Comparative efficacy of pitavastatin and simvastatin in high-risk patents: A Randomized Controlled Trial

BACKGROUND:

- Other studies have shown that patients with dyslipidemia do not meet lipid targets in current consensus guidelines, even though they are being treated with a statin.
- This study wanted to address the need for managing the burdens of dyslipidemia with a more potent lipid lowering agent such as pitavastatin.

OBJECTIVE:

- To show non-inferiority of pitavastatin 2mg once daily compared to simvastatin 40 mg once daily in reducing LDL-C concentrations.
- It also assessed the long term efficacy of the two drugs in achieving the LDL-C targets recommended by the NCEP Adult Treatment Panel III and the European Atherosclerosis Society, and to compare their effects on other lipid measurements and high sensitivity C-reactive protein.

METHODS

- A phase III, randomized, double blind, double dummy, parallel-group, active controlled study at 37 multi-national centers in Denmark, the Netherlands, Spain, Sweden, and the UK.
- There was a6-8 week dietary run-in period. An 8 week wash-out period if patients had been on previous lipid modifying therapy or 6 weeks if no previous therapy.
- After a 12 hour fast, blood samples were taken during the run in period and at weeks 0,2,4,8, and 12 of the study.
- **Inclusion criteria**included those aged 18-75 years and with primary hypercholesterolemia or combined dyslipidemia that was uncontrolled, despite dietary measures. Patients must have had at least two of the following cardiovascular risk factors: cigarette smoking, blood pressure ≥140/90 mmHg or receiving antihypertensive therapy, an HDL-C concentration ≤ 40 mg/dL (1 mmol/L), family history of CHD in a 1st degree relative male < 55 or female <65 years of age, age > 45 years in men or > 55 years in women. Any HDL-C > 1.55 mmol/L (60 mg/dL) was considered to offset one risk factor.
- **Exclusion criteria** included homozygous familial hypercholesterolemia, unstable medical conditions, or conditions associate with secondary dyslipidemia, conditions that may affect pharmacokinetics of study drug, significant cardiovascular disease, or symptomatic heart failure or cerebrovascular disease, uncontrolled or poorly controlled HTN, uncontrolled diabetes (>8% glycated Hg), impaired liver or kidney function. Negative pregnancy tests from women of childbearing potential were required during run in period and before starting treatment. They were encouraged to use sufficient contraception during the study.
- 300 patients, 200 in the pitavastatin group and 100 in the simvastatin group, were needed for a power of at least 99% to reject the null hypothesis that the mean percentage decrease in LDL-C concentrations from baseline would be at least 6% greater in the simvastatin group than in the pitavastatin group, assuming a standard deviation of 12, for percentage decrease from baseline LDL-C, and a one-tailed significance of 2.5%.
- The full analysis set (FAS) was all randomized patients who received at least one dose of study medication and at least one lipid assessment during the study. It was used for evaluations in the non-inferiority analysis and other lipid assessments.
- The per protocol populations (PP) were patients who had lipid assessment at 12 weeks and no major protocol deviations.
- **Primary efficacy endpoint**: percentage change in LDL-C concentrations from baseline to 12 weeks.
- **Secondary efficacy endpoint**: portion of patients reaching NCEP and EAS LDL-C targets, percentage change from baseline in concentrations of triglycerides, total cholesterol, HDL-C,

non-HDL-C, Apo-B, Apo-A1, and absolute changes from baseline in concentrations of oxidized LDL and hs-CSP and ratios of total cholesterol: HDL-C, non-HDL: HDL-C, and Apo-B:Apo-A1.
- **Data handling**method was per protocol.

RESULTS
- **Reasons for drop out:** withdrew consent (6), adverse events (15), lack of lipid assessments (28), protocol violations (38), and other reasons (3).
- **Primary outcome measures:** adjusted mean difference between simvastatin and pitavastatin was -0.31% (95% CI: -2.47, 3.09, P=0.829) which was within the predefined limits of non-inferiority. With the PP population the mean treatment difference was -0.61% (95% CI: -3.17, 1.94, P=0.637).
- **Secondary outcome measures**: the mean differences in the amount of patients achieving LDL-C targets were -1.5% for NCEP tarts and -5.8% for EAS targets. The only significant difference pitavastatin provided in secondary lipid variable was a greater reduction in triglycerides -19.8% vs. -14.8% (P=0.044).
- **Authors Conclusion:** This study has shown that pitavastatin 4mg is as effective as simvastatin 40 mg in lowering LDL-C concentrations in dyslipidemic patients at high risk of CHD, and also has effects on other lipid fractions, notably HDL-C and triglycerides.

STRENGTHS
- Showed that a high proportion (81-87%) of patients in both treatment groups achieved the LDL-C targets recommended in the NCEP and EAS guidelines.
- It also showed that pitavastatin had a significantly greater effect than simvastatin on triglycerides, producing a mean reduction of approximately 20% from baseline.
- Both statins were well tolerated with similar adverse event profiles.
- Patients received dietary counseling throughout the study.

LIMITATIONS
- A 2:1 ratio was used was used to randomized patients to treatment groups which provided the pitavastatin group with a greater percentage of patients to show its effect on.
- Simvastatin 40 mg was used instead of 80 mg or an alternative statin that may have been more potent.
- Physical activity was not controlled.
- Patients could have been randomized based on their LDL-C concentrations; to provide a better overall picture of how effectively each statin lowered LDL-C concentrations.
- Pitavastatin showed a statistically significant effect on triglycreides; however, further studies need to be done to show whether there is a clinical difference.

CONCLUSION
- Pitavastatin is much more expensive than simvastatin and validating its use for patients and health care providers would require stronger evidence.
- Further research could be done with an equal amount of patients in each study group with physical activity recommendations and a more potent active medication in order to determine what additional lipid parameters difference statins may have an effect on.

Michelle Gianni, Doctor of Pharmacy Candidate