

A review on the rationale and clinical use of concomitant rosuvastatin and fenofibrate/fenofibric acid therapy

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Abstract: Mixed dyslipidemia, characterized by a lipid triad of elevated triglycerides (TG), elevated low-density lipoprotein-cholesterol (LDL-C) and reduced high-density lipoprotein-cholesterol (HDL-C), is a common and frequently difficult to manage condition. The use of combination medications is often needed to effectively treat the lipid triad. The co-administration of statins and fibrates may provide the desired endpoints but safety issues such as toxicity to the muscles, liver and kidneys are a concern. Given the potency of rosuvastatin to lower LDL-C and fenofibrate's effectiveness in lowering TG, the use of this specific combination may be desirable in treating mixed dyslipidemia. Pharmacokinetic studies revealed no significant interactions with the concomitant use of rosuvastatin and fenofibrate or its active metabolite fenofibric acid. Clinical studies evaluating the efficacy and safety of this combination therapy demonstrate significant reductions in TG and LDL-C levels, and elevations in HDL-C. Safety data from clinical trials reveal no major adverse reactions. However, case reports of adverse events have been published and monitoring for potential adverse reactions of the individual agents is advised. Overall, current data suggest the combination of rosuvastatin and fenofibrate or fenofibric acid is a safe combination to utilize when managing difficult to treat mixed dyslipidemia patients.

Keywords: dyslipidemia, rosuvastatin, fenofibrate, fenofibric acid

Introduction

Mixed or atherogenic dyslipidemia is characterized by a lipid triad of elevated triglycerides (TG), elevated low-density lipoprotein-cholesterol (LDL-C) and reduced high-density lipoprotein-cholesterol (HDL-C).^{1,2} A high prevalence of mixed dyslipidemia occurs because many patients present with common risk factors such as obesity, diabetes mellitus or insulin resistance, metabolic syndrome and physical inactivity. A higher risk of coronary heart disease (CHD) has been associated with mixed dyslipidemia.

The National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) emphasizes the need for weight reduction and increased physical activity in the management of mixed dyslipidemia.^{1,2} The use of medications to treat the lipid triad may necessitate the use of combination therapy. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA reductase inhibitors or statins) have a primary effect of lowering LDL-C with a modest effect on lowering TG and raising HDL-C.^{3,4} To further lower TG and increase HDL-C, other pharmacologic agents are used such as a fibrate (fenofibrate, clofibrate, gemfibrozil, fenofibric acid) or niacin.⁵⁻⁷ The co-administration of statins and fibrates may provide a positive effect on the lipid triad but safety issues such as toxicity to the muscles, liver and kidneys are a concern.^{8,9} The newest statin to enter the market is rosuvastatin.¹⁰⁻¹² Rosuvastatin reduces LDL-C

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by 45%–63% with doses of 5–20 mg per day, which is a greater mean reduction compared to equivalent doses of other statins. Given the potency of rosuvastatin to lower LDL-C and fenofibrate's effectiveness in lowering TG, the use of this combination may be desirable in treating mixed dyslipidemia patients. A new fibrate, fenofibric acid, is available for treating mixed dyslipidemia to lower TG and increase HDL-C in patients already receiving optimal statin doses.^{9,13} Medical literature was reviewed to support the use of this newer drug combination. This article will evaluate the efficacy and safety of the concomitant use of rosuvastatin with fenofibrate or fenofibric acid for mixed dyslipidemia.

Data sources

A literature search was conducted using the terms rosuvastatin, fenofibrate, fenofibric acid, and ABT-335. MEDLINE, BIOSIS, EBSCOhost, and OVID databases were primary search sites from 1991 to January 2010. All English-based articles and abstracts obtained from the literature searches were reviewed. Additional information was obtained from references cited in the articles.

Rationale to use rosuvastatin and fenofibrate/fenofibric acid combination

Rosuvastatin works similar to other statins by inhibiting HMG-CoA reductase.¹⁴ The inhibition of this enzyme increases the number of LDL-C receptors on hepatocytes, thus facilitating the removal of LDL-C from the plasma. Other positive effects on lipid parameters include plasma reductions in total cholesterol (TC), apolipoprotein B (ApoB), TG, and an increase in HDL-C (Table 1).¹⁵ The effect of rosuvastatin on these parameters is more pronounced compared to other statins therefore it may be advantageous to utilize this agent to reach desired treatment goals in difficult to treat patients.¹⁴

Fenofibrate is rapidly metabolized by esterases to its active form of fenofibric acid.¹⁶ Both fenofibrate and fenofibric acid are available commercially and are primarily utilized for lowering TG and raising HDL-C through activating the peroxisome proliferator-activated receptor alpha (PPAR-alpha).⁹ This receptor is expressed in a variety of tissues and results in the breakdown of lipids and removal of TG from the plasma. The increase in PPAR-alpha activation also results in the facilitation of LDL-C removal from the plasma, a decrease in ApoB, and an increase in HDL-C through the stimulation of apolipoprotein A-I (ApoA-I) and apolipoprotein (ApoA-II) synthesis. The effects of fenofibrate and fenofibric acid monotherapy on lipid parameters

Table 1 Mean percent changes in lipid parameters in patients with hyperlipidemia and mixed dyslipidemia^{15–17}

	Rosuvastatin				Fenofibrate ^a	Fenofibric acid
Dose	5 mg	10 mg	20 mg	40 mg	145 mg	135 mg
TC	-33	-36	-40	-46	-18.7	-12.4
LDL-C	-45	-52	-55	-63	-20.6	-5.1
TG	-35	-10	-23	-28	-28.9	-31
HDL-C	13	14	8	10	11	16.3
ApoB	-38	-42	-46	-54	-25.1	-15.6

Note: ^aPooled cohort.

