[Review Article] Pitavastatin: A Comprehensive Overview of its Mechanisms, Pharmacokinetics, Pharmacodynamics, and Adverse Effects

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Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.

Abstract

Pitavastatin emerges as a prominent therapeutic option for individuals grappling with combined dyslipidaemia and hypercholesterolemia, particularly those afflicted with low HDL-C levels. Acting with remarkable efficacy, statins exhibit an affinity for HMG-CoA reductase surpassing that of the natural substrate by a thousandfold, while bearing structural resemblance to HMG-CoA itself. Through inhibition of mevalonate synthesis from HMG-CoA and consequent reduction in intracellular cholesterol levels, statins amplify LDL receptor activity and facilitate the clearance of non-HDL particles from systemic circulation. Both in vitro and in vivo experimentation corroborate the pivotal role of statins in attenuating mevalonate pathway metabolites and curbing cholesterol accumulation, albeit with potential repercussions on β-cell function and insulin sensitivity. To delineate the therapeutic virtues of Pitavastatin calcium and elucidate its precise mechanism of action, a comprehensive survey of the extant literature was undertaken.

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Keywords: Pitavastatin, Dyslipidemia, Diabetes, Mevalonate pathway.

1. Introduction

Although there are several medications used to treat hyperlipidemia, none is as extensively researched or prescribed as the class of medications known as "statins," which inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [1]. Like most statins, pitavastatin is delivered as the calcium salt of the active b-hydroxy acid form; lovastatin and simvastatin are the exceptions [2]. The molecule is made up of a dihydroxy heptanoic acid side chain, which binds to the target enzyme, HMG-CoA reductase, just like all statins do [3]. It is used to raise HDL (good) cholesterol and decrease triglycerides and LDL (bad) cholesterol in the blood. This medication is intended to help lower the risk of a heart attack or stroke in conjunction with other lifestyle modifications and a nutritious diet [4]. Compared to simvastatin or pravastatin, pitavastatin binds to HMG-CoA reductase with an affinity that is 1.6-3.5 times greater, respectively [5]. Pitavastatin calcium is a fundamental lipid-lowering medication classified as BCS II by the Biopharmaceutics Classification System (BCS). An IVIVC (In vitro-in vivo correlation) model was developed to predict the BE (Bioequivalence) result of formulations produced by two manufacturers [6]. Pitavastatin inhibits the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase, which is responsible for catalyzing the initial, rate-limiting step in the manufacture of cholesterol by converting HMG-CoA to mevalonate [7]. Compared to other medications in its class, pitavastatin exhibits a more robust effect on cholesterol levels due to its new, totally synthetic nature [8]. It was first made accessible in Japan in 2003, and it is currently being sold in South Korea and India under permission [9]. Pitavastatin has been a popular first-line treatment for lipid-modifying treatments according to preclinical findings [10]. In people with both mixed dyslipidemia and primary hyperlipidemia, pitavastatin is recommended to be an adjuvant treatment to nutrition in order to enhance high-density lipoproteins and decrease increased levels of triglycerides, apolipoprotein B, low-density lipoprotein cholesterol, and total cholesterol [11]. It has been demonstrated that statins, which are very successful at decreasing cholesterol, minimize cardiovascular morbidity and mortality in both people with and without coronary heart disease (CHD) [12].

2. Chemical Structure

Pitavastatin is a widely accepted and efficacious therapy for individuals with combined dyslipidemia as well as hypercholesterolemia, particularly for patients with low HDL-C. That ought to contribute to higher rates of LDL-C target attainment by lowering the risk of undertreatment, minimizing adverse events, and lowering the risk of DDIs in patients who need polypharmacy. [13]. Statins often bind to HMG-CoA reductase with several thousand times greater affinity than HMG-CoA, and their structures are comparable to that of HMG-CoA [5]. Pitavastatin is recognized by its chemical term, (+) monocalcium bis-{(3R,5S,6E)-7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoate}, and its molecular weight is 880.98[1]. Fungal-derived inhibitors of HMG-CoA reductase, including Lovastatin, Pravastatin, and Simvastatin, and wholly synthetized molecules, including Atorvastatin, Cerivastatin, Fluvastatin, Pravastatin, Pitavastatin, and Rosuvastatin [12], are known. Another new HMG-CoA reductase inhibitor that has demonstrated significant effects on lowering plasma total cholesterol and triglycerides is Pitavastatin [14].

