoprotein (LDL) or apolipoprotein A1 (apo A1) comprise high-density lipoprotein (HDL) or apo B lipoproteins measured a causative factor for developed atherosclerosis by transferring lipid toward vessels layer. However, modulation of Apo B lipoproteins forming by liver (VLDL, IDL, LDL) and intestine (chylomicrons). Consequently, defending utility of apo A1 lipoproteins can excerpt cholesterol beyond plaque to bringing down LDL cholesterol (LDL-C) or expanding HDL cholesterol (HDL-C). While, VLDL moves the majority of triglycerides (TG) and cholesterol-rich compound i.e. LDL involved in TG hydrolysis of VLDL because of protective value of Apo A1 lipoproteins (HDL) neutralizes vascular disintegration for attaining cholesterol from peripheral tissues with atheroma (arterial plaque) or return backwards to liver [6].

Atherosclerosis is a major progressive process that distressing vast or intermediate size arteries include aorta, coronary, carotid, renal or femoral arteries and a moderate consuming incident preliminary by lipoprotein permeation inward sub endothelium, prompting retaining

of lipoproteins, oxidative changes, endothelial dysfunction, enlistment of phagocytic components or initiation of inflammatory reaction self-disseminated through spells of cell death stimulating chronic chemotaxis, bulk extension or plaque variability. Nonetheless, Ischemic significances of plaque development signify main origin of disease, hospitalization, lost efficiency or death in developing world [6].

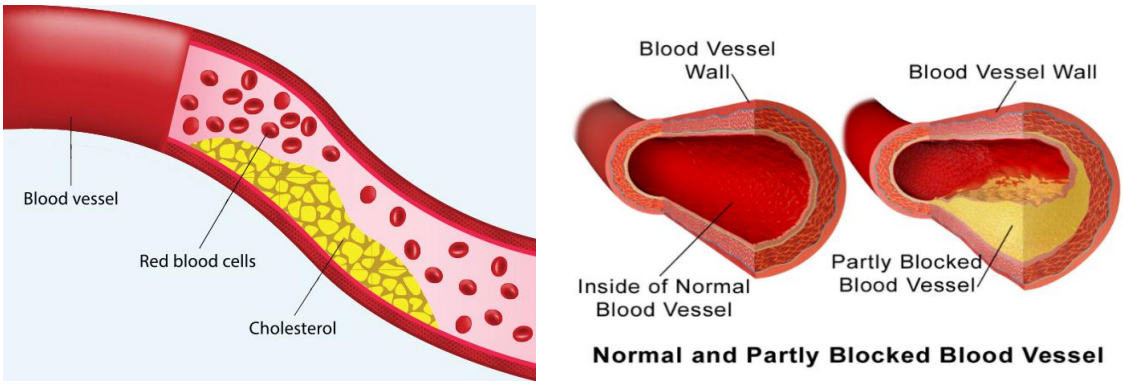

Figure No. 1: Dyslipidemia developing process [7,8].

Normally, cholesterol level equal to 200 mg/dl for total cholesterol and up to 100 mg/dl for LDL cholesterol [5], lower or above 70mg/dl in patient with diabetes and heart disease [3], or for women is not less than 50 mg/dl or in man about 40mg/dl [3,5] or also under 150mg/dl HDL cholesterol (HDL-C) or triglyceride level [3]. Once plasma cholesterol intensities beat above levels that stated to hypercholesterolemia [5].

Recent therapy for treatment of hyperlipidemia contains HMG CoA reductase inhibitors, fibrates, bile acid sequestering agents, nicotinic acid, ezetimibe etc. The more one treatment with statins is very operative preference for hyperlipidemia or ASCVD threat-reduction to bringing down the LDL-C, expressively decrease the chance of coronary heart disease or because of its safety and efficacy and their pleiotropic effect such as antioxidant, anti-inflammatory and antithrombotic [2,4]. In between the statins, Rosuvastatin and Pitavastatin shows substantial higher reductions in LDL-C or highly effective toward rise HDL-C level. Additionally, lipid lowering agents are less effective and less tolerated than statins, but for a better result they used in combination with statins [4]. Hence, treatment and diagnosis of dyslipidemia, are perilous for lessening the prevalence, mortality of CAD or cerebral infarction [9].

RISK FACTOR

Hypothyroidism, Chronic renal failure, Nephritic syndrome, Obesity, Alcohol consumption, Metabolic syndrome, Type 2 DM, Acute viral or bacterial infection, HIV, Hepatitis Systemic lupus erythematosus, Juvenile rheumatoid arthritis, Kawasaki disease, Anorexia nervosa, Solid organ transplantation, Drugs (Antihypertensive agents, Diuretics, Oral contraceptives, Corticosteroids, glucocorticoids) [10,11].

TYPES AND CLASSIFICATION OF DYSLIPIDEMIA

Primary dyslipidemia

Some monogenic disorders defined dissimilar form of dyslipidemias, yet numerous events, etiology of dyslipidemia is polygenic. These conditions distress plasma lipoprotein intensities through abnormal formation of lipoproteins and reduced clearance [12].

Familial (Primary)

According to Fredrickson classification, familial hyperlipidemias are classified on basis of arrangement of lipoproteins at electrophoresis and ultracentrifugation that should be after approved through World Health Organization (WHO) [13]. Familial hypercholesterolemia (FH) are main hereditary disorder of cholesterol uptake involved increasing the LDL-C level since birth and prompts early ASCVD marks 1 in each 200 persons in heterozygous system [10,11]. Patients with this disorder have raises plasma concentrations of very low-density lipoprotein (VLDL) and LDL causes hypercholesterolemia or hypertriglyceridemia by poor lifestyle and dietary habits [14].

According to “FREDRICKSON” classification

• Type I - Elevated cholesterol plus excessive triglyceride concentrations

• Type II – Abnormal cholesterol plus regular triglyceride levels

• Type III - Higher cholesterol or triglycerides

• Type IV - Higher triglycerides, atheroma or elevated uric acid

• Type V - High triglycerides [9]

Phenotype	I	IIa	IIb	III	IV	V
Lipoprotein, elevated	Chylomicrons	LDL	LDL and VLDL	Chylomicron and VLDL remnants	VLDL	Chylomicrons and VLDL
Triglycerides	↑↑↑	N	↑	↑↑	↑↑	↑↑↑
Cholesterol (total)	↑	↑↑↑	↑↑	↑↑	N/↑	↑↑
LDL-cholesterol	↓	↑↑↑	↑↑	↓	↓	↓
HDL-cholesterol	↓↓↓	N/↓	↓	N	↓↓	↓↓↓
Plasma appearance	Lactescent	Clear	Clear	Turbid	Turbid	Lactescent
Xanthomas	Eruptive	Tendon, tuberous	None	Palmar, tuberoeruptive	None	Eruptive
Pancreatitis	+++	0	0	0	0	+++
Coronary atherosclerosis	0	+++	+++	+++	+/–	+/–
Peripheral atherosclerosis	0	+	+	++	+/–	+/–
Molecular defects	LPL and ApoC-II	LDL receptor, ApoB-100, PCSK9, LDLRAP, ABCG5 and ABCG8		ApoE	ApoA-V	ApoA-V and GPIHBP1
Genetic nomenclature	FCS	FH, FDB, ADH, ARH, sitosterolemia	FCHL	FDBL	FHTG	FHTG

Figure No. 2: Fredrickson classification of Dyslipidemia (Hyperlipidemia) [15].

