

Efficacy and safety of fenofibric acid in combination with atorvastatin and ezetimibe in patients with mixed dyslipidemia

BACKGROUND:

- Treatment of patients with mixed dyslipidemias often requires multiple drugs. Patients with mixed dyslipidemia have high levels of LDL-C and triglycerides and low levels of HDL-C. These patients often remain at high risk of risk of cardiovascular events even if they reach their LDL goal with statin monotherapy. Further treatment aimed at triglycerides, HDL, ApoB, and non-HDL is often required. Fenofibric acid has been shown to have a beneficial effect on triglycerides and HDL and may help these patients reach their secondary lipid goals and reduce their cardiovascular risk.

OBJECTIVE:

- The objective of the study is to evaluate the safety and efficacy of fenofibric acid plus atorvastatin and ezetimibe compared to atorvastatin and ezetimibe alone in patients with mixed dyslipidemia.

METHODS:

- This study is a randomized, double-blind, parallel, multicenter trial with active comparator.
- Patient were enrolled over a four-month period and followed for 12 weeks each.
- Inclusion Criteria:
 - At least 18 years old
 - Triglycerides 150 mg/dL to 400 mg/dL
 - HDL < 40 mg/dL in men OR HDL < 50 mg/dL in women
 - LDL \geq 130 mg/dL
- Exclusion Criteria:
 - Recent-onset or unstable cardiovascular disease
 - Type 1 Diabetes Mellitus
 - Uncontrolled Type 2 DM (Hg A1C > 8.5%)
 - Uncontrolled hypertension (SBP > 180 or DBP > 110)
 - Pregnant
 - History of cancer other than nonmelanoma skin cancer in last 5 years
 - Hereditary or acquired myopathy
 - Hypersensitivity to any of the study drugs
 - ALT, AST, or bilirubin > 1.5x ULN
 - Creatine phosphokinase > 3x ULN
 - eGFR < 30 mL/min/1.73m²
- 543 patients randomized to receive either fenofibric acid plus atorvastatin plus ezetimibe (study group, 272 patients) or atorvastatin plus ezetimibe (control group, 271 patients)
- **Primary Outcome Measures:** Percentage change in HDL-C and percentage change in triglycerides
- **Secondary Outcome Measures:** Percentage change in LDL, ApoAI, VLDL, ApoCIII, non-HDL, ApoB, and high-sensitivity CRP. Attainment of various lipid goals:

- LDL < 100
 - LDL < 100 & Non-HDL < 130
 - LDL < 100, Non-HDL <130, & Apo B < 90
 - LDL < 70
 - LDL < 70 & Non-HDL < 100
 - LDL < 70, Non-HDL <100, & Apo B < 80
- Power for change in HDL was calculated to be 90% with an alpha level of 0.05 and standard deviation of 19% to detect a 6% treatment difference with 460 patients
 - Power for change in triglycerides was calculated to be > 99% with an alpha level of 0.05 and standard deviation of 30% to detect a 17% treatment difference with 460 patients.
 - Data handling method was modified intent-to-treat: All patients who received a dose were included in the safety analysis; Patients who had a baseline and ≥ 1 follow-up lipid panel were included in the primary efficacy analysis with imputation with last observation carried forward for missing data.

RESULTS:

- 246 patients in the study group and 240 in the control group completed the study
- **Primary outcome measures:** Statistically significant greater increase in HDL-C in the study group compared to the control group (+13.0 % vs. +4.2%, p < 0.001). Statistically significant greater decrease in triglycerides in the study group compared to the control group (-57.3% vs. -39.7%, p < 0.001).
- **Secondary outcome measures:** There were statistically significant differences in secondary lipid measures.

Outcome Measure	Study Group	Control Group	p-value
LDL	-52.9%	-52.0%	NR
Non-HDL	-55.6%	-51.0%	<0.001
ApoB	-49.1%	-44.7%	<0.001
ApoAI	+1.8%	-1.3%	0.004
VLDL	57.8%	-41.1%	<0.001
ApoCIII	-42.5%	-25.3%	<0.001
hsCRP	52.1%	-40.3%	<0.001

The proportion of patients that attained each lipid goal was reported, but p-values were not.

<u>Lipid Goal</u>	<u>Control Group</u>	<u>Study Group</u>
LDL < 100	86.3%	92.7%
LDL < 100 mg/dL & Non-HDL <130 mg/dL	84.0%	91.2%
LDL < 100 mg/dL, Non-HDL < 130 mg/dL, & ApoB < 90 mg/dL	80.8%	88.4%
LDL < 70 mg/Dl	56.5%	55.0%
LDL < 70 mg/dL & Non-HDL <100 mg/dL	51.1%	54.6%
LDL < 70 mg/dL, Non-HDL < 100 mg/dL, & ApoB < 80 mg/dL	51.3%	53.4%

- Adverse events rates were mostly similar in both groups. Incidence of AE of special interest was 9.6% in the study group and 8.1% in the control group. Myalgia was reported in 2.6% of study group patients and 3.7% of control group patients. No p-values were reported for AE incidence.
- Creatinine clearance decreased by 14.00 mL/min (11.9%) in the study group and increased 0.19 mL/min (0.2%) in the control group.

- **Authors' conclusion:** The authors concluded that in patients with mixed dyslipidemia, the addition of fenofibric acid to a regimen of atorvastatin and ezetimibe can help patients reach other lipid and apolipoprotein goals without increased side effects.

STRENGTHS:

- Randomized, controlled, double-blind study design
- High power for primary efficacy endpoints

WEAKNESSES:

- Lack of compliance monitoring
- Poor statistical reporting of adverse event rates and achievement of lipid goals
- Duration of 12 weeks may be too short to observe consistent HDL response
- Surrogate endpoints used; true clinical benefit is not proven
- Study population was about 90% white
- Excluded patients at high risk of cardiovascular complications (uncontrolled DM, uncontrolled hypertension)

CONCLUSIONS:

- It is unclear whether adding fenofibric acid to a lipid regimen of atorvastatin and ezetimibe is safe and clinically effective. Further research is needed to examine long-term cardiovascular outcomes and adverse events.
- The added benefit of ezetimibe is questionable, and it would be interesting to see how atorvastatin/fenofibric acid compares to atorvastatin/ezetimibe/fenofibric acid.
- Triple-lipid therapy may be used in patients that cannot reach goal HDL and triglyceride levels with standard therapy, but the patient should be closely monitored for changes in hepatic enzymes, renal function, and myalgia.
- Future research should focus on:
 - Long-term risk/benefit
 - Adverse effects (myalgia, hepatic function, renal function)
 - Long-term lipid panel changes
 - Clinical benefit of improved HDL, triglycerides, and secondary lipid markers
 - Correcting study weaknesses of poor compliance monitoring and adverse effect reporting/analysis
 - Comparing atorvastatin/ezetimibe/fenofibric acid to other anti-lipid combinations that include other statins, gemfibrozil, niacin, and/or fish oil.

Reference: Jones PH, Goldberg AC, Knapp HR, et al. Efficacy and safety of fenofibric acid in combination with atorvastatin and ezetimibe in patients with mixed dyslipidemia. *Am Heart J.* 2010 Oct; 160(4): 759-66.

Prepared by: Christopher Hale, PharmD Candidate, Class of 2011