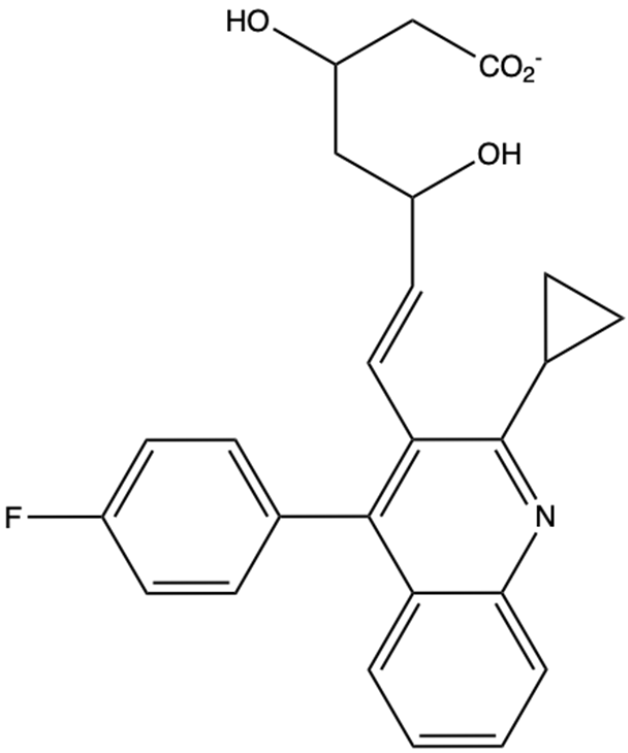

Fig. 1. Pitavastatin Calcium

3. Pharmacodynamics of Pitavastatin

Pitavastatin was mostly absorbed in the small intestine rather than the colon; bioavailability (51%), Tmax 1 hour. When pitavastatin is taken after a fatty meal, the Cmax drops by 43% [4]. Since pitavastatin showed substrate-competitive type inhibition of HMG-CoA reductase with an IC50 of 6.8 nM, which is 2.4- and 6.8-times more effective than that of simvastatin and pravastatin, respectively, foods that interact with specific statins should be ingested with caution.[15].

3.1. *Mechanism of Action*

Statins attach to HMG-CoA reductase with a thousand-times higher affinity than the natural substrate and share structural similarities with HMG-CoA [16]. By suppressing the synthesis of mevalonate from HMG-CoA and lowering intracellular cholesterol, this raises the activity of the LDL receptor and promotes adoption of non-HDL particles from the systemic circulation[16]. Data from both inside and outside of living organisms; experiments show that statins limit the formation of products from the mevalonate pathway & raise cholesterol accumulation, which impairs the function of β-cells and reduces their sensitivity to insulin and release of it [17]. Although it was previously believed that this impact was related to the drug class, new research indicates that both pitavastatin and pravastatin may have neutral effects on glycaemic indices in both patients with and without diabetes mellitus [18]. According to in vitro research, pitavastatin has a 1.6- and 3.5-fold higher affinity for HMGCoA reductase than simvastatin or pravastatin, respectively [16]. There are several methods for evaluating insulin activity in vivo, including the glucose clamp, HOMA, MIDMOD, and QUICKI. Using one of these methods, statins were evaluated against a control in a crossover/parallel design within a meta-analysis conducted on individuals without diabetes. Statins did not significantly affect insulin sensitivity when compared to controls [18]. Compared to other statins, pitavastatin efficiently lowers LDL-C levels at lower dosages[16].