Hereditary Hypertriglyceridemia

Genetic origins of hypertriglyceridemia are substantially extra regularly in primary care sceneries and measured increased in TG level about ≥500 mg/dl by changes in lipoprotein lipase property, ApoCII or ApoA5 develop risk of monogenic hyperchylomicronemia [10]. Genetic defect of hypertriglyceridemia cause dysfunction of low-density lipoprotein (LDL) receptors by raise of LDL-C level to 2-3 times of overall population that assessed 0.2% in U.S. population [14]. An example of Familial chylomicronemia syndrome (FCS) a hereditary problem categorized via lipoprotein lipase (LPL) deficient caused hypertriglyceridemia by nonappearance of LPL, extreme concentration of accumulate chylomicrons or plasma TG amounts about 1,000 mg/dl or almost 5,000 FCS patients in worldwide or generally existing by nausea, vomiting, obvious corneal arcus, eruptive xanthomas, premature CAD, lipemia retinitis, hepatosplenomegaly, recurrent abdominal pain, failure to thrive or severe/acute pancreatitis [10,14].

Secondary dyslipidemia

A few clinical circumstances allied with mild and severe dyslipidemia without causal genetic disorder. Secondary Causes of Lipoprotein Irregularities are mentioned as:

Hypercholesterolemia

Hypothyroidism, Obstructive liver disease, Nephrotic syndrome, Anorexia nervosa, Acute irregular porphyria, Drugs- progestogens, cyclosporine, thiazides.

Hypertriglyceridemia

Obesity, Diabetes mellitus, Pregnancy, Chronic renal failure, Lipodystrophy, Glycogen storage disease, Alcohol, Bypass surgery, Stress, Sepsis, Acute hepatitis, Monoclonal gammopathy, Drugs- estrogen, beta blockers, glucocorticoids, thiazides.

Low HDL

Type-2 diabetes mellitus, Rheumatoid arthritis, Malnutrition, Obesity, Cigarette smoking, Beta blockers, Anabolic steroids [12].

SIGN AND SYMPTOM OF DYSLIPIDEMIA [11]

- Xanthoma (thickening of tendons because of deposition of cholesterol).
- Xanthelasma palpabrum (yellowish patches around the eyelids).
- Arcus senilis (white mark of peripheral cornea).
- Atherosclerosis (abdominal and carotid bruits, weakened peripheral pulses, ankle-brachial index ≤0.9).
- Angina Pectoris.
- Myocardial Infarction.
- Transient Ischemic Attack (TIA).
- Cerebrovascular events/stroke.
- Peripheral artery disease.

DIAGNOSIS

Blood Test: To measure a lipid profile of cholesterol, lipid, triglycerides, levels of total cholesterol, VLDL cholesterol, LDL cholesterol or HDL cholesterol in the blood or by collecting blood sample [16]. The major laboratory test to observed lipid profile is "Fasting lipid test" involving to ensure the patient should quick for at any rate 12 hours earlier taking the blood sample, to measure the fasting total cholesterol, triglyceride and HDL-C values and LDL-C concentration can be determined by utilizing Friedewald equation [17].

Skin Assessment Test: Skin assessment test can be performed by biopsy method to measured xanthelasmas or xanthomas are fatty accumulated beneath skin exterior that usually

establish in patients have metabolic disorders, higher blood lipids or hereditary issues i.e. familial hypercholesterolemia [13].

COMPLICATIONS

- Pancreatitis
- Early coronary artery disease
- Heart attack
- Stroke
- Atherosclerosis
- Myocardial infarction
- High blood pressure [18,13].

PATHOPHYSIOLOGY

Pathophysiology of dyslipidemia is yet poorly understood but the factor and component interfere in developing dyslipidemia are hereditary, environmental or together. Hereditary faults of cholesterol production regulation, hepatic cholesterol metabolism, cell membrane receptor utility or environmental factors such as dietary habits and poor lifestyle are also well predictable [19]. Pathophysiology of dyslipidemia occurs from elevated serum levels of total cholesterol, LDL-C, triglycerides and low serum levels of HDL-C. Plasma LDL-C are oxidized, (process to recruit's macrophages) and transfer to spoiled endothelium towards extracellular milieu of artery wall. Nonetheless, inflammatory response cause formation of erratic arterial plaque on interior part of artery that might be break, activating clot development or certain adverse clinical consequences include heart attack or stroke. Plaques that produce under half (50%) stenosis of luminal thickness stand inclined to break, whereas beating 70% stenosis naturally origin manifestations of ischemia i.e. angina pectoris are predictable [20]. Although, the pathogenesis of diabetic dyslipidemia occurs from fluctuations in lipoprotein such as increase in level of triglycerides (TG), VLDL, small dense LDL and decrease in HDL in patients with reduced fasting glucose, glucose tolerance and T2DM [21].

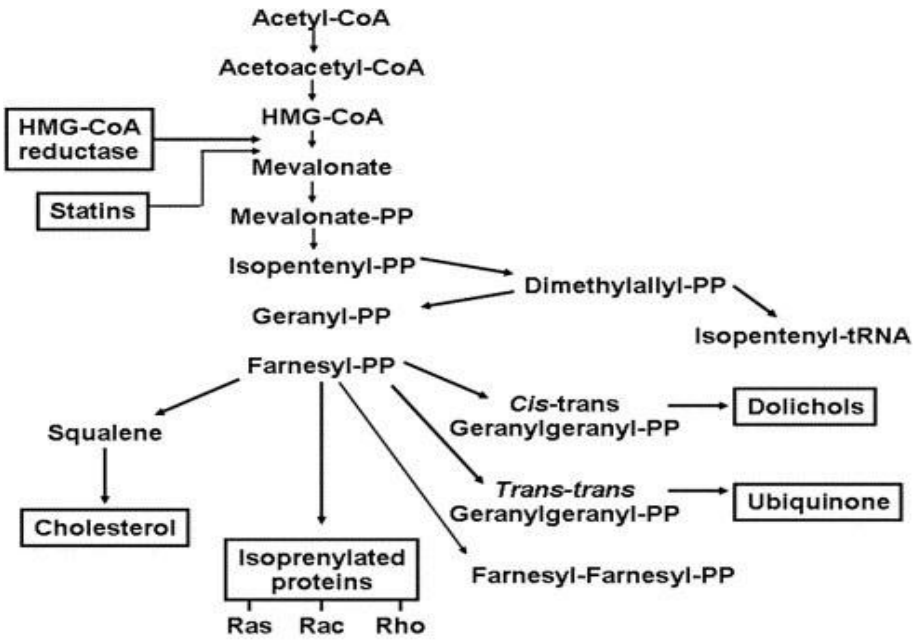

Figure No. 3: Pathophysiology of Dyslipidemia [22]

EPIDEMIOLOGY

Cardiovascular (CV) disease is a major health problem and leading cause of death worldwide with 31.4% of deaths in year of 2012 [23]. Dyslipidemia is a vital menace cause for develop ischemic coronary illness or stroke in across the world. The global incidence of dyslipidemia contributes to one third of ischemic heart disease estimated total cholesterol ≥5.0mmol/L existed 37% in adult men or 40% in adult women in year of 2008. Whereas, 2.6 million deaths or 29.7 million inability balanced life years are estimated globally [1].

