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REVIEW

Fenofibric Acid: Safety and Efficacy in the Treatment of Dyslipidemia, Hypertriglyceridemia and Hyperlipidemia

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Abstract: Adequate control of lipids is a cornerstone in the management of coronary heart disease. Numerous studies have demonstrated the effectiveness of HMG-Co A reductase inhibitors (statins) in controlling LDL-C. Unfortunately, the effect of statins on other lipid parameters, such as HDL-C and triglycerides, is not as robust. Emerging evidence suggests that these other lipid parameters may contribute to residual cardiovascular risk. The recent release of fenofibric acid offers a potential therapy which can be used in conjunction with statins to achieve an optimal lipid profile. Clinical trials have demonstrated fenofibric acid to be safe for use as dual therapy with low and moderate dose statins. The following article will address the safety and efficacy of fenofibric acid in the treatment of lipid disorders, both alone and as combination therapy with statins. Additionally, the potential role of fenofibric acid in the management of the complex cardiovascular patient with abnormal lipid parameters will be evaluated.

Keywords: mixed dyslipidemia, hypertriglyceridemia, fenofibric acid

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Introduction

Treatment of abnormal lipid parameters is critical to maintaining cardiovascular health. The benefits of adequate treatment of LDL-C with HMG Co-A reductase inhibitor (statin) therapy for both primary and secondary prevention are well documented.[1,2] Clearly, however, adverse cardiovascular outcomes are not eradicated with statin therapy. Major adverse cardiac events can persist despite treatment of LDL-C to goal and other important lifestyle modifications. There is emerging evidence that some of this residual risk may be due to other abnormal lipid parameters, such as elevated triglycerides and decreased HDL-C.[3–9] Taken together, the constellation of these two findings along with elevated LDL-C represents a highly atherogenic form of dyslipidemia. Treatment options to address these factors have been limited in the past by untoward side effects and safety issues.[10] Recently, a new formulation of fenofibrate has become available. Fenofibric acid is a choline salt of fenofibrate which shows promising results and a favorable safety profile when administered with low and moderate dose statin therapy.[11,12]

Pharmacodynamics

Fenofibric acid is a peroxisome proliferator activated receptor (PPAR) alpha agonist. PPAR alpha is a nuclear transcription factor found in tissues with high rates of fatty acid catabolism which helps regulate the genes involved in fatty acid and triglyceride metabolism.[13] Specifically, it controls fatty acid uptake and esterification and promotes the beta-oxidative degradation of fatty acids. In addition, PPAR alpha has been shown to display some anti-inflammatory properties, including reduction of cytokine-induced vascular cell adhesion moelecule-1 (VCAM-1) and endothelin-1 (ET-1), a potent vasoconstrictor.[14] Fibrates are synthetic ligands for PPAR alpha and as such, both stimulate lipoprotein lipase production and decrease apo C-III expression, which is an inhibitor of lipoprotein lipase. The resulting increase in lipoprotein lipase improves fatty acid uptake and decreases fatty acid production. By decreasing triglycerides, LDL particle number is effectively decreased and LDL particle size is increased. Additionally, they contribute to increased HDL-C levels by stimulating production of apo A-I and A-II.[15–17]

Pharmacokinetics

Fenofibric acid differs from its predecessor, fenofibrate, primarily by demonstrating improved bioavailablity. Fenofibrate is poorly soluble in water and highly lipophilic.[18] These properties result in slow and unpredictable dissolution in the GI tract, limiting its absorption. In contrast, fenofibric acid has high water solubility and near complete dissolution in the GI tract.[19] Absolute absorption in the GI tract has been reported at 81% for fenofibric acid versus 69% for fenofibrate.[20] Peak plasma levels are achieved within four to five hours, irrespective of fasting status. Concomitant use with bile acid sequestrants may decrease absorption. It is therefore recommended that fenofibric acid be taken at least one hour before or four to six hours after a bile acid sequestrant. Fenofibric acid is excreted primarily in the urine and may accumulate in patients with severe kidney disease. It is metabolized through CYP3A4 and is therefore prone to interaction with other medications using this pathway. Increased nephrotoxicity and rhabdomyolysis have been reported when used with cyclosporine. Fenofibric acid is highly protein bound and prudent use with warfarin is advised, as fenofibric acid may prolong the prothrombin time.[15] Unlike its predecessor, gemfibrozil, fenofibric acid does not significantly interact with statins. Early fibrate formulations inhibited the biliary secretion and glucuronidation of statins which resulted in increased levels and toxicity.[21,22]

Clinical Trials

Three randomized trials have evaluated fenofibric acid in combination with statin therapy and have found the combination of fenofibric acid with low and moderate dose statin to be safe and effective.[23–25] All three trials studied fenofibric acid at a dose of 135 mg/day. Patients were randomized to either monotherapy with low, moderate or high dose statin or to combination therapy with fenofibric acid and low or moderate dose statin. Each of the three trials evaluated fenofibric acid with a distinct statin. The three statins evaluated were rosuvastatin, simvastatin and atorvastatin. Enrolled patients had mixed dyslipidemia at baseline. Changes in fasting cholesterol, apolipoprotein B and hsCRP were compared at baseline and throughout the trials up to twelve weeks. The three trials demonstrated consistent improvements in lipid parameters

and an encouraging safety profile in the combination therapy arms. (see Tables 1, 2 and 3). In general, the highest treatment related adverse event rate and the highest dropout rate occurred in the high dose statin monotherapy arms. A 52-week extension trial combined the patients in these trials in a study to examine the long term safety and efficacy of fenofibric acid with moderate dose statin therapy.[11] Improvement in lipid profiles was seen by four weeks of dual therapy and was sustained throughout the 52-week trial. Decreases in other lipid parameters, including non-HDL-C, total cholesterol and apo lipoprotein B levels, were also seen. A positive safety profile persisted throughout the extension study. Only eight patients out of 2201 had major treatment related adverse events. These typically involved cholecystitis, choletlithiasis and abdominal pain. Elevated liver function test or CPK were seen in only 1% of patients. No cases of rhabdomyolysis were observed.

A post-hoc analysis of the three 12–week trials was performed to determine any effects fenofibric acid therapy either alone or in combination with statin therapy had on the prevalence of Metabolic Syndrome or its diagnostic components.[26] At baseline, data was available for all five metabolic syndrome criteria in the majority of patients. Diagnostic criteria for the diagnosis of metabolic syndrome was present in 82.5% of patients upon enrollment. Patients were reassessed at the end of 12 weeks for diagnostic criteria for metabolic syndrome. Combination therapy with fenofibric acid with low or moderate dose statin therapy decreased the number of patients meeting diagnostic criteria for the metabolic syndrome by nearly 36% when compared with statin monotherapy. Additionally