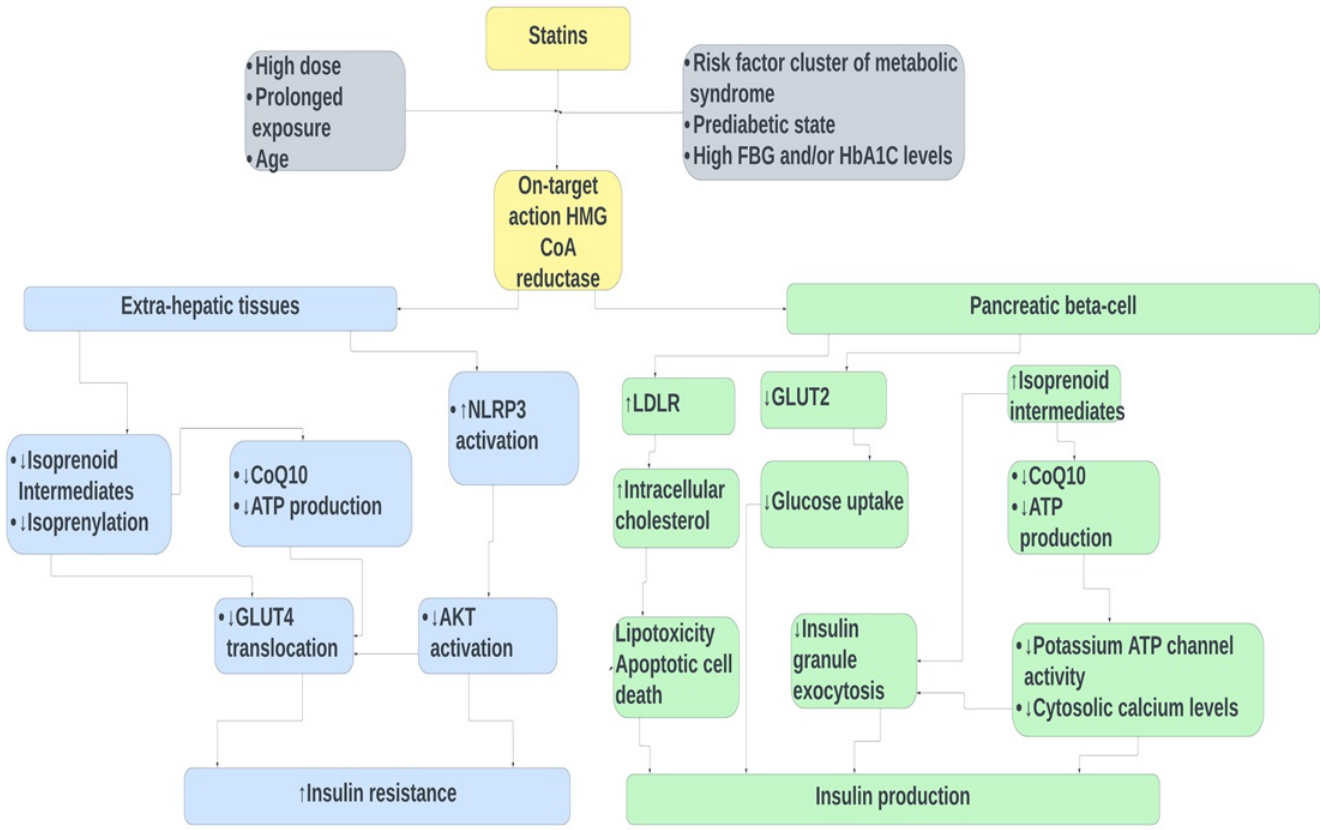

Fig. 2. MOA of Pitavastatin

3.2. *Other Effects*

Recent research indicates that statins may improve vascular function in ways that go beyond those brought about by decreasing cholesterol alone; this is known as the "pleiotropic" effect [19]. Pitavastatin has been demonstrated to enhance angiogenesis, decrease the creation of ROS [18], enhance endothelial performance[20], raise the production of nitric oxide [21], prevent the attachment of cells[18], suppress the contraction of smooth muscle cells[20], and promote the production of Apo AI [19]. Statins have several advantageous benefits that go beyond lowering LDL-C, including reducing inflammation and having positive effects on the endothelium and coagulation cascade [15].

4. Pharmacokinetics of Pitavastatin

4.1. *Absorption and Distribution*

Pitavastatin's maximum plasma concentration (Cmax) in humans is reached approximately one hour after oral administration; its absolute bioavailability is 51%, and its absorption rate is 80%. The Cmax is decreased when pitavastatin is administered with a high-fat meal, but the AUC (area under the plasma concentration-time curve) remains unaffected [19]. Pitavastatin is thought to have a lower effect on LDL-C because of its longer half-life when compared to other statins[15]. Food has no clinically significant effects on Pitavastatin’s pharmacokinetic profile[19].