Around the world reason for hypercholesterolemia estimated 56% ischemic coronary illness or 18% strokes cause 4.4 million demises yearly. Rates of Hyperlipidemia/hypercholesterolemia increased from 18% to 31% at aged of 35-59 in adults, 49% at age of 40 years in men or 32% in women developing lifetime risk of CHD and even at age of 70 years, threat is 35% in men or 24% in women developing lifespan danger of CVD at 50 years old assessed 1 to 2 in men or 2 to 5 in women in USA as it were. Several epidemiologic surveys reported age, sex, higher LDL C level, low HDL-C level, DM, alcoholism or smoking remain important stake reasons for causing CHD [24,9].

In year of 2010 statics establish that 31.9% US deaths and globally 17.7 million deaths in 2015, accounted of CV disease with high majority of ischemic heart disease and stroke that signifies one-third of all deaths [25,23].

The global rate of CV disease was predictable to be $863 billion in 2010 that probable 22% increase in 2030. Studies cover the time period of 1980 to 2010 in United States, Canada, and Europe that assessed 19%–46% total decrease in the rate of coronary heart disease (CHD) death by decreasing total cholesterol levels with respect to changing lifestyle and pharmacologic treatment [23].

A meta-analysis and studies described the incidence of dyslipidemia in Bangladesh estimated 41.5% in urban regions with 8% of cardiovascular Disease (CVD) increasing by ~0.12/year from 1970s till 2010s and 34.4% in overall population. Although, the meta-analysis data of 14 randomized trials of Statins with cholesterol treatment as of 90,056 people exhibited 1 mmol/L decrease in LDL-C with 20% consequences of cardiovascular events and 12% decrease in all-basis death [1].

As per National Cholesterol Education Programme (NCEP) ATP III strategies issued in 2001 report that patients by recognized CHD, non-coronary atherosclerosis, diabetes mellitus and two or more cardiac menace aspects through optional target ≥20% determined Framingham threat score are most perilous to LDL-C ≤70 mg/dL to 100 mg/dl in patients [26]. Nonetheless, incidence of CHD is increasing with 65 years of age elderly people with life expectation recently assessed women are ≥20 years or men are ≥17 years in high-income nations. However, predictable incidence of coronary heart disease (ASCVD) in United States resolve expected enhance 43% in year of 2030 by demographic deviations as well as enlarge in direct expenses would to be 198%. Thus, it is a key task for social orders to guarantee a healthful elderly populace [27].

PHARMACOLOGY OF PITAVASTATIN

Pitavastatin comes under a class or a new member of HMG-CoA reductase inhibitor of statin family was first presented at Japan in 2003 for the treatment of decrease higher levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, apolipoprotein (Apo) B, triglycerides and improve levels of high-density lipoprotein (HDL) in primary hyperlipidemia and mixed dyslipidemia patients. Pitavastatin has been approved in 13 countries worldwide i.e. USA, Japan, China, Germany and Spain and newly permitted in 20 further countries such as UK, Australia, and France and also incomplete approval in other 12 countries [28,29]. Adjuvant therapy of this medication laterally utilized with nutritious diet or added everyday life deviations to reduced threat of coronary failure and stroke [30,29].

Pitavastatin formed negligible metabolism by cytochrome P450 (CYP) enzyme influence in low tendency for drug-drug collaborations among drugs metabolized via CYP enzymes (CYP3A4 substrate) [30]. A study regards Pitavastatin IC50 for HMG-CoA reductase inhibition in rat liver microsomes occurred 6.8 nm presence 2.4-fold beyond simvastatin or 6.8-fold more than pravastatin initiate IC50 inhibition of cholesterol production as of acetic acid in cultured human hepatoma cell line HepG2 found 5.8 nm and 2.9-fold greater than simvastatin or 5.7-fold exceeding atorvastatin. However, these outcomes specify that Pitavastatin has greater inhibition of HMG-CoA reductase through impacts of medications on initiation of LDL receptor associated by normalized focus dictated via inhibitory activity of medications on cholesterol production. Although, ED50 of oral Pitavastatin for inhibition of sterol making in rat liver found 0.13 mg/kg with 2.8-fold or 15.9-fold exceeding simvastatin in rats or guinea pigs that specified Pitavastatin withdrawn VLDL exudation and TG-rich lipoproteins in the liver [31].

CHEMISTRY OF PITAVASTATIN

The distinctive structure of Pitavastatin consist a basic structure of heptanoate and quinoline ring at central and fluorophenyl or cyclopropyl moieties in side chain [31]. Linked by another statins, Pitavastatin have a distinctive structure [30] which enhanced pharmacokinetics with ideal action equally HMG-CoA reductase inhibitor or improved drug absorption [31].

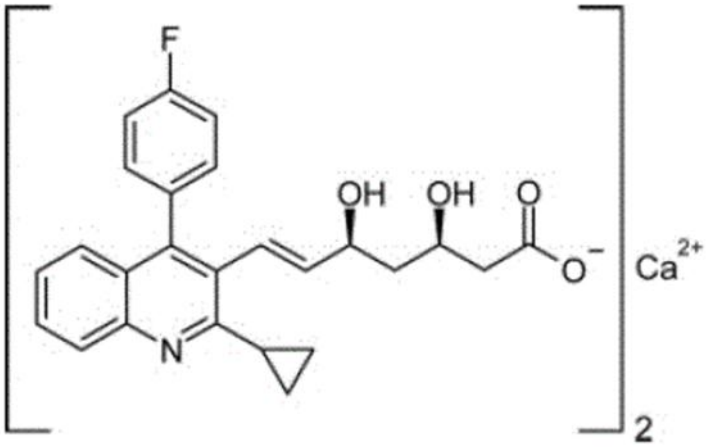

Figure No. 4: Structure of Pitavastatin drug [32].

Chemical name-Monocalcium (+) bis {(3R, 5S, 6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5dihydroxy-6-heptenoate}

Structural or empirical formula- $C_{50}H_{46}CaF_2N_2O_8$.

Molecular weight-880.98.

Physical property-odor- odorless.

Color-white to light-yellow powder.

Solubility-Soluble in pyridine, chloroform, dilute hydrochloric acid or tetrahydrofuran, ethylene glycol, sparingly dissolvable in octanol, somewhat soluble in methanol, marginally soluble in water and ethanol or insoluble in acetonitrile and diethyl ether.

Stability-Pitavastatin is hygroscopic or marginally unstable in light [29].

MODE OF ACTION

Mode of action of Pitavastatin is directly inhibits HMG CoA reductase enzymes [33] involved in HMG CoA reductase pathway. The molecular degree of statins is like HMG-CoA which act on HMG-CoA enzyme or diminish rate to generate mevalonate and later molecule in cascade to production of cholesterol [13]. The rate-defining enzyme in hepatic cholesterol production, LDL-C receptors are increased in liver that increase the elimination of LDL-C from the blood and ultimately reduced the level of cholesterol [33]. However, statins directly block the production of cholesterol in liver and reduce the concentrations of "bad cholesterol" (LDL), triglycerides or also rising concentrations of "good cholesterol" (HDL) [13].