Abbreviations: TC, total cholesterol; LDL-C, low density lipoprotein-cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein-cholesterol; ApoB, apolipoprotein B.

are summarized in Table 1.^{16,17} The effect on the lipid profile will vary and may depend on the baseline lipid profile and lipid phenotype.¹³ A more dramatic increase in HDL-C occurs when initial HDL-C levels are less than 40 mg/dL. Lowering of TG may range from 20%–50% with the greatest reductions seen in patients with baseline TG greater than 500 mg/dL.^{13,16} While LDL-C reductions up to 20% may occur, typical lowering is usually much less. Fibrates may actually increase LDL-C in subjects with TG greater than 300 mg/dL, therefore they are not typically used for additional LDL-C lowering.^{13,18} The overall effects of fenofibrate on lipid parameters compliment the positive effects seen with rosuvastatin therapy.⁹

The major individual pharmacokinetic properties of fenofibrate, fenofibric acid and rosuvastatin are summarized in Table 2.^{15–17} Pharmacokinetic interaction studies have been conducted evaluating the use of fibrates with rosuvastatin. Gemfibrozil has been shown to have a significant pharmacokinetic interaction with rosuvastatin as the concentrations of rosuvastatin were approximately doubled.¹⁹ This interaction leads to concern for potential toxicities (ie, myopathy) related to the combination therapy of fibrates and rosuvastatin. A study by Prueksaritanont et al evaluated the metabolism of fibrates and statins when used together and suggests that all fibrates may not be the same in regards to interacting with statins.²⁰ While gemfibrozil appears to have a significant impact on the metabolism pathway of rosuvastatin, fenofibrate appears to lack a significant interaction.

Pharmacokinetic studies evaluating the concomitant use of fenofibrate or fenofibric acid plus rosuvastatin have been conducted. A 3-way crossover study by Martin et al evaluated the pharmacokinetics of rosuvastatin 10 mg daily and fenofibrate 67 mg 3 times daily.²¹ Fourteen healthy Caucasian males were given each agent alone or in combination for 7 days. A 3-week washout period was required between treatments. Assessment after 1 week revealed a 7% increase

Table 2 Pharmacokinetic properties¹⁵⁻¹⁷

	Rosuvastatin	Fenofibrate	Fenofibric acid
Half-life	19 hours	20 hours	20 hours
Metabolism	~10% via CYP450 2C9	Rapidly hydrolyzed to fenofibric acid	Conjugation via glucuronic acid
Elimination	~90% fecal	60% urine, 25% fecal	Primarily urine
Renal impairment	Dose adjust if CrCl < 30 mL/min	Dose adjust if CrCl 30–80 mL/min	Dose adjust if CrCl 30–80 mL/min
Hepatic impairment	Avoid in active liver disease	Avoid if CrCl < 30 mL/min	Avoid if CrCl < 30 mL/min
		No data	No data

Abbreviation: CrCl, creatinine clearance.

in the area under the curve (AUC) of rosuvastatin when given with fenofibrate versus rosuvastatin alone. A 21% increase in the maximum concentration (C_{max}) of rosuvastatin was seen when given with fenofibrate compared to rosuvastatin alone. Both of these increases were not statistically significant. The C_{max} and AUC of fenofibrate were not affected by concomitant rosuvastatin therapy. This data suggests no clinically significant pharmacokinetic interaction exists between rosuvastatin and fenofibrate. However it should be noted that the population was limited to healthy, Caucasian males, and higher doses of rosuvastatin were not evaluated.

The pharmacokinetics of concomitant fenofibric acid and rosuvastatin were evaluated by Zhu et al in a 3-period cross-over trial.²² Sixteen men and 2 women were given rosuvastatin 40 mg, fenofibric acid 135 mg, or the combination for ten days. A 2-week washout period occurred between treatments. Results of this study revealed rosuvastatin had no effect on the half-life, time to maximum concentration (T_{max}), C_{max}, minimum concentration (C_{min}), AUC or oral clearance of fenofibric acid. Analysis of rosuvastatin pharmacokinetics demonstrated fenofibric acid had no effect on the half-life, T_{max}, C_{min}, AUC, and oral clearance of rosuvastatin. A 19.6% increase in rosuvastatin C_{max} occurred when fenofibric acid was given in combination versus rosuvastatin alone. The authors proposed

this effect may be attributed to the mild to moderate inhibition of fenofibric acid on CYP450 2C9, but determined that the small increase was not likely to have clinical implications.

Studies evaluating the combination of rosuvastatin and fenofibrate

Durrington et al studied the effect of fenofibrate alone or in combination with rosuvastatin in type 2 diabetics with elevated TG and TC.²³ Patients included in the multicenter study were men and women with type 2 diabetes at least 18 years of age with a TG range of ≥ 200 to < 800 mg/dL, TC ≥ 200 mg/dL, hemoglobin A_{1c} (HBA_{1c}) $< 10\%$, and compliance with the National Cholesterol Education Program (NCEP) step I diet. A total of 216 patients were enrolled in the study. After 6 weeks of the NCEP diet, patients were randomized to a 6-week fixed dose phase of rosuvastatin 5 mg, rosuvastatin 10 mg, or placebo (divided into 2 groups). This was followed by an 18-week dose-titration period with options of increasing the rosuvastatin dose, adding fenofibrate, or receiving fenofibrate alone (Table 3). Patients could then move to the next dose level every 6 weeks if the LDL-C was greater than 50 mg/dL. Endpoint assessment, at 6 and 24 weeks, were TG, TC, LDL-C, HDL-C, VLDL, apolipoprotein (Apo) A-I, ApoB, LDL-C:HDL-C ratio, TC:HDL-C ratio,

Table 3 Treatment groups in the Durrington study²³

	Placebo	Rosuvastatin 5 mg	Rosuvastatin 10 mg	Placebo
Fixed-Dose Phase Week 6	Placebo	Rosuvastatin 5 mg	Rosuvastatin 10 mg	Placebo
Dose-Titration Phase Week 12	Rosuvastatin 10 mg	Rosuvastatin 5 mg Plus Fenofibrate 67 mg every day	Rosuvastatin 10 mg Plus Fenofibrate 67 mg every day	Fenofibrate 67 mg every day
Dose-Titration Phase ^a Week 18	Rosuvastatin 20 mg	Rosuvastatin 5 mg Plus Fenofibrate 67 mg twice a day	Rosuvastatin 10 mg Plus Fenofibrate 67 mg twice a day	Fenofibrate 67 mg twice a day
Dose-Titration Phase ^a Week 24	Rosuvastatin 40 mg	Rosuvastatin 5 mg Plus Fenofibrate 67 mg three times a day	Rosuvastatin 10 mg Plus Fenofibrate 67 mg three times a day	Fenofibrate 67mg three times a day

