Efficacy and Safety of Rosuvastatin 5 mg in Combination with Fenofibric Acid 135 mg in Patients with Mixed Dyslipidemia – A Phase 3 Study

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BACKGROUND:

- Although statin monotherapy is the primary choice of treatment for mixed dylipidemia, statins alone may not sufficiently improve lipid parameters in these patients. One therapeutic option is to combine a statin (such as rosuvastatin) with fenofibric acid.

OBJECTIVE

- This study evaluated the efficacy and safety of rosuvastatin 5 mg in combination with fenofibric acid 135 mg, compared with corresponding monotherapies in patients with mixed dyslipidemia.

METHODS

- **Design**: randomized, placebo-controlled, double-blinded, parallel-group study
- **Duration**: 12 weeks (6-week screening period, 12-week treatment period)
- **Inclusion Criteria:** men and women $\geq$18 years of age, triglycerides $\geq$150 mg/dl, HDL <40 mg/dl for men and <50 mg/dl for women, LDL $\geq$130 mg/dl, life expectancy >6 months, and willingness to adhere to an American Heart Association recommended diet
- **Exclusion Criteria**: pregnancy or breastfeeding, hypersensitivity to study drug formulations, use of any investigational drug within 42 days of baseline, type 1 diabetes or history of diabetic ketoacidosis, uncontrolled type 2 diabetes (hemoglobin A_{1C} >10.5%), uncontrolled hypertension (systolic >180 mm Hg or diastolic >110 mm Hg), evidence of unstable cardiovascular disease, ALT or AST > 1.5 times the upper limit of normal, creatinine phosphokinase level > 3 times the upper limit of normal, calculated creatinine clearance <50 ml/min, abonormal TSH, and treatment with excluded medications within 6 weeks of baseline visit
- **Number of Patients Enrolled:** 760 patients were randomized to therapy: 253 were assigned to rosuvastatin 5 mg monotherapy, 254 were assigned to fenofibric acid 135 mg monotherapy, and 253 were assigned to combination therapy with both.
- **Drug Regimens:** Patients were instructed to take all study medication at approximately the same time of day, with or without food.
- **Primary Outcome Measures**: The primary efficacy variables were mean percent change in HDL and triglycerides (in the rosuvastatin monotherapy versus rosuvastatin plus fenofibric acid groups) and changes in LDL (in the fenofibric acid monotherapy versus rosuvastatin plus fenofibric acid groups).
- **Secondary Outcome Measures**: Secondary efficacy variables were differences between groups in non-HDL cholesterol, VLDL, apolipoprotein (or Apo B), high-sensitivity C-reactive protein, and total cholesterol.
- **Power:** The planned sample size provided >99% power to detect differences of 17% in triglycerides and 30% in LDL. The sample size also provided a 90% power to detect a 5% difference in HDL, assuming a 15% rate of premature discontinuation.
- **Data Handling Method:** intent-to-treat

RESULTS

- **Number of Patients Who Completed the Study:** 231 patients in the rosuvastatin monotherapy group, 220 patients in the fenofibric acid monotherapy group, and 212 patients in the combination group completed the study.

- **Findings and Statistical Results:** Treatment with rosuvastatin plus fenofibric acid (when compared with rosuvastatin monotherapy) resulted in significantly greater mean percent changes in HDL (a 23.0% vs. 12.4% increase, p-value <0.001) and triglycerides (a 40.3% vs. 17.5% decrease, p-value <0.001), and resulted in higher mean percent decreases in LDL, compared with fenofibric acid monotherapy (a 28.7% vs. 4.1% decrease, p-value <0.001). Treatment with rosuvastatin plus fenofibric acid also resulted in statistically significant greater improvements in non-HDL when compared to fenofibric acid and rosuvastatin monotherapies, and statistically significant greater improvements in ApoB and hsCRP, as well as VLDL and total cholesterol than rosuvastatin monotherapy. P-values were significant in all categories.
- **Author's conclusions:** The authors concluded that rosuvastatin 5 mg plus fenofibric acid 135 mg resulted in comprehensive improvements in the lipid profile of patients with mixed dyslipidemia, compared with rosuvastatin and fenofibric acid monotherapies, without additional safety concerns. They also stated that this combination may be an appropriate therapeutic option for the treatment of mixed dyslipidemia in patients who require a lower starting dose of rosuvastatin.

STRENGTHS

- The study was double-blinded.
- Statistical tests used were appropriate.
- Uncontrolled diabetes and uncontrolled hypertension were defined.

LIMITATIONS

- Authors were affiliated with the makers of the study medications.
- Compliance was not addressed in this study.
- The study reported standard error of the mean instead of standard deviation for certain primary and secondary endpoints.
- The study did not clearly define their inclusion and exclusion criteria.

CONCLUSION

- **My Conclusion:** Rosuvastatin, when combined with fenofibric acid, may help lower cholesterol levels in patients with mixed dyslipidemia who cannot tolerate higher doses of rosuvastatin. However, this lower dose of rosuvastatin may not provide additional benefit in patients with normal renal function of non-Asian descent. These patients may derive more benefit from higher strengths of rosuvastatin as monotherapy or in combination with fenofibric acid.
- **Results Relating to Practice:** The current role of rosuvastatin is treatment of high cholesterol, either as monotherapy or in combination with other medications such as fenofibric acid. Rosuvastatin 5mg is indicated for patients who require lower doses of rosuvastatin, such as patients of Asian descent or patients with renal impairment.
- **Future Research:** Further research may be needed in patients with uncontrolled hypertension, unstable cardiovascular disease, and uncontrolled diabetes because these patients were not included in this series of studies. Further studies may also be needed to see if the diet the patients were on during the study affected the results.

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