ABSORPTION AND DISTRIBUTION

Oral tablet of Pitavastatin generally like a calcium salt accessible in potencies of 1 mg, 2 mg or 4 mg [34,33]. Systemic bioavailability of Pitavastatin ranges 50% are more bioavailable than 5% of simvastatin, lovastatin and Fluvastatin [35] that should be 51-60% bioavailable or reaches his peak plasma concentration (Cmax) around 1 hour later oral administration [34]. High-fat meal declines 43% drug's Cmax, while AUC concentration is rather unchanged/vary when Pitavastatin was taken in morning or evening [33]. Plasma protein binding of Pitavastatin differs more than 95% with than that of 50% for pravastatin, simvastatin, atorvastatin and lovastatin [35]. Pitavastatin are 99% bound in human plasma of albumin or alpha1-acid glycoprotein that selectively distributed to the liver. Pitavastatin is also excreted from bile or reabsorbed via intestine or redistribute to liver by enterohepatic distribution [34].

METABOLISM AND EXCRETION

Pitavastatin are mainly metabolized by hepatic glucuronidation with slight metabolism through cytochrome P450 2C9 and CYP 2C8 [33,34]. The cyclopropyl group influenced the potency of Pitavastatin that seems to keep from metabolism via CYP3A4 and also be less probable for interactions with other drugs. Pitavastatin is commonly administered by orally route as a vigorous acidic form that should be bio-transformed by Glucuronosyltransferase (UGT). The results of UGT biotransformation are truly temperamental or quickly change to lactone metabolite that goes through fast metabolism via CYP450 isoenzymes [22]. Although clearance of Pitavastatin is 23.6 L/h, volume of distribution is 148 L [29], Half-life is 12 hours and 79% of Pitavastatin evacuated through feces or 15% excreted in urine [33,34,29].

ADVERSE EFFECT

Common side effect

Chest pain, back pain, constipation, diarrhea, muscle aches, pain in arms or legs and headache

Severe side effect

Muscle problems-Severe muscle pain, muscle soreness, muscle weakness

Kidney problems-Fatigue, confusion, nausea, shortness of breath, swelling in legs, ankles, feet and diminished urination.

Liver problems-Jaundice, itching pain in upper right adjacent of stomach region, nausea, vomiting, loss of appetite, dark or pale colored urine, tiredness, abdominal pain, rash and diarrhea [36,37].

DRUG INTERACTIONS

Antibiotics

Taking antibiotics with Pitavastatin that increase the quantity of Pitavastatin in body as well as increases the risk of side effects from Pitavastatin. e.g. Erythromycin, clarithromycin.

Blood-thinning drug

Warfarin is a blood thinning agent, taking with Pitavastatin increase the effects of warfarin along with raises the risk of bleeding.

Cholesterol drugs

Taking other cholesterol lowering drugs with Pitavastatin can raises the risk of myopathy and rhabdomyolysis. e.g. Gemfibrozil, fenofibrate, niacin.

Immunosuppressant drugs

Cyclosporine is an immunosuppressant drug that taking with Pitavastatin can increase the quantity of Pitavastatin in the body.

Tuberculosis drugs

Rifampin is an antituberculotic drug that taking with Pitavastatin can increase the quantity of Pitavastatin in the body as well as increases the risk of side effects from Pitavastatin.

Gout drugs

Colchicine drug is used in treatment of gout flares that taking with Pitavastatin can raises the risk of side effects of myopathy or rhabdomyolysis [36].

Antiviral drugs (HIV/AIDS)

Protease Inhibitors, Amprenavir, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Lopinavir, Ritonavir, Nelfinavir, Saquinavir, Ritonavir, Tipranavir [29].

Pitavastatin could interrelate by OATP1B1 inhibitors that distinct contact with ciclosporin and doesn't interrelate with agents which prevent and stimulate CYP3A4, help to decreasing threat of drug–drug or drug–diet collaborations equated to further statins [35].

CONTRAINDICATIONS

1-Patients with an identified hypersensitivity (rash, pruritus, and urticaria) to with product have been informed to doctor with LIVALO (Pitavastatin) [38].

2- People with liver disease must be talk over to doctor about the risks and benefits earlier starting a statin. If liver disease is stable and chronic patient must be used low dose of statin

have better benefit than risk. If liver disease is progressive statins are not counseled to take and but liver disease progresses at time of taking statins informed the doctor to dose reduction, changing medication or discontinuing the use of statin [37].

3- Discontinuing the treatment of statin in patients with develop acute, severe myopathy and provoking threat of end stage renal disease, rhabdomyolysis, hypotension, dehydration, electrolyte imbalances and major surgery [39].

4- In pregnant women, HMG-CoA reductase inhibitors reduced the cholesterol production or additional biologically effective essences imitative from cholesterol. Pitavastatin can produce fetal impairment after administered to pregnant females though using this medication, patient would describe probable risk about fetus weakening or nonappearance of recognized clinical advantage through continual usage in pregnancy [38]. It is usually suggested that people taking statins should not use in combination of following medications such as protease inhibitors, erythromycin, itraconazole, clarithromycin, diltiazem, verapamil, fibrate drugs [37].

5- Peoples taking statins must avoid grapefruits and their juice because of hazardous effects of an interaction [37].

DOSAGE AND ADMINISTRATION

Dosage of Pitavastatin about 1 to 4 mg orally administered once every day whenever of day irrespectively [38]. Evening doses of statins improves the consequences of circadian rhythm of lipid metabolism [19]. The initial dosage was 2 mg or maximum dosage was 4 mg. Initial dosage of Pitavastatin ought to be administer direct as per understanding qualities just as objective of treatment or reaction [38]. Dose should be adjusted at interval of 4 weeks after evaluated LDL‐C levels [38,19].

Patients with mild-to-moderate diminishing hepatic activity take maximum dosage of 2 mg once day by day with close observing [19] and patients with moderate and critical renal damage alongside end-stage renal disease getting hemodialysis must taking preliminary dosage of Pitavastatin (LIVALO) 1 mg every day or maximum dosage 2 mg regularly [38,37,20].

Dosage and use :
See Package Insert for Full Prescribing Information.

Each film-coated tablet contains 1.045 mg pitavastatin calcium equivalent to 1 mg pitavastatin.

Store at 25°C (77°F), excursions permitted from 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature].

Protect from moisture and light. Dispense in an appropriate tight, light-resistant, child-resistant container.

NDC 76333-157-14

Pitavastatin Tablets

1 mg

Rx only
90 Tablets

orientPHARMA CO.,Ltd.

Manufactured and Marketed by:
Orient Pharma Co., Ltd.
8 Kehu 1st Road
Huwei Chen
Yunlin, Taiwan 63247

Lot. Exp.

6PP0501000
001

Dosage and use :
See Package Insert for Full Prescribing Information.

Each film-coated tablet contains 2.09 mg pitavastatin calcium equivalent to 2 mg pitavastatin.

Store at 25°C (77°F), excursions permitted from 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature].

Protect from moisture and light. Dispense in an appropriate tight, light-resistant, child-resistant container.