Notes: ^aDose of rosuvastatin or fenofibrate monotherapy groups titrated upward if LDL-C > 50 mg/dL.

non-HDL-C:HDL-C ratio, and ApoB:Apo A-I ratio. Table 4 summarizes the outcomes. At week 24, the percentage of patients achieving the LDL-C goal of <100 mg/dL was 86% with rosuvastatin 40 mg (n = 50), 75.5% with rosuvastatin

10 mg plus fenofibrate 67 mg 3 times a day (n = 53), 75% with rosuvastatin 5 mg plus fenofibrate 67 mg 3 times a day (n = 60) and 4.1% with fenofibrate 67 mg 3 times a day (n = 49). Treatment-related adverse effects in the rosuvastatin

Table 4 Lipid outcomes in the Durrington study at 6 and 24 weeks²³

	Placebo ^a then rosuvastatin 10/20/40 mg n = 51	Rosuvastatin 5 mg plus fenofibrate group n = 60	Rosuvastatin 10 mg plus fenofibrate group n = 53	Placebo ^a then fenofibrate group n = 49
TG				
Baseline mmol/L (SD)	3.6 (1.0)	3.5 (1.2)	3.5 (1.3)	4.2 (1.8)
Mean percent change from baseline at 6 weeks (%)	4.7	-24.5 ^b	-29.5 ^b	4.7
Mean percent change from baseline at 24 weeks (%)	-30.3	-40.9	-47.1 ^c	-33.6
LDL-C				
Baseline mmol/L (SD)	3.7 (0.7)	3.9 (0.8)	3.9 (0.8)	3.7 (0.8)
Mean percent change from baseline at 6 weeks (%)	-0.6	-40.7 ^b	-45.8 ^b	-0.6
Mean percent change from baseline at 24 weeks (%)	-46.7	-34.1 ^d	-42.2	0.7 ^d
TC				
Baseline mmol/L (SD)	6.2 (0.7)	6.5 (0.8)	6.4 (0.9)	6.3 (0.9)
Mean percent change from baseline at 6 weeks (%)	1.1	-31.4 ^b	-36.6 ^b	1.1
Mean percent change from baseline at 24 weeks (%)	-36.6	-31.0	-36.3	-7.5 ^d
HDL-C				
Baseline mmol/L (SD)	1.0 (0.2)	1.1 (0.2)	1.0 (0.2)	1.0 (0.2)
Mean percent change from baseline at 6 weeks (%)	1.2	9.9 ^b	10.1 ^b	1.2
Mean percent change from baseline at 24 weeks (%)	6.4	10.8	11.7	9.2
VLDL-C				
Baseline mmol/L (SD)	1.7 (0.7)	1.6 (0.6)	1.4 (0.6)	1.8 (0.9)
Mean percent change from baseline at 6 weeks (%)	4.7	-33.9 ^b	-34.9 ^b	4.7
Mean percent change from baseline at 24 weeks (%)	-43.6	-46.8	-44.2	-30.1
LDL-C:HDL-C ratio				
Baseline (SD)	3.8 (1.0)	3.7 (0.8)	3.8 (0.9)	3.9 (1.0)
Mean percent change from baseline at 6 weeks (%)	-2.0	-45.6 ^b	-50.6 ^b	-2.0
Mean percent change from baseline at 24 weeks (%)	-48.9	-38.8 ^e	-46.8	-6.3 ^d
TC:HDL-C ratio				
Baseline mmol/L (SD)	6.4 (1.4)	6.2 (1.1)	6.3 (1.2)	6.7 (1.5)
Mean percent change from baseline at 6 weeks (%)	0.5	-36.5 ^b	-42.0 ^b	0.5
Mean percent change from baseline at 24 weeks (%)	-39.2	-36.2	-41.9	-13.9 ^d
Non-HDL-C:HDL-C ratio				
Baseline mmol/L (SD)	5.4 (1.4)	5.2 (1.1)	5.3 (1.2)	5.7 (1.5)
Mean percent change from baseline at 6 weeks (%)	0.5	-43.7 ^b	-50.3 ^b	0.5
Mean percent change from baseline at 24 weeks (%)	-47.3	-43.5	-50.4	-16.6 ^d
ApoA-I				
Baseline g/dL (SD)	139.4 (17.8)	144.8 (21.3)	141.1 (20.2)	139.5 (22.8)
Mean percent change from baseline at 6 weeks (%)	-1.4	0.7	3.0 ^f	-1.4
Mean percent change from baseline at 24 weeks (%)	2.7	4.7	5.4	5.0
ApoB				
Baseline mg/dL (SD)	163.4 (29.0)	168.0 (21.3)	164.4 (25.6)	163.3 (28.0)
Mean percent change from baseline at 6 weeks (%)	-0.4	-34.2 ^b	-38.9 ^b	-0.4
Mean percent change from baseline at 24 weeks (%)	-41.4	-35	-40.2	-7.6 ^d
ApoB: ApoA-I				
Baseline (SD)	1.2 (0.3)	1.2 (0.2)	1.1 (0.2)	1.2 (0.3)
Mean percent change from baseline at 6 weeks (%)	1.6	-33.5	-39.8	1.6
Mean percent change from baseline at 24 weeks (%)	-41.9	-37.2	-42.7	-11.3 ^d

Notes: ^aSix week data combined for two placebo groups; ^bP < 0.001 compared to placebo; ^cP = 0.001 compared to placebo/rosuvastatin 10/20/40 mg group; ^dP < 0.001 compared to placebo/rosuvastatin 10/20/40 mg group; ^eP < 0.017 compared to placebo/rosuvastatin 10/20/40 mg group; ^fP < 0.0253 compared to placebo.

