**Pitavastatin: The Statin with a Difference**

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**Introduction**

Pitavastatin is the latest statin to get approval worldwide. It is the competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase enzyme. Inhibiting this (rate-limiting) enzyme impedes cholesterol synthesis in the liver, thereby increasing low-density lipoprotein cholesterol (LDL-C) receptor expression which subsequently reduces LDL-C and total cholesterol levels. Pitavastatin has many unique properties which makes it different from other available statins. Some of these properties have been described hereafter:

- Pitavastatin is more effective in increasing high-density lipoprotein cholesterol (HDL-C) compared to other statins. In an Indian double blind randomised controlled trial, 100 dyslipidaemia patients were randomised to 4 mg/day pitavastatin or 20 mg/day atorvastatin and followed-up for 8 weeks. The increase in HDL-C levels was significantly higher in the pitavastatin group (11%) vs. the atorvastatin group (5.35%) ($p<0.001$). In a sub-analysis of the LIVALO Effectiveness and Safety (LIVES) study in patients with low HDL-C levels who were treated with pitavastatin for 104 weeks, there was a 32% increase in HDL-C levels. Patients who were shifted from other statins to pitavastatin also showed significant increase in HDL-C levels.

- Pitavastatin has significant pleiotropic effects including anti-inflammatory effects which might be beneficial for atherosclerosis regression. In the Kansai Investigation of Statin for Hyperlipidaemic Intervention in Metabolism and Endocrinology (KISHIMEN) trial, dyslipidaemia patients were treated with pitavastatin 1-2 mg for 12 months. Pitavastatin significantly reduced high sensitivity C reactive protein (hs-CRP) levels by 28.6% in overall subjects and by 62.4% in the highest quartile at 12 months.

- Statin therapy is known to increase blood glucose levels and increase the risk of new onset diabetes in non-diabetic patients. Pitavastatin has shown neutral or beneficial effects on blood glucose levels in both diabetic and non-diabetic patients. In the Japan Prevention Trial of Diabetes by Pitavastatin in Patients with Impaired Glucose Tolerance (J-PREDICT) study, 1269 patients with impaired glucose tolerance were treated with 1-2 mg pitavastatin or placebo for up to 5 years. There was a significant 18% reduction in the risk of developing new onset of diabetes.

- Pitavastatin has been shown in many studies to be well tolerated in patients who are intolerant to other statins. In a study, 3 out of 4 (76%) patients who were intolerant to >2 statins were able to tolerate pitavastatin for 6 months. Better tolerability of pitavastatin is possibly due to a lower decrease in coenzyme Q10 (CoQ10) compared to other statins. Pitavastatin should be considered a preferred statin when a patient requires statin therapy but fails to tolerate other statins.
Figure 1: Risk of new onset diabetes with pitavastatin or placebo in J-PREDICT study

REAL-CAD Study

The Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy With Pitavastatin in Coronary Artery Disease (REAL-CAD) was a randomized, multicentric, active controlled clinical trial done to evaluate cardiovascular disease (CVD) prevention by moderate cholesterol lowering (pitavastatin 1mg/day) or aggressive cholesterol lowering (pitavastatin 4 mg/day) in 13,054 patients with stable CAD (coronary artery disease). A composite of cardiovascular death, non-fatal myocardial infarction, non-fatal ischemic stroke, or unstable angina requiring emergency hospitalisation was the primary endpoint for this study. Patients were followed up for a median period of 3.9 years. At the time of enrolment, 91% of patients were taking statins and had a mean LDL-C level of 93 mg/dL. During the entire course of follow-up, LDL-C in the 4 mg pitavastatin group was lower by 14.7 mg/dL than in the 1 mg pitavastatin group ($p<0.001$). High-dose pitavastatin as compared with low-dose significantly reduced the risk of the primary end point by 19% (hazard ratio, 0.81; 95% confidence interval, 0.69-0.95) (Figure 2). The risk of several other secondary end points like all-cause death (19%), myocardial infarction (43%) and clinically indicated coronary revascularization (14%) were significantly reduced with high dose pitavastatin. Muscle related adverse events were more common in 4 mg pitavastatin group (1.9%) than in the 1 mg pitavastatin (0.7%), though there was no difference in both the groups for rhabdomyolysis and new onset diabetes. The study concluded that 4 mg pitavastatin (considered to be moderate intensity statin therapy) significantly reduced cardiovascular events in Asian patients with stable CAD. Pitavastatin 2-4 mg is recommended as an option for moderate intensity statin therapy as per the European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines for management of dyslipidaemia.

Figure 2: Incidence of primary end point in the REAL-CAD trial
The REAL CAD is the first cardiovascular outcome study comparing different intensities of statin therapy in Asian patients for secondary prevention. Success of this trial has opened newer horizons for management of dyslipidaemia by so-called “moderate” intensity statin (4 mg pitavastatin) in Asian patients suffering from CAD.

With several studies documenting unique benefits with the use of Pitavastatin, it undoubtedly is the statin with a difference.

**Summary**

Pitavastatin is an extensively studied molecule. It elevates high density lipoprotein cholesterol (HDL-C), has anti-inflammatory effects and salutary effect on blood glucose. It is the best tolerated drug of its class and is one of the few members of its class to have data documenting secondary prevention of cardiovascular disease.

**Declaration of conflicting interests**

The author declares no conflict of interest.

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**References**