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Lot. Exp.

6PP0601000
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Figure No. 5: Bottle packaging of Pitavastatin tablets (1mg, 2mg, 4mg) [40].

Table No. 1: Dosage range of Pitavastatin in treatment for various diseases [29].

Disease	Primary dose	Maintenance dose	Maximum dose
Hyperlipidemia	2 mg orally daily	1-4 mg orally daily	4 mg/day
Dyslipidemia	2 mg orally daily	1-4 mg orally daily	4 mg/day
Moderate to severe renal dysfunction	1 mg orally daily	-	2 mg orally daily
Liver Dosage Adjustments	1 mg orally daily	-	2 mg orally daily
Dialysis	1 mg orally daily	-	2 mg orally

CLINICAL EFFICACY OF PITAVASTATIN

Pre-marketing clinical analyses of Pitavastatin directed in Japan, Korea and Europe shows it is very beneficial to lowering serum LDL-C via 31% to 34%, 36% to 42% or 43% to 47% as well as total cholesterol by 22 to 23%, 26 to 29% and 31% to 33% in hyperlipidemic patients or mixed dyslipidemia with dose range 1 mg, 2 mg or 4 mg [41].

A study in 2003 reports that rosuvastatin is more effective compared with atorvastatin in various clinical findings conducted in Netherlands, England or Canada. But, efficacy or safety of Pitavastatin at elevated dosages ought to be related with rosuvastatin just as atorvastatin. Due to unique pharmacokinetic profile of Pitavastatin are possibly correlated to

lower the serious drug-drug interactions that remain essential to determine the effectiveness as lipid-modulating medications in clinical routine with statins [42].

Pitavastatin considered as a strong statin because of their comparable LDL-C-decreasing activity than that atorvastatin at starting dose. However, efficiency of Pitavastatin occurred estimated in 30 heterozygous patients with familial hypercholesterolemia that influenced in lowering the 40% of serum LDL-C levels with 2mg administered Pitavastatin as well as 48% lowered LDL-C level after added 4 mg drug dose that detected after 8-week administration. These clinical results define that LDL-C-reducing property of Pitavastatin at dosages 2 to 4mg act equally statin than 10 to 20mg drug dosages of atorvastatin [31].

Additionally, 2 mg Pitavastatin is more efficacious than 20 mg dose of simvastatin. A clinical study conducted in 29 patients with hypercholesterolemia define impact of drug on HDL after administered 2 mg of Pitavastatin for 4 weeks that show a better results of lowering serum total cholesterol about 26.9% as well as serum LDL-C levels about 39.8% through increasing serum HDL-C is 6.0% or HDL2-C levels is 9.0% but no change on serum HDL3-C level or in reduction serum preβ1-HDL level. However, a randomized finding of Pitavastatin 2mg on elevating effect of HDL-C associating with atorvastatin 10 mg for 52 weeks shows Pitavastatin are more effective than atorvastatin with raising serum HDL-C levels or also be fraction alter in serum Apo A-1 level is higher in Pitavastatin gathering (5.1%) compared to atorvastatin group (0.6%) [31].

Another study in 20 patients regarded with Pitavastatin 2 mg for 2 years deserted and joined medication of Pitavastatin 2 mg and plus ezetimibe 10 mg for 3 months that shows 49% serum LDL-C diminished with Pitavastatin treatment in deserted or 63% decreased with therapy of Pitavastatin and plus ezetimibe. Such reports and various studies proposed Pitavastatin is greatest powerful LDL-C-lessening medications accessible at existent in case of increasing statin dosage or excessive-dosage statin treatment essential to precluded and constant raise the serum HDL-C of 48.5 to 58.5 mg/dL stayed 3.2% to 8.9% suggesting in randomized controlled study of 4 to 12 weeks [41].

SAFETY AND TOLERABILITY OF PITAVASTATIN

Safety is essential mainly in combination therapy with statin particularly in elderly who take multiple medications for other complications that altering in pharmacokinetics, pharmacodynamics profile and levels of tolerability to affecting the obedience to medication.

Moreover, it is significant to attentive the probable side effects of statins including liver and muscles, statin induced myopathy and rhabdomyolysis [43].

Muscle toxicity and interrelated manifestations, myalgia, hepatic dysfunction, hyperglycemia exist most common unfavorable impacts of statins in mature people. However, higher dose of statins is not permitted for pediatric patients because adverse effect of statin is unidentified as well as restricted occurrence or period of statin usage in pediatric patients. Additionally, statins ought to be escaped in pregnancy because of reducing the cholesterol production that influencing the mental health or utility appeared in pediatric homozygous FH preliminaries to use of statin starts in primitive 2 years of age [10].

A LIVES study evaluated the safety of Pitavastatin in 19,925 patients for 2 year shows 10.4% patients suffered with unfavorable outcomes among 84% of side effects were mild and 1% were severe were analyzed as well as adverse events include blood creatine phosphokinase (2.74%), alanine aminotransferase (1.79%), myalgia (1.08%), aspartate aminotransferase or g-glutamyl transferase (1.00%) stood increased and approx. 7.4% patients withdrawn Pitavastatin later emerging unfavorable outcomes [29].

Additionally, the JUPITER study employed in healthy peoples with LDL-C under 130 mg/dl or hs-CRP more prominent than 2.0 mg/l occurred randomly received rosuvastatin 20 mg daily and placebo. Consequently, cohort study surveyed combined key terminal incidence of Myocardial infraction, stroke, arterial revascularization, unstable angina and may mortality due to cardiovascular events [43].

Adverse events usually characterized by mild to moderate to severe or arisen in 5.3–16.7% patients take Pitavastatin 2 and 4 mg once every day equated with 1.9–14.4% patients accepting atorvastatin 10 and 20 mg once day by day or 8.2–23.5% patients acquire simvastatin 20 mg and 40 mg once day by day. The rate of adverse events occurs ≥2% with treatment of Pitavastatin 1–4 mg/day and also be ≥2% of other adverse events such as dizziness (2.9%), indigestion (2.2%), nasopharyngitis (2.7–3.2%), headache (2.2–3.4%) are formed in short-range controlled findings for12 weeks [30].

CLINICAL STUDIES

In elderly patient

Incidence of cardiovascular disease are more likely occur in 65 years aged of elderly peoples or older and main cause of death occur in almost half of this aged group with 75–80% of 80 years display atherosclerosis [35]. A randomized report suggests that 2,800 patients with 43% (12,09) were ≥65 years of age to received Pitavastatin 1 mg to 4 mg in controlled clinical reports detected no expressive changes in effectiveness or safety among ageing patients [44].

Additionally, in double-blind analyses of 545 patients plus 65 years aged and older received Pitavastatin 2 or 4 mg every day for 60 week reported undesirable outcome incidences alike over the entire dosage limit of mutually medications as well as reduction in LDL‑C or further atherogenic lipid factors or also be improved HDL‑C by 9.6% compared to double-blind proportional phase/study [35]. Subsequently time period of 60 weeks, the 99% patients achieved NCEP levels of LDL‑C per dose of 2 mg Pitavastatin as well as 70% achieved NCEP targets at week 60 with higher dose and effects of 4mg dosage at further lipid factors existed like 2mg Pitavastatin [35].