Abbreviations: TG, triglycerides; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; VLDL-C, very-low density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein-cholesterol; ApoA-I, apolipoprotein AI; ApoB, apolipoprotein B.

plus fenofibrate groups were myalgia (3/115), creatine kinase (CK) greater than three times upper limits of normal (4/115), increased aspartate aminotransferase (AST) (6/115), and increased alanine aminotransferase (ALT) (6/115). None of these patients with AST/ALT elevations were symptomatic and all continued treatment. No subject had a clinically significant increase in CK of greater than ten times upper limit of normal (ULN).

Studies evaluating the combination of rosuvastatin and fenofibric acid

The efficacy and safety of fenofibric acid (ABT-335) with low or moderate dose rosuvastatin was evaluated by Jones et al in a phase 3 multicenter, randomized, double-blind, active-controlled trial.²⁴ The study was designed with a 6-week washout period of lipid lowering medications followed by a 12-week treatment period where patients were randomized to oral administration of fenofibric acid at 135 mg, fenofibric acid 135 mg with rosuvastatin 10 mg or 20 mg, or rosuvastatin alone at 10 mg, 20 mg or 40 mg. A 30-day safety period evaluation followed the 12-week treatment phase. Male and non-pregnant female patients at least 18 years of age were included in the study that had mixed dyslipidemia (fasting TG \geq 150 mg/dL, HDL-C < 40 mg/dL for men and < 50 mg/dL for women, LDL-C \geq 130 mg/dL). Extensive inclusion and exclusion criteria were previously published.²⁵ It was recommended that patients adhere to the American Heart Association diet.²⁴ The screening TG level of \leq 250 or >250 mg/dL along with diabetic status was part of the stratification for randomization. The mean percent change of HDL-C, TG, and LDL-C values from baseline were the primary efficacy endpoints. Additional secondary efficacy endpoints were non-HDL-C, VLDL-C, TC, ApoB, and high sensitivity C-reactive protein (hsCRP). Statistical comparisons were with fenofibric acid plus rosuvastatin compared to rosuvastatin alone for HDL-C, TG, and secondary endpoints. The statistical analyses of LDL-C and non-HDL-C changes were with a comparison of fenofibric acid plus rosuvastatin 10 or 20 mg vs fenofibrate alone. The primary and secondary efficacy endpoints are summarized in Table 5. The high dose rosuvastatin 40 mg was not evaluated for statistical significance due to low enrollment in this treatment group. The safety profile assessed specific adverse effects along with laboratory monitoring (Table 6). The most common adverse event was myalgia which was slightly lower in occurrence when fenofibric acid was combined with rosuvastatin. Creatine kinase elevation greater than 5 times the ULN was reported in 7 patients receiving fenofibric acid with rosuvastatin compared to 5 patients using rosuvastatin

alone. No cases of rhabdomyolysis were documented. Elevation in ALT and AST greater than 3 times ULN was rare in occurrence.

Following the conclusion of the initial study by Jones et al subjects were eligible to enroll in a 52-week open label extension trial of fenofibric acid 135 mg with moderate dose rosuvastatin at 20 mg.²⁶ Subjects who completed 2 other identically designed trials that utilized low to moderate doses of atorvastatin²⁷ and simvastatin²⁸ were also included in this 52-week open label follow-up trial, and continued their respective statin therapy. Published efficacy results in this 1-year follow-up trial did not separate the statin utilized; therefore reported efficacy results include a moderately dosed statin (simvastatin 40 mg, atorvastatin 40 mg or rosuvastatin 20 mg) plus fenofibric acid 135 mg.²⁶ At 52 weeks continued effects on TG, HDL-C, and LDL-C was observed. The incidence of treatment-related adverse effects when combining all fenofibric acid and statin groups was 27.4% which led to discontinuation in 8.3% of patients. The combined treatment group adverse effects were CK > 5 times ULN (1.3%), ALT > 3 times ULN (1.2%), AST > 3 times ULN (0.5%), and serum creatinine \geq 2 times baseline value (0.9%). Specific analysis of the rosuvastatin and fenofibric acid combination treatment arm showed a similar adverse effect profile as the combined statin groups plus fenofibric acid (Table 7). Of the 1186 patients receiving fenofibric acid and rosuvastatin, treatment-related adverse effects occurred in 27.7% (328/1186) which led to 8.3% discontinuing therapy. Adverse effects reported were CK > 5 times upper limits of normal (1.7%), ALT > 3 times upper limits of normal (1.2%), AST > 3 times upper limits of normal (0.4%), and serum creatinine \geq 2 times baseline (0.6%). Treatment-related serious adverse events were reported in 0.3% of subjects, but no treatment-related rhabdomyolysis or death was documented.

Following the completion of the 52-week trial by Bays et al subjects were eligible to enroll in a 52-week extension study (year 2) conducted by Kipnes et al.²⁹ Subjects continued to take the same treatments as previously utilized in the initial 52-week trial by Bays et al. Of the 310 patients included in the year 2 trial, 174 subjects received fenofibric acid 135 mg and rosuvastatin 20 mg. A sustained effect on lipid efficacy variables was reported with this combination. Efficacy results were reported as the mean change at the end of the year 2 study as compared to baseline data at enrollment in one of the three initial trials, which spread over 116 weeks (12-week trial +52 week trial +52 week trial). The mean percent changes from baseline to week 116 in TG, LDL-C, non-HDL-C, TC, VLDL-C, and HDL-C are reported in Table 8. The first occurrence of an