4.2. *Metabolism and Excretion*

The passage of PTVS is along basal hepatic cytochrome P450 (CYP) metabolism; as a result, it penetrates the enterohepatic circulation, extending its half-life of elimination (t½) to roughly 11-12 hours [19]. The primary circulating metabolite is formed when the liver metabolizes it and uridine 5-diphosphate glucuronosyl transferases (UGT1A3 and UGT2B7) glucuronidate it [4]. These results imply that pitavastatin is not likely to interact with other medications when taken together[22]. The recently approved treatment for hyperlipidaemia involves the use of pitavastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor. Previous research has been conducted on the pharmacokinetic characteristics of pitavastatin [23]. Additionally, statins exhibit varying affinities for membrane transporters implicated in metabolic processes such as renal, biliary, intestinal, and hepatic excretion [24]. Numerous pharmacokinetic investigations have demonstrated that in healthy individuals, single nucleotide polymorphisms in this gene substantially affect pitavastatin pharmacokinetics [19]

5. Lipid Lowering Agents

5.1. *Patients with Dyslipidaemia*

Pitavastatin has high binding and inhibitory effects on the active site of 3-hydroxy-3-methyl-glutaryl-CoA reductase, which enables it to exert its effective pharmacologic action. It also has strong lowering effects on low-density lipoprotein cholesterol[15]. Pitavastatin is a new type of statin that causes plaque regression. It is not worse than atorvastatin and, in

some cases, better than pravastatin and simvastatin when taken by older adults [25]. Nine extensive trials ranging in length from eight to fifty-two weeks have examined the hypolipidemic impact of pitavastatin in those suffering from dyslipidemia [19]. One major consequence of dyslipidemia is coronary heart disease. A more often prescribed drug for the treatment of dyslipidemia is pitavastatin [26]. The overall cholesterol levels, including triglycerides, as well as LDL, dropped significantly, and in vivo, the treatment outcome was sustained for more than 3 weeks, according to the pharmacodynamic investigation conducted in hyperlipidemic rats [27]. Pitavastatin would be a great imaging agent for hOATP, which is why we looked at making this agent synthetic [28]. Pitavastatin has also been shown to have lipid-lowering effects in many research studies [19].

5.2. *Patients with Diabetes*

Asian patients free of severe hypertension or uncontrolled diabetes have been the focus of most pitavastatin research. Pitavastatin has been shown in head-to-head trials to be non-inferior to simvastatin and atorvastatin when it comes to decreasing LDL-C [29]. Compared to many other statins, pitavastatin undergoes limited metabolism, which reduces the likelihood of drug-drug interactions; however, it can interact with some medications that block drug transporters [30]. Against approximately 89% of the studied strains, pitavastatin demonstrated broad-spectrum synergistic interactions with both voriconazole and fluconazole [31]. Type 2 diabetes (T2D) is linked to decreased β-cell mass and obesity. Due to its incretin secretagogue capability, L-glutamine has been linked to the improvement of T2D; nevertheless, findings regarding pitavastatin's capacity to potentiate adiponectin are inconsistent [32]. The sick individuals had hyperlipidemia, type 2 diabetes mellitus, or glucose intolerance. In patients with type 2 diabetes, PTVS significantly lowered the baseline numbers of triglycerides, total cholesterol, and LDL cholesterol [19]. In non-diabetic people, there was a significant rise in fasting glucose in direct proportion to strict and heavy statin treatment [33]. We must determine the best course of action to reduce the hyperglycaemic impact of statins and enhance their cardiovascular benefits [32].

6. Drug Interaction

Pitavastatin is a new and strong inhibitor of HMG-coenzyme A reductase, and it has already been shown that OATP-1B1 plays a major role in its uptake by human hepatocytes. Since OATP2B1 is likewise found in the human liver's basolateral membrane, we used two methods to validate OATP2B1's negligible role in the liver's absorption of pitavastatin [34]. Polypharmacy, ADRs, and statin-drug interactions: terms such as "statin" (along with others, such as "HMG CoA reductase inhibitor"), terms concerning polypharmacy (such as "polypharmacy" or "interaction" or "concomitant" or "co-morbid"), and words concerning ADRs (such as "adverse drug reaction" or "adverse event" or "side-effect" OR "myopathy" and others were searched). In a recent study, 543 hospitalized patients over 75 years old were given an average of 7.4 drugs; the literature said that "polypharmacy in old age is the rule rather than the exception." Furthermore, within the cases taking >6 prescription drugs, the quantity of the advised medication was nearly exactly correlated with the incidence of potential DDIs6. This may be because most physiological processes, such as liver and kidney function, gradually decline with age12. In fact, aging has an impact on every stage of the pharmacokinetic process, from absorption

to excretion [35]. Furthermore, affinity for the bile salt export pump, P-gp, the multi-drug resistance protein (MRP2), and the BCRP is shared by all statins. The latter transporters could be slightly involved in the drug interactions of statins. Ultimately, it seems that CYP metabolism and these transporter proteins are in a delicate balance [36]. Since many patients with hyperlipidemia also suffer from conditions like diabetes and hypertension, statins are frequently used in conjunction with other medications. This raises the possibility of harmful drug-drug interactions and may have important therapeutic ramifications [37]. The degree of cytochrome P450 (CYP)-mediated metabolism of individual statins determines how concurrent medications affect the pharmacokinetics of statins [24].