A study described that 82% patients in 60-week trial of Pitavastatin developed 14.3% adverse events related to drug treatment such as myalgia (2.6%), raised serum creatine kinase (1.9%) or nausea (1.5%) and under 7% patients suspended Pitavastatin treatment due to harmful incidents. Moreover, 48 reasons of myalgias over 14 be measured therapy associated or not identified critical effect. Just 4 patients suspended Pitavastatin therapy because of myalgia or no instances of myopathy, myositis, rhabdomyolysis was recognized [44].

Moreover, treatment with Pitavastatin 4 mg/day ensured an increase rate of rises liver enzymes (ALT or AST) in 60 weeks. One or two patients had a raise AST or ALT 3 instants upper limit of normal (ULN), 1 in excess 5 instants and one more than ten times. Thus, 2 patients were withdrawn the study because of raises in ALT and AST, measured as mild strength or just one recognized as therapy-associated, needful to suspension treatment with significant liver injury by liver function tests (LFTs). Adverse events should be interfered in older patients who have been estimated weak comprises with combined weakness, slowness, tiredness, immobility or hesitation. However, information upon safety of Pitavastatin in weak oldest patients are not completely understood or required more investigation [44].

In pregnant women

Statin therapy may cause the risks of fetal harm and suggest to stop treatment instantly to women taking statins and who become pregnant, and also be advised on exhaustive lifestyle changes. Females who intend to become pregnant must suspend the utilization of statin by any rate 1 to 3 months previously trying to perceive. Statin therapy may continue after end of breastfeeding [45].

Premarketing studies

Premarketing clinical studies in Japan, Korea or Europe signify adverse drug reactions (ADRs) in type of signs and symptoms stated in 50 out of 886 patients i.e. 5.6% and approx. ADRs in 167 out of 886 patients (18.8%) comprised high serum concentration of gamma-glutamyl transferase (γ-GTP), creatine kinase (CK/CPK), alanine aminotransferase (ALT/GPT), aspartate aminotransferase (AST/GOT) that are described by irregular laboratory test results. These results of ADRs were not particular related with regularities or severities of ADRs with Pitavastatin dose about prevalence 20.3% patients (26/128) receiving Pitavastatin 1mg or 23.3% (121/519) among Pitavastatin 2 mg as well as 20.9% (50/239) among Pitavastatin 4 mg. However, these results clear that there is no increase in incidence, severity and presence of any new ADRs were informed through continuing Pitavastatin therapy [41].

Postmarketing studies

Postmarketing surveillance study in Japan were identified by LIVES to evaluating the Pitavastatin efficiency or wellbeing reported in 18,031 patients receive dose of Pitavastatin as their early lipid-lowering therapy for 2 weeks and 18.9% patients earlier receive lipid-lowering therapy in clinical practice. However, within 4 weeks Pitavastatin diminished LDL‑C via 29.1% start of DL‑C level was stayed for 2-year follow-up [35].

The total observation period of 2 years treatment with Pitavastatin reported 10.4% arisen of ADRs and occurrences of myopathy (2.1%) and hepatic dysfunction (1.0%) related ADRs with use of statins. Although, minor ADRs were identified in 1,045 patients, moderate ADR in 155 patients or severe ADRs in 6 patients. However, rates of raised serum CK (CPK) or serum transaminase levels were lesser as equated with described further potent statins. Additionally, no critical rise in rate of ADRs identified in patients treated with azole

(antifungal), macrolide (antibiotics), coumarin (anticoagulants), antiplatelet agents, antihypertensive agents and antidiabetic agents [41].

NON-CLINICAL TOXICOLOGY STUDIES

Carcinogenesis

The analysis of 92-week carcinogenicity conducted in mice by administered Pitavastatin with greatest tolerated dosage 75 mg/kg daily with systemic maximum exposures (AUC) 26 times clinical maximum exposure at 4 mg daily exhibit a nonappearance of medication-related tumors. Moreover, the same study conducted in rats via administered Pitavastatin at doses 1, 5, 25 mg/kg daily via oral gavage displayed substantial improve in occurrence of thyroid follicular cell tumors with 25 mg/kg daily, and also signifies multiple times human systemic exposures dependent on AUC at 4 mg daily maximum human dosage. Another, 26-week carcinogenicity study carried out in transgenic mouse strain (TgrasH2) administered Pitavastatin at doses 30, 75, 150 mg/kg daily via oral gavage displayed no clinically critical tumors [38].

Impairment of Fertility

Pitavastatin didn't show any harmful consequences in male or female rat fertility with oral dosages 10 or 30 mg/kg daily at systemic exposures 56 or 354-instants clinical exposure at 4 mg/day as per AUC. Additionally, Pitavastatin therapy in rabbits caused mortality in males or females taken 1 mg/kg daily at higher in fertility study (30- instants clinical systemic exposure at 4 mg/day as per AUC). While, the reason of mortality can't be estimate in rabbits but exhibit significant traces of renal noxiousness symptomatic of conceivable ischemia. However, lesser dosages (15-instants human systemic exposure) didn't indicate any substantial noxiousness in adult males or females and also detected reduced implantations, enhanced resorptions or reduced feasibility of fetuses [38].

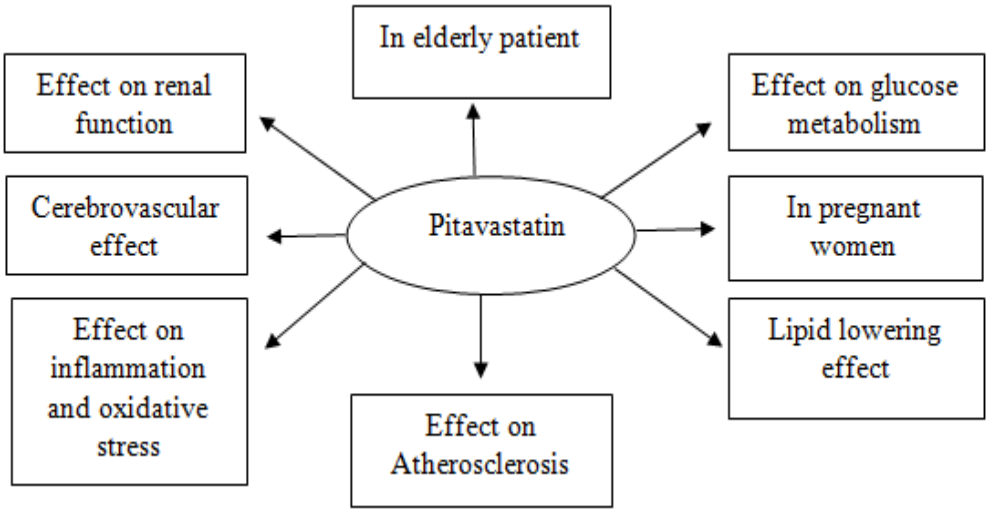
ANIMAL TOXICOLOGY

CNS Toxicity

CNS vascular abrasions, considered with perivascular hemorrhages, edema or mononuclear cell invasion of perivascular places are detected in dogs remedied with various class member of statin. In a synthetic alike medication of such group formed dose-reliant optic nerve relapse in dogs at plasma drug concentration approx. 30 instants elevated than mean drug

concentration in individuals pleasing elevated suggested dosage but, optic nerve relapse is not detected besides Pitavastatin. Although, cascades or lens opacities existed perceived in dogs given for 52 weeks at dosage concentration 1mg/kg daily with 9 instants clinical introduction at utmost human dosage 4mg daily as per AUC examinations [38].