Table 5 Lipid outcomes in the Jones study²⁴

	Fenofibric acid	Rosuvastatin 10 mg	Fenofibric acid + rosuvastatin 10 mg	Rosuvastatin 20 mg	Fenofibric acid + rosuvastatin 20 mg	Rosuvastatin 40 mg
HDL-C	n = 220	n = 239	n = 224	n = 236	n = 225	n = 127
Baseline mean (mg/dL)	38.5	38.2	38.5	38.5	38.0	37.4
Final mean (mg/dL)	43.9	41.0	45.7	41.6	44.9	40.6
Mean percent change from baseline (%)	15.0	8.5	20.3 (P < 0.001 ^a)	10.3	19.0 (P < 0.001 ^b)	9.3
TG	n = 242	n = 252	n = 252	n = 255	n = 249	n = 127
Baseline mean (mg/dL)	267.4	295.9	282.8	292.8	292.9	282.4
Final mean (mg/dL)	167.9	202.6	141.6	196.1	145.9	177.1
Mean percent change from baseline (%)	-32.6	-24.4	-47.1 (P < 0.001 ^a)	-25.6	-42.9 (P < 0.001 ^b)	-32.1
LDL-C	n = 223	n = 243	n = 231	n = 238	n = 230	n = 127
Baseline mean (mg/dL)	155.8	152.2	152.7	154.4	155.5 ^c	153.2
Final mean (mg/dL)	142.3	93.8	94.8	83.1	91.8	74.6
Mean percent change from baseline (%)	-6.5	-38	-37.2 (P < 0.001 ^c)	-45.0	-38.8 (P < 0.001 ^d)	-50.6
Non-HDL-C	n = 220	n = 238	n = 224	n = 236	n = 225	n = 115
Baseline mean (mg/dL)	218.7	218.7	217.7	220.9	220.8	219.0
Final mean (mg/dL)	176.5	130.9	119.9	118.6	118.5	105.9
Mean percent change from baseline (%)	-18.5	-39.8	-44.7 (P < 0.001 ^{a,c})	-45.8	-45.3 (P < 0.001 ^c ; P = 0.704 ^b)	-51.5
VLDL-C	n = 235	n = 244	n = 243	n = 243	n = 237	n = 126
Baseline mean (mg/dL)	63.3	69.8	66.9	70.5	67.9	68.1
Final mean (mg/dL)	35.7	38.2	26.5	36.5	27.0	31.0
Mean percent change from baseline (%)	-31.9	-41.0	-55.8 (P < 0.001 ^a)	-42.1	-50.6 (P = 0.038 ^b)	-49.1
TC	n = 242	n = 252	n = 252	n = 255	n = 249	n = 127
Baseline mean (mg/dL)	256.2	258.2	257.9	260.0	258.3	258.1
Final mean (mg/dL)	220.2	173.3	167.8	161.7	164.0	147.0
Mean percent change from baseline (%)	-13.5	-32.5	-34.4 (P = 0.08 ^a)	-37.3	-35.7 (P = 0.138 ^b)	-42.7
ApoB	n = 239	n = 248	n = 252	n = 252	n = 244	n = 123
Baseline mean (mg/dL)	143.1	145.5	144.7	146.1	145.6	145.4
Final mean (mg/dL)	119.7	94.8	87.6	87.0	86.8	79.2
Mean percent change from baseline (%)	-16.2	-34.1	-39.2 (P < 0.001 ^a)	-39.6	-39.2 (P = 0.729 ^b)	-45.0
hsCRP	n = 241	n = 249	n = 252	n = 254	n = 246	n = 125
Baseline median (mg/dL)	0.28	0.27	0.35	0.27	0.31	0.29
Mean percent change from baseline (%)	-12.1	-22.9	-33.8 (P = 0.013 ^a)	-29.9	-40.8 (P = 0.01 ^b)	-33.1

Notes: ^aP-value comparison of rosuvastatin 10 mg to fenofibric acid + rosuvastatin 10 mg; ^bP-value comparison of fenofibric acid + rosuvastatin 20 mg to fenofibric acid + rosuvastatin 10 mg; ^cP-value comparison of fenofibric acid + rosuvastatin 20 mg to fenofibric acid + rosuvastatin 20 mg.

Abbreviations: HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; VLDL-C, very-low-density lipoprotein-cholesterol; TC, total cholesterol; ApoB, apolipoprotein B; hsCRP, high-sensitivity C-reactive protein.

Table 6 Adverse events reported in the Jones study, n (%)²⁴

	Fenofibric acid n = 259	Rosuvastatin 10 mg n = 261	Fenofibric acid plus rosuvastatin 10 mg n = 261	Rosuvastatin 20 mg n = 266	Fenofibric acid plus rosuvastatin 20 mg n = 261	Rosuvastatin 40 mg n = 131
Incidence of myalgia	7 (2.7)	15 (5.7)	10 (3.8)	9 (3.4)	7 (2.7)	9 (6.9)
Discontinuation due to myalgia	2 (0.8)	1 (0.4)	2 (0.8)	2 (0.8)	2 (0.8)	4 (3.1)
CK > 5 times ULN	0	1 (0.4)	5 (1.9)	1 (0.4)	2 (0.8)	3 (2.3)
CK > 10 times ULN	0	0	1 (0.4)	1 (0.4)	0	2 (1.5)
Discontinuation due to increased CK	0	0	2 (0.8)	0	0	1 (0.8)
ALT and/or AST > 3 times ULN on 2 consecutive visits	5 (1.9)	0	3 (1.1)	0	4 (1.5)	0
Discontinuation due to increased ALT and/or AST	4 (1.5)	0	0	0	3 (1.1)	0
Creatinine increase > 50% and above ULN	7 (2.7)	3 (1.1)	7 (2.7)	1 (0.4)	7 (2.7)	1 (0.8)
Discontinuation due to increased creatinine	1 (0.4)	1 (0.4)	3 (1.1)	0	1 (0.4)	0
Discontinuation due to any adverse event	28	10	25	13	25	10

Abbreviations: CK, creatine kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limits of normal.

adverse effect was tracked over the study period. The majority of adverse effects occurred early in therapy. In the extension period, adverse effects reported were CK > 5 times ULN (2.3%, 4/174), ALT > 3 times ULN (1.1%, 2/174), AST > 3 times ULN (0.6%, 1/174), and serum creatinine \geq 2 times baseline (1.7%, 3/174). Two patients discontinued treatment due to myalgia; however no rhabdomyolysis or deaths were reported. The combined treatment group adverse effects were elevated CK (1.6%, 5/310), ALT (0.6%, 2/310), AST (0.3%, 1/310), and serum creatinine (2.3%, 7/310). Further details on adverse effects are listed in Table 7.

