Section A -Research paper

PITAVASTATIN:PHARMACOKINETIC, PHARMACODYNAMIC, THERAPEUTIC USES, DRUG INTERACTIONS AND SIDE EFFECTS

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Abstract:

Background: The growing number of trials that have highlighted the benefit of intensive lowering of total- and low density lipoprotein (LDL)-cholesterol levels especially with statins has created a need for more efficacious agents. Pitavastatin is a new synthetic 3-hydroxy-3-methyl glutaryl coenzyme A reductase inhibitor, which was developed, and has been available in Japan since July 2003.Metabolism of pitavastatin by the cytochrome P450 (CYP) system is minimal, principally through CYP 2C9, with little involvement of the CYP 3A4 isoenzyme, potentially reducing the risk of drug–drug interactions between pitavastatin and other drugs known to inhibit CYP enzymes. Human and animal studies have shown pitavastatin to be potentially as effective in lowering LDL-cholesterol levels as rosuvastatin; although, head-to-head studies are yet to be conducted.

Keywords: Pitavastatin ,HMG-COA reductase inhibitor ,LDL.

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Introduction

Pitavastatin is a potent HMG-CoA reductase inhibitor which induces a substantial increase in LDL receptor activity and lowers LDL-C. It has a characteristic structure with a quinoline ring at the core, a cyclopropyl moiety, and a flourophenyl group, similar to other statins, especially fluvastatin and rosuvastatin **(1)**. This structure improves pharmacokinetics, with better absorption and activity . After oral administration of pitavastatin, the concentration is 54 times greater in the liver than in serum. Pitavastatin is more potent at inhibiting cholesterol synthesis in vitro and is more effective at induction of LDL receptor expression and activity than any other statin **(2).**

The chemical structure

Pitavastatin, (+)–monocalcium bis (3R,5S,6E)-7-[2-cyclopropyl4-(4-fluorophenyl)-3-quino- lyl]-3,5-dihydroxy-6-heptenoate] (M.W. 880.98) is a synthetic enantiomer (3R,5S) with a dihydroxypentenoic acid chain statin. It was first synthesized by Nissan Chemical Industries Ltd Tokyo, Japan, and later developed by Koya Co. Ltd, Tokyo, Japan (**3)**. Chemically, pitavastatin is a moderately lipophilic drug with a log P of 1.49, which may explain its good absorption after oral administration and its relatively long half-life (**4)**. Like other statins, pitavastatin binds to the active site of the target enzyme, HMG-CoA reductase,via its dihydroxy heptenoic acid side chain (**5)**.