7. Other Side Effects

A considerable load of cardiovascular disease risk factors is linked to chronic kidney disease (CKD). Elevated levels of cholesterol and triglycerides are linked to a faster decline in kidney function, and dyslipidaemia is more common in chronic kidney disease patients compared to the general population [38]. Globally, the prevalence of chronic kidney disease has been rising, and high cholesterol is a common complication for CKD patients [39]. As a result, medication repurposing has been studied for several illnesses and has emerged as an effective drug discovery technique [40]. It has been demonstrated that the statin drug class is a novel class of medications with pharmacological advantages in a variety of solid tumours [41]. Pitavastatin, the only lipid-lowering research with statins, has shown a correlation between drug-induced increases in HDL-C and decreased cardiovascular risk [42]. Pitavastatin causes apoptosis. It shows that using two extracts, PTVS exposes the cell feasibility: sunflower oil, which dramatically restored the action of PTVS in cell proliferation, and milk, which cannot verify that the results in the assay reflected cell death [43]. Few studies suggest that using statins causes skeletal muscle contractions to behave favourably [44]. Pitavastatin is well tolerated and efficiently alters atherogenic lipid profiles, lowering the risk of cardiovascular disease and cerebrovascular accident in Japanese individuals with hypercholesterolemia, according to the LIVES research [45]. Even with the broad availability of efficacious statins, an intolerably high percentage of patients (47-84%) do not achieve their intended LDL-C level in a medical setting [46]. More effectively, pitavastatin medication decreased the incidence of new cancer cases. In addition, to improve the antitumor efficacy and lessen adverse causes, a novel mixed tumour therapy containing PTVS will increase later [47].

8. Discussions

HMG coenzyme hydroxymethyl One of the drugs that doctors prescribe most frequently in Asia is a reductase (HMGCoA) inhibitor, sometimes known as a statin [48]. Pitavastatin has good tolerance. The safety of 19,925 patients using pitavastatin in clinical practice was examined in the post-marketing LIVES trial [25]. The pharmacokinetics of pitavastatin and its metabolites, as well as treatment safety, were the main objectives [49]. Additionally, pitavastatin had no effect on fasting glucose levels [50]. A recent addition to the statin family, pitavastatin regularly and potently improves lipid markers [19]. The primary outcome of this investigation was the considerable reduction of cardiovascular events in individuals with lipid disorders who had more than one hazard component for ASCVD when PTVS (2 mg/day) medication was administered [51]. Pitavastatin pretreatment decreased periprocedural ischemic complications (CAS) after carotid

artery stenting substantially [52]. Pitavastatin will be especially helpful in treating patients with mixed dyslipidemia since it effectively lowers triglycerides while raising HDL cholesterol [53]. To forecast the medicative causes and pharmacokinetics and pharmacodynamics interactions, it is crucial to understand the pitavastatin transporter profiles; the bile duct is a significant location for statin acceptance and medicative aim [54]. Even in the heart that has hypertrophied, pitavastatin can stop the progression of heart failure [55]. Additional research is necessary to determine any potential variations in risk amongst statins [56].

9. Conclusions

In clinical trials, pitavastatin potently and consistently lowered LDL and total cholesterol levels, and it was consistently linked to an increase in HDL cholesterol levels [19]. Pitavastatin can raise HDL-C more than other statins; however, its pharmacological advantages should be considered. With augmentation from RCT [57], pitavastatin treatment appears to increase the generation of the poor lipid precursor high-density lipoprotein or apoA-I, resulting in lower consequent challenges via connections to high-density lipoprotein-C techniques. PTVS may have some benefits, especially in the medication for the management of diseases linked to HDL [58]. To clarify the underlying processes and pitavastatin's potential function in the future for patients at high risk of diabetes, more research is necessary [59]. Pitavastatin has good tolerability [17].

Statements and Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

Funding

The review article has not been funded by any of the funding sources.

Declaration of competing interest

The authors declare that there is no conflict of interest.

Authors' contributions

All authors have equally contributed to completing the article.

Acknowledgments

The authors are thankful to all those who helped to compile the article.

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