Another phase III study, published as an abstract, with 760 patients, evaluated the efficacy and safety of fenofibric acid with rosuvastatin in patients with mixed dyslipidemia (LDL-C \geq 130 mg/dL, TG \geq 150 mg/dL, HDL-C < 40 mg/dL males, < 50 mg/dL females).³⁰ The 12-week study randomized individuals to fenofibric acid 135 mg/day, rosuvastatin 5 mg/day or fenofibric acid 135 mg/day plus rosuvastatin 5 mg/day. Statistically significant results, when comparing rosuvastatin to fenofibric acid with rosuvastatin, were a mean percent change from baseline of HDL-C (rosuvastatin 12.4%, combination 23.0%), TG (rosuvastatin -17.5%, combination -40.3%), VLDL-C (rosuvastatin -22.2%, combination -41.3%), ApoB (rosuvastatin -26.4%, combination -30.9%), TC (rosuvastatin -25%, combination -28.1%) and hsCRP (rosuvastatin -11.4%, combination -28%). The decrease in LDL-C reached statistical significance when comparing fenofibric acid to fenofibric acid with rosuvastatin (fenofibric acid -4.1%, combination -28.7%). The use of fenofibric acid with rosuvastatin was well tolerated.

Safety concerns with combination rosuvastatin and fenofibrate/fenofibric acid therapy

Myopathy, hepatotoxicity and renal damage are possible adverse effects associated with the combination use of fibrates and statins.³¹ A database review further defining the risk, reports an approximate 15 times lower risk of rhabdomyolysis when fenofibrate is used in combination with the currently available statins compared to gemfibrozil.³² Although there are limitations to database reviews, which may under-report adverse events, the significant difference in event rates suggests that each fibrate is not the same in regards to statin interactions. Pharmacokinetic reasons for differences in toxicity associated with the combination of fenofibrate and statins has been previously discussed.

Due to reports of increased myopathy associated with the combination of fibrates and statins, prescribing information

Table 7 Adverse events in the Bays²⁶ and Kipnes²⁹ trials, n (%)

	Fenofibric acid plus rosuvastatin 20 mg at 52 weeks n = 1167	Fenofibric acid plus rosuvastatin 20 mg at 116 weeks n = 174
CK > 5 times ULN	20 (1.7)	4 (2.3)
CK > 10 times ULN	6 (0.5)	3 (1.7)
Discontinuation due to increased CK	11 (0.9)	1 (0.6)
Rhabdomyolysis	0	0
ALT > 3 times ULN on 2 consecutive visits	14 (1.2)	2 (1.1)
AST > 3 times ULN on 2 consecutive visits	5 (0.4)	1 (0.6)
Discontinuation due to increased ALT and/or AST	9 (0.8)	1 (0.6)
Creatinine > 2 mg/dL	14 (1.2)	3 (1.7)
Creatinine $\geq 2 \times$ baseline	7 (0.6)	3 (1.7)
Discontinuation due to increased creatinine	15 (1.3)	0

Abbreviations: CK, creatine kinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limits of normal.

of rosuvastatin, fenofibrate and fenofibric acid lists a warning when using these medications together.^{15–17} Specific clinical studies evaluating the use of rosuvastatin with fenofibric acid,^{24,26,29,30} or fenofibrate²³ suggests that combination use is well tolerated and is as safe as therapy with the individual agents used as monotherapy. The majority of these studies specifically evaluated fenofibric acid with concomitant rosuvastatin therapy and data up to 2 years supports the safety of this combination.²⁹ The use of fenofibrate may be equally safe to use since fenofibrate is rapidly metabolized to fenofibric acid and no pharmacokinetic interaction was identified when used with concomitant rosuvastatin therapy.²¹ However, formal long-term safety trials have not been conducted with the use of rosuvastatin and fenofibrate. Another potential concern is the lack of data regarding the use of high dose statin therapies with any form of fenofibrate.^{17,18} Therefore, practitioners should confirm safety with lower doses of rosuvastatin before progressing to rosuvastatin 40 mg when used in conjunction with either fenofibrate or fenofibric acid.

Although current study data reports no major problems with rosuvastatin and fenofibrate, safety concerns still may exist given the possibility of an additive toxicity as each of the individual agents have reports of myopathy and hepatotoxicity.³¹ Individual case reports of possible toxicities with combination therapy have been published. A report by Ireland et al describes a 67-year-old patient with an elevated CK (13,808 U/L), and serum creatinine (3.6 mg/dL) following the addition of fenofibrate 160 mg to rosuvastatin therapy.³³ The patient was taking rosuvastatin 10 mg for 9 months with a recent dose increase to 20 mg. In this case it is difficult to determine if the exact cause of rhabdomyolysis was due to the recently-increased rosuvastatin dose, addition of fenofibrate or perhaps a combination of the two changes. A report by Dedhia et al describes a 68-year-old male with evidence of rhabdomyolysis following the addition of fenofibrate 160 mg

daily to rosuvastatin 10 mg daily.³⁴ After 3 weeks of taking both medications, he had symptoms of myopathy and renal failure with a CK level of 23,665 U/L and a serum creatinine of 2.3 mg/dL. Both therapies were stopped and the patient was treated with hydration. The patient reportedly recovered and subsequently tolerated rosuvastatin and ezetimibe therapy.

Overall the risk of severe adverse effects with the combination of rosuvastatin and fenofibrate is minimal.