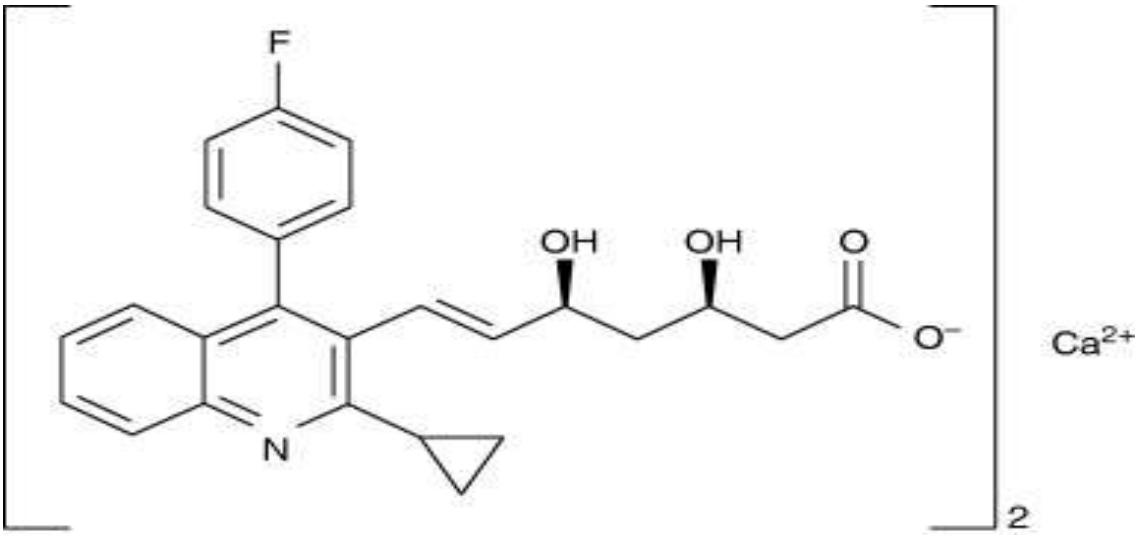

Figure (1):chemical structure of pitavastatin (**6)**

Pharmacokinetic of pitavastatin

Compared with other statins, pitavastatin is a moderately lipophilic compound (logP [N-octanol/water partition coefficient]: 1.49). Of note, the oral absorption (80%) of pitavastatin is good and, unlike other statins, is not affected by food, and it has high absolute bioavailability (>60% of the administered dose). However, the most important differences between pitavastatin and other statins relate to metabolic differences. The presence of the cyclopropyl group in pitavastatin affects the biotransformation of the drug by enzymes that are mainly in the liver. As a result, pitavastatin is excreted mainly unchanged in the bile, is reabsorbed in the small bowel and has a prolonged duration of action (**7)**. Furthermore, the cyclopropyl group diverts metabolism of pitavastatin away from CYP3A4, differentiating pitavastatin from the many other drugs that are metabolized by this route. Bearing in mind that the majority of pitavastatin is not biotransformed, the minor metabolic pathway for pitavastatin mainly relates to the action of CYP2C9 (**8)**.

Pitavastatin undergoes some glucuronidation (to pitavastatin glucuronide), which, via an elimination reaction of the glucuronic acid moiety, converts to a lactone derivative (which is in equilibrium with the acid [parent] form of pitavastatin) . Importantly, compared with other statins, the acid (parent) form of pitavastatin is not metabolized by CYP3A4 and the lactone metabolite undergoes only minor biotransformation via CYP3A4 . Furthermore, a study in human hepatic microsomes showed that both the acid and lactone forms of pitavastatin are metabolically stable compared with other statins **(9).**

Pharmacodynamics of pitavastatin

Pitavastatin is an oral antilipemic agent which inhibits HMG-CoA reductase. It is used to lower total cholesterol, low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apoB), non-high density lipoprotein-cholesterol (non-HDL-C), and trigleride (TG) plasma concentrations while increasing HDL-C concentrations. High LDL-C, low HDL-C and high TG concentrations in the plasma are associated with increased risk of atherosclerosis and cardiovascular disease (**10).**

Uses :

Pitavastatin is indicated for the treatment of adult patients with primary hyperlipidemia or mixed dyslipidemia to reduce elevated total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), triglycerides (TG), and to increase high-density lipoprotein cholesterol (HDL-C). It is also indicated for the treatment of pediatric patients aged 8 years and older with heterozygous familial hypercholesterolemia (HeFH) to reduce elevated TC, LDL-C, and Apo B **(11).**

Prescribing of statin medications is considered standard practice following any cardiovascular events and for people with a moderate to high risk of development of CVD. Statin-indicated conditions include diabetes mellitus, clinical atherosclerosis (including myocardial infarction, acute coronary syndromes, stable angina, documented coronary artery disease, stroke, trans ischemic attack (TIA), documented carotid disease, peripheral artery disease, and claudication), abdominal aortic aneurysm, chronic kidney disease, and severely elevated LDL-C levels (**12)**.

Drug interaction :

Pitavastatin has minimal drug drug interactions; only ciclosporin and erythromycin, multitransporter inhibitors, have a moderate–strong interaction with pitavastatin, whereas all other evaluated drugs have no, or only a weak (not clinically relevant), interaction. In clinical practice, ciclosporin is contraindicated as it has been shown to increase pitavastatin AUC 4.6-fold; erythromycin increases pitavastatin plasma concentrations 2.8-fold, requiring a ‘drug holiday’ when the two drugs are administered concomitantly (**8)**. Importantly, gemfibrozil (1.4-fold), rifampicin (1.3-fold) and atazanavir (1.3-fold) have no clinically relevant effect on

pitavastatin plasma concentrations (**13)**. By comparison, erythromycin and atazanavir are contraindicated with simvastatin (ciclosporin requires simvastatin and atorvastatin dose restriction), and cyclosporin is contraindicated with rosuvastatin.

Adverse effects

Adverse effects include back pain, constipation, diarrhea, myalgia, and pain in extremities (**14).** The most common adverse reactions which occurred, resulting in discontinuation of treatment, were elevated creatine phosphokinase (0.6% on 4 mg) and myalgia (0.5% on 4 mg). Laboratory abnormalities reported with the use of pitavastatin, aside from elevated creatine phosphokinase, were elevated transaminases, alkaline phosphatase, bilirubin, and glucose Other reported adverse effects included arthralgia, headache, influenza, and nasopharyngitis **(15)**.

Conclusion

Pitavastatin shows potential as an effective lipid-lowering agent with the added benefit of reducing plasma triglyceride levels. Data so far, suggests that pitavastatin is at least as potent if not more so than atorvastatin approaching or equalling rosuvastatin and more potent than other available statins . Direct comparative studies will be required to confirm this. At its lower doses, pitavastatin appears to be well tolerated with a safety profile similar to the other statins. That it is minimally metabolised by the liver and CYP may lead to the possibility of less drug interactions; although, it is suggested that alternative pathways to CYP may be responsible for some of the toxic interactions and side effects of statins.

Conflicts of Interest: The authors declare no conflict of interest.

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