ALTERNATIVE EFFECT OF PITAVASTATIN



Cerebrovascular effect

Statins are recognized likely preemptive and therapy decisions for certain neurological situations i.e. stroke, epilepsy, depression, cancer, brain or spinal cord injury. Alike studies display statins impacts upon neurocognitive conditions are not completely understood due to absence of information regards molecular mode of action of statins in neurological ailments [46].

Alternative, statins is beneficial to brings down the threat of stroke in moderate-menace peoples with number needed to treat (NNT) of 90 more than 5 years, liberated of age, sex, LDL-C concentration, earlier vascular disease finding and risk of hemorrhagic stroke yet meta-analysis of 31 assessments didn't determine a relationship among statin utilization or hemorrhagic stroke probability [45].

Effect on Atherosclerosis

Many analyses established beneficial result of Pitavastatin upon relapse or maintenance of atherosclerotic plaque in thoracic aorta, carotid or coronary arteries. While, various studies

reports, Pitavastatin is not only improved the arthrosis but very effective for regression of thickness of carotid intima-media and also be reduced formation of plaques estimated via utmost standard benefits through PET/CT in thoracic aorta or carotid artery [34].

Pitavastatin expressively recovered atherosclerosis associated with dietary or way of life in hypercholesterolemia patients estimated by 6–7 months trials. A randomized study in 32 patients besides hypercholesterolemia or atrial fibrillation experiencing transesophageal echocardiography existed receiving Pitavastatin 1–2 mg daily or diet has expressively better decrease in intimal media thickness (IMT) of arterial media (-11.7% v/s +6.3%, $p \leq 0.001$) and corrected integrated backscatter (c-IBS) (-12.9% v/s +8.7%, $p \leq 0.001$). Though, intimal plaque expressively better increase in corrected integrated backscatter (c-IBS) (+32.4 v/s +19.0%, $p \leq 0.01$) or reduction in initial media thickness (IMT) (-10.8% v/s +8.3%, $p \leq 0.001$) associated patients gathering diet unaccompanied [30].

Additionally, study in 82 patients experiencing intravascular ultrasound (IVUS) showed percutaneous coronary intervention (PCI) were allotted to low-fat diet with administered Pitavastatin 2 mg every day in 48 hours of PCI group and low-fat diet unaided group. While, those group got Pitavastatin would be better diminishes total or LDL cholesterol level related with diet alone group and reduction in plaque volume index (PVI) in patients accepting Pitavastatin equated with diet group approx.-10.6% vs +8.1%, $p \leq 0.001$ [30].

Effect on glucose metabolism or diabetes patient

Various clinical studies stated the property of Pitavastatin 1 mg and 2 mg on glucose metabolism by administered in 79 form 2 diabetic patients with hypercholesterolemia who has not treated with statins, or assessed impacts upon fasting plasma glucose, hemoglobin A1c (HbA1c), AST, ALT, γ-GTP, HOMA-IR, CK concentration for 8 weeks results, there is no statistically deviations in fasting plasma glucose concentration as of 8.2 ± 2.7 to 8.3 ± 2.1 mmol/L and HbA1c concentration are 7.3% ± 1.6% to 7.3% ± 1.5% in administration of Pitavastatin. Additionally, glycemic constraint estimated in Type 2 diabetic patients administered atorvastatin 10 mg, pravastatin 10 mg and Pitavastatin 2 mg for 3 months but, casual blood glucose or HbA1c concentration declined uniquely in atorvastatin faction [31, 33].

An examination-based study observes glucose uptake via insulin below giving atorvastatin, simvastatin, pravastatin and Pitavastatin with 3T3-L1 cells results, glucose uptake was

diminished in atorvastatin or simvastatin factions but no variation saw in pravastatin and Pitavastatin faction. Decrease of solute carrier group 2, member 4 (SLC2A4) or CCAAT/enhancer binding protein (C/EBP) α expressions influenced in glucose uptake through cells cause reduction in glucose uptake by taking atorvastatin [31].

Effect on renal function

Several meta-analysis studies exhibited that statins are useful for decrease in albuminuria or inhibition of renal weakening in CKD patients with dyslipidemia. Additionally, essential findings with statins presented Reno protecting impacts had beneficial for improvement in inflammatory or fibrotic reactions in kidney through his inhibitory consequences for oxidative stress, progressive glycation end product (AGE), monocyte chemoattractant protein-1 (MCP-1) or transforming growth factor-β (TGF-β). Moreover, the "Assessment of clinical Usefulness in CKD patients with Atorvastatin (ASUCA) reports" considered estimation of statin employs in preventive consequences for parameters of renal utility with glomerular filtration rate (eGFR), urine albumin-creatinine ratio (UACR), lipid/glucose metabolism, oxidative stress or arterial rigidity in CKD patients with dyslipidemia and albuminuria being assessed with diet therapy but report associated with are not completely understood [47].

Pitavastatin has been effective for reduced clinical signs of CKD with non-diabetic CKD, primary diabetic nephropathy or may have hyperlipidemia. Various studies demonstrated that Pitavastatin is effective in nondiabetic patients with mild CKD and normal lipid levels has significant decreases urinary liver-type fatty acid-binding protein (L-FABP) concentrations (28.0 v/s 88.5 mg/g creatinine, $p \leq 0.05$) and urinary albumin elimination (1.0 v/s 1.8 g/day, $p \leq 0.05$) by administered daily Pitavastatin 1mg for 6- and 12-months. However, these deviations were independent on effects of lipid parameters but not in serum concentration of total cholesterol or triglycerides stayed perceived [30].

Lipid lowering effect

LDL-C-reducing impact and safety risk of statins raises in dosage related behavior as well as dose increase. LDL-C-lessening impact on early dosage is significant due to considered strong statins of atorvastatin, rosuvastatin and others. The dose-locating analyses conducted in Japan among hypercholesterolemia patients wherever Pitavastatin was initially established to LDL-C-lowering impact after administration 34% (n=81) at dosage 1 mg, 42% (n=75) at

dosage 2 mg or 47% (n=76) at dosage 4 mg for 12-week. In phase III examinations, observed impact of administered Pitavastatin 2 mg existed related with pravastatin 10 mg for 12-week treatment results, the average fraction decrease in LDL-C is 38% (n=120) with Pitavastatin treatment or 18% (n=105) with pravastatin treatment as well as 46% (n=25) with 4 mg Pitavastatin detected next 8-week administration in added phase II report alike dosage observing analyses. Moreover, in Phase III trials led in Korea observed average fraction diminution in LDL-C was 38% (n=49), after administration Pitavastatin 2 mg for 8-week that similar in control group of 20 mg simvastatin (n=46). While, Phase III analyses led in Europe showed average fraction decline in LDL-C was 38% (n=315) after administered Pitavastatin 2 mg and 45% with 4 mg (n=298) Pitavastatin for 12-week of administration that similar to observed in control group of 10 mg and 20 mg atorvastatin (n=102) and an alternative Phase III investigations in Europe related Pitavastatin or simvastatin observed 39% (n=307) reduction in LDL-C after administered 2 mg Pitavastatin and 35% (n=107) with 20 mg simvastatin. Whereas, 44% (n=319) of Pitavastatin 4 mg and 43% (n=110) of simvastatin 40 mg proved similar decrease in LDL-C [31].