Table 8 Lipid outcomes in the Kipnes trial²⁹

	Fenofibric acid + rosuvastatin 20 mg
HDL-C n = 161	
Baseline mean (mg/dL)	38.3
Final mean at 116 weeks (mg/dL)	45.0
Mean percent change from baseline (%) \pm SD	19.2 \pm 25.23
TG n = 161	
Baseline mean (mg/dL)	294.5
Final mean at 116 weeks (mg/dL)	137.5
Mean percent change from baseline (%) \pm SD	-48.2 \pm 22.61
LDL-C n = 159	
Baseline mean (mg/dL)	152.5
Final mean at 116 weeks (mg/dL)	87.0
Mean percent change from baseline (%) \pm SD	-40.9 \pm 20.66
Non-HDL-C n = 161	
Baseline mean (mg/dL)	222.6
Final mean at 116 weeks (mg/dL)	113.2
Mean percent change from baseline (%) \pm SD	-48.6 \pm 13.58
VLDL-C n = 152	
Baseline mean (mg/dL)	71.4
Final mean at 116 weeks (mg/dL)	26.6
Mean percent change from baseline (%) \pm SD	-56.8 \pm 25.17
Total-C n = 161	
Baseline mean (mg/dL)	260.9
Final mean at 116 weeks (mg/dL)	158.1
Mean percent change from baseline (%) \pm SD	-38.7 \pm 12.16

Abbreviations: HDL-C, high-density lipoprotein-cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; non-HDL-C, non high-density lipoprotein-cholesterol; VLDL-C, very-low density lipoprotein-cholesterol; total-C, total cholesterol.

However, given the rare case reports of myopathy and rhabdomyolysis, patients should be cautioned to report any abnormal muscle pain. Patients should also be monitored for hepatotoxicity with periodic monitoring of liver function tests.¹⁵⁻¹⁷ Although an increased risk of liver toxicity has not been reported with the combination, monitoring is appropriate. In patients taking rosuvastatin, liver function tests (LFTs) should be monitored prior to therapy and after 12 weeks of therapy.¹⁵ Additional testing should occur 12 weeks after any dose increase. If the LFTs are normal then monitoring may occur every six months. Patients with a history of renal insufficiency, heart failure, and severe debilitation should not use the combination of rosuvastatin (or other statins) and fenofibrate as these conditions may make them more susceptible to adverse effects.³⁵ Prescribing information also suggests a higher incidence of myopathy in patients with diabetes or hypothyroidism.¹⁷

Recommendation

The successful treatment of mixed dyslipidemia has proven to be very difficult due to the numerous lipid abnormalities that occur simultaneously. Therefore, in order to achieve the desired lipid goals, combination drug therapy is frequently needed. On the surface, implementing combination drug therapy appears to be a relatively easy and effective approach. However, combining lipid lowering agents is often associated with increased risks of developing medication adverse effects.

Concomitant statin and gemfibrozil therapy used to treat mixed dyslipidemia, has been associated with a significant increase in adverse effects such as myopathy and rhabdomyolysis. Fenofibrate and fenofibric acid are also primarily used to lower TG levels and used in combination with statin therapy to treat mixed dyslipidemia. Although the combination of statin therapy with fenofibrate or fenofibric acid therapy carries a lower risk of increased adverse effects than gemfibrozil concern for potential increased adverse effects still exists.³²

Based on a review of the available literature, combination therapy with rosuvastatin and fenofibrate or fenofibric acid appears to be effective. The Durrington study demonstrated that combination rosuvastatin and fenofibrate therapy in type 2 diabetics resulted in significant reductions in TG and LDL-C levels along with an increase in HDL-C.²³ The combination therapy was well-tolerated with minimal adverse effects.

The Jones trial assessed the use of various doses of rosuvastatin either alone or in combination with fenofibric acid.²⁴ The results from this study demonstrated that statistically significant changes were seen with combination therapy (rosuvastatin plus fenofibric acid) compared to rosuvastatin alone with TG lowering and elevations in HDL-C. The combination of rosuvastatin and fenofibric acid were well-tolerated

in this study. A year-long extension of the Jones trial was then completed with rosuvastatin 20 mg with fenofibric acid 135 mg.²⁶ Similar to the first phase of this trial, the one-year follow-up demonstrated a continued effect on TG, LDL-C, and HDL-C with combination therapy. The rosuvastatin and fenofibric acid combination was well tolerated and demonstrated similar rates of adverse effects as other statin agents plus fenofibric acid. A second year phase of this trial was then completed comparing the same treatments in the one year follow-up trial.²⁹ The results of the 2-year follow-up demonstrated a sustained benefit on lipid profiles, similar to what was seen in the 1-year follow-up phase.

Based on review of the literature, rosuvastatin can be safely and effectively combined with fenofibrate or fenofibric acid to treat mixed dyslipidemia. Studies demonstrated that this combination results in significant reductions in TG and LDL-C levels, and elevations in HDL-C. Dosing of rosuvastatin in the combination treatment groups involved low-moderate doses (5–20 mg per day). Rosuvastatin 40 mg with concomitant fenofibrate or fenofibric acid has not been evaluated therefore caution should be utilized before prescribing this higher dose. Long-term studies with rosuvastatin and fenofibrate or fenofibric acid will be needed to determine if there is a benefit in clinical outcomes (mortality reduction) when treating mixed dyslipidemia. When this combination therapy is used, patients should be monitored closely for any potential adverse effects.

Conclusion

Treatment of mixed dyslipidemia is fraught with difficulty because of the need to reduce LDL-C and TG levels, while trying to elevate HDL-C levels. In order to succeed in doing this, combination drug therapy is often the only effective option. Unfortunately, the drug combinations utilized for mixed dyslipidemia potentially increase the risk for adverse events. Rosuvastatin, the newest in its class, is the most potent statin currently available and provides significant reductions in LDL-C and TG and elevations in HDL-C. In addition, fenofibrate and fenofibric acid provides significant effects in lowering TG levels and raising HDL-C. When used in combination to treat mixed dyslipidemia, rosuvastatin and fenofibrate or fenofibric acid demonstrate beneficial effects in this patient population and is well tolerated with no greater risk of adverse events.

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References

1. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143–3421.
2. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *Circulation*. 2004;110:227–239.
3. Jones PH. Statins as the cornerstone of drug therapy for dyslipidemia: monotherapy and combination therapy options. *Am Heart J*. 2004;148:S9–S13.
4. Baigent C, Keech A, Kearney PM, et al. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
5. Ashen MD, Blumenthal RS. Low HDL cholesterol levels. *N Engl J Med*. 2005;353:1252–1260.
6. Brunzell JD. Hypertriglyceridemia. *N Engl J Med*. 2007;357:1009–1017.
7. Farnier M. Update on the clinical utility of fenofibrate in mixed dyslipidemias: mechanisms of action and rational prescribing. *Vasc Health Risk Manag*. 2008;4:991–1000.
8. Davidson MH, Armani A, McKenney JM, Jacobson TA. Safety considerations with fibrate therapy. *Am J Cardiol*. 2007;99 Suppl:3C–18C.
9. Yang LPH, Keating GM. Fenofibric acid: in combination therapy in the treatment of mixed dyslipidemia. *Am J Cardiovasc Drugs*. 2009;9:401–409.
10. Olsson AG, McTaggart F, Raza A. Rosuvastatin: a highly effective new HMG-CoA reductase inhibitor. *Cardiovasc Drug Rev*. 2002;20:303–328.
11. Shepherd J, Hunninghake DB, Barter P, McKenney JM, Hutchinson HG. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin and simvastatin for achieving lipid-lowering goals. *Am J Cardiol*. 2003;91(5A):11C–17C.
12. McKenney JM. Efficacy and safety of rosuvastatin in treatment of dyslipidemia. *Am J Health Syst Pharm*. 2005;62:1033–1047.
13. Filippatos T, Milionis HJ. Treatment of hyperlipidemia with fenofibrate and related fibrates. *Expert Opin Investig Drugs*. 2008;17:1599–1614.
14. Cheng JW. Rosuvastatin in the management of hyperlipidemia. *Clin Ther*. 2004;26:1368–1387.
15. Crestor (rosuvastatin calcium) Prescribing information. AstraZeneca 2009 October. URL: <http://www1.astrazeneca-us.com/pi/crestor.pdf> Accessed Feb 11, 2010.
16. Tricor (fenofibrate) Prescribing information. Abbott 2008 Dec. URL: <http://www.rxabbott.com/pdf/tricorpi.pdf>. Accessed Feb 10, 2010.
17. Trilipix (fenofibric acid) Prescribing information. Abbott 2008 Dec. URL: http://www.rxabbott.com/pdf/trilipix_pi.pdf. Accessed Feb 10, 2010.
18. Davidson MH, Robinson JG. Safety of aggressive lipid management. *J Am Coll Cardiol*. 2007;49:1753–1762.
19. Schneck DW, Birmingham BK, Zalikowski JA, et al. The effect of gemfibrozil on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther*. 2004;75:455–463.
20. Prueksaritanont T, Tang C, Qiu Y, Mu L, Subramanian R, Lin JH. Effects of fibrates on metabolism of statins in human hepatocytes. *Drug Metab Dispos*. 2002;30:1280–1287.
21. Martin PD, Dane AL, Schneck DW, Warwick MJ. An open-label randomized, three-way crossover trial of the effects of coadministration of rosuvastatin and fenofibrate on the pharmacokinetic properties of rosuvastatin and fenofibric acid in healthy male volunteers. *Clin Ther*. 2003;25:459–471.
22. Zhu T, Awni WM, Hosmane B, et al. ABT-335, the choline salt of fenofibric acid, does not have a clinically significant pharmacokinetic interaction with rosuvastatin in humans. *J Clin Pharmacol*. 2009;49:63–71.
23. Durrington PN, Tuomilehto J, Hama A, Kallend D, Smith K. Rosuvastatin and fenofibrate alone and in combination in type 2 diabetes patients with combined hyperlipidaemia. *Diabetes Res Clin Pract*. 2004;64:137–151.
24. Jones PH, Davidson MH, Kashyap ML, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with rosuvastatin in patients with mixed dyslipidemia: A phase 3 study. *Atherosclerosis*. 2009;201:208–215.
25. Jones PH, Bays HE, Davidson MD, et al. Evaluation of a new formulation of fenofibric acid, ABT-335, co-administered with statins. *Clin Drug Invest*. 2008;28:625–634.
26. Bays HE, Jones PH, Mohiuddin SM, et al. Long-term safety and efficacy of fenofibric acid in combination with statin therapy for the treatment of patients with mixed dyslipidemia. *J Clin Lipidology*. 2008;2:426–435.
27. Goldberg AC, Bays HE, Ballanyne CM, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. *Am J Cardiol*. 2009;103:515–522.
28. Modiuddin SM, Pepine CJ, Kelly MT, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with simvastatin in patients with mixed dyslipidemia: a phase 3 randomized, controlled study. *Am Heart J*. 2009;157:195–203.
29. Kipnes MS, Roth EM, Rhyne JM, et al. Year two assessment of fenofibric acid and moderate-dose statin combination. *Clin Drug Investig*. 2010;30:51–61.
30. Roth EM, Rosenson RS, Carlson DM, et al. A phase III study evaluating the efficacy and safety of 135 mg fenofibric acid (ABT-335) in combination with 5 mg rosuvastatin in patients with atherogenic dyslipidemia. *J Am Coll Cardiol*. 2009;53:Suppl A208.
31. Muscari A, Puddu GM, Puddu P. Lipid-lowering drugs: are adverse effects predictable and reversible? *Cardiology*. 2002;97:115–121.
32. Jones PH, Davidson MH. Reporting rate of rhabdomyolysis with fenofibrate + statin versus gemfibrozil + any Statin. *Am J Cardiol*. 2005;95:120–122.
33. Ireland JH, Eggert CH, Arendt CJ, Williams AW. Rhabdomyolysis with cardiac involvement and acute renal failure in a patient taking rosuvastatin and fenofibrate. *Ann Intern Med*. 2005;142:949–950.
34. Dedhia V, Muni SC. Myopathy Caused by a Combination Rosuvastatin and Fenofibrate. *J Assoc Physicians India*. 2007;55:152–153.
35. Hou R, Goldberg AC. Lowering low-density lipoprotein cholesterol: statins, ezetimibe, bile acid sequestrants, and combinations: comparative efficacy and safety. *Endocrinol Metab Clin North Am*. 2009;38:79–97.

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