Comparative examination in early hypercholesterolemia patients, hyperlipidemia and mixed dyslipidemia determine efficacy with treated Pitavastatin 1 to 4 mg once every day contrasted with pravastatin 10 mg, simvastatin 10 to 20 mg or atorvastatin 10 to 20 mg involving changes the baseline of several lipid parameters include LDL cholesterol levels, or non-HDL cholesterol concentration and percentage of patients reaching LDL cholesterol target. Though, lipid-diminishing impact of Pitavastatin will not further discussed or arrived in minor investigations and minor endpoint analyses, yet Pitavastatin produces substantial reductions in serum concentration of total LDL or non-HDL cholesterol from baseline. The 52 weeks assessments, Pitavastatin is effective for reducing 21.0–32.4% of total cholesterol concentrations and 30.3–44.6% LDL cholesterol levels along with 34.7–41.1% of HDL cholesterol levels were allied with baseline degrees. As per National Cholesterol Education Program (NCEP) Adult Treatment Panel III standards suggest LDL cholesterol target levels were 56.8–93.9% using of people and 56.8–78.5% utilizing European Atherosclerosis Society (EAS) models [30].

Effect on Inflammation and Oxidative Stress

The impact on inflammation or oxidative stress in IL-2 concentrations and marker of T cell initiation, provoked phorbol myristate acetate (PMA) plus ionomycin were expressively

obstructed 32% via Pitavastatin, 17% by atorvastatin or 22% by rosuvastatin in human essential T cells. Moreover, inhibitory effects on exudation of IL-6, IFN- or TNF-induced phorbol myristate acetate (PMA) plus ionomycin- initiated T cells stayed estimated through treatment of Pitavastatin, atorvastatin, and rosuvastatin, observed 59% IL-6 concentration were prevented via Pitavastatin, 24% by atorvastatin, or 15% by rosuvastatin and 34% of IFN concentration were obstructed via Pitavastatin, 12% by atorvastatin as well as 61% of TNF- levels were withdrawn via Pitavastatin, 43% by atorvastatin or 44% by rosuvastatin in human primary T cells. Another property of Pitavastatin in suppression phosphorylation of ERK or p38 were evaluated except can't found any significant role in c-Jun N-terminal kinase (JNK). Pitavastatin impacts on NFB pathway observed it doesn't influence and act in phorbol myristate acetate (PMA) plus ionomycin-stimulated phosphorylation of IκBα involved in activation of NFκB to remind the continual NFκB transcriptional activity. However, these data propose that Pitavastatin is very effective for decrease the exudation of pro-inflammatory cytokines by MAPK pathways such as ERK or p38 yet never JNK or NFκB signaling [48].

Several studies report that Pitavastatin produced beneficial effect for baseline reductions in serum concentration of tumor necrosis factor-α (TNF-α) in patients with acute coronary syndrome (ACS), plasminogen activator inhibitor-1 (PAI-1) in Type 2 DM patients, pentraxin related protein (PTX3), and matrix metalloproteinases 2 or 3 (MMP2,3) in hypercholesterolemia patients and furthermore show valuable impacts for indicators of bone contouring such as calcium or N-terminal telopeptide of type I collagen for 3-month analyses. Moreover, Pitavastatin therapy presents a significant improvement in indicators of oxidative stress such as lectin-like oxidized LDL cholesterol ligands, 8-hydroxy-20-deoxyguanosine (8-OHdG) or malondialdehyde-modified (MDA) LDL [30].

Effect on coronary heart disease

In treatment of Pitavastatin with ischemic and non-ischemic coronary illness observed a substantial elevation in left ventricular discharge fraction about 42% v/s 48%, $p \leq 0.002$ or reduction in left ventricular end-systolic dimension was 43 v/s 40mm, $p \leq 0.001$from baseline in 7.5 months duration but not significant variation from baseline has been seen in left ventricular end-diastolic dimension or E/A wave velocity fraction [30].

Moreover, effectiveness of Pitavastatin 2 mg/day equated with atorvastatin 10 mg/day observed the lessening in essential endpoint happened often in Pitavastatin 9 patients

grouping about 2.9% and 8.1% in atorvastatin group with 25 patients i.e. HR, 0.342, 95% CI, 0.160–0.734, P=0.006) and in multivariate Cox relapse. However, the evidence of power trial for predominance of Pitavastatin treatment for essential primary end point viability estimated 0.9561 suggests that increasing 5-year prevalence of initial end point were substantially lesser in Pitavastatin class (2.9%) equated atorvastatin category (8.1%) [49].

Various controlled and uncontrolled studies associated with effectiveness of Pitavastatin for improvements of cardiac function in hyperlipidemia, type 2 diabetes mellitus, heart disease, or in smokers' patients has been carried out for 12 months duration. Balanced heart disease patients or serum total cholesterol concentration ≤220 mg/dL, Pitavastatin produces better result for consequential diminishing plasma brain natriuretic peptide concentration was 65.0 v/s 83.1 mg/mL, p≤ 0.05 and an expansion in E/A wave velocity fraction (assessed by echocardiographic) about 0.790 v/s 0.741, p≤0.05 from reference but never be any remarkable fluctuations are assessed in controls group [30].

The several randomized, double-blind, dynamic-controlled, non-inferiority analyses of effectiveness of Pitavastatin (LIVALO) was compared with simvastatin in phase-3 trials of 351 early hyperlipidemia patients and combined dyslipidemia with greater than 2 threat causes of coronary illness. Following 6 to 8 week of dietary preface interval, patients existed randomized treated with LIVALO (Pitavastatin) or simvastatin for 12 weeks. However, Pitavastatin 4mg was non-lesser to simvastatin 40 mg for fraction variation in pattern to endpoint LDL-C considered with lower bound 95% CI of mean treatment difference was 0% (-2%, 3%) [38].

A research report about the efficacy of Pitavastatin in reducing cardiovascular diseases have not significant found with regards primary or secondary end-point. A proportional study to estimation of preventive effect of Pitavastatin and other statins (Atorvastatin, Pravastatin) and no statin on cardiovascular events carried out for 7 years in 743 Japanese patients who experienced percutaneous coronary interference that displayed each statin treatment expressively reduced persistent cardiac consequences assessed with negative statin and found that Pitavastatin is extra viable than further statin therapy. Thus, there is no disbelieve about Pitavastatin efficiency in increasing HDL-C or enhancing lipid outline, the additional pleiotropic impacts or its durable consequences for relapse and regulation of atherosclerotic plaque, characterize adequate information for Pitavastatin effectiveness for decreasing cardiovascular menace [34].

ACKNOWLEDGEMENT

We express my words of thanks to the CT Institute of Pharmaceutical Sciences, Jalandhar and the administration of CT Group of Institutions, Jalandhar for providing supportive, friendly atmosphere and excellent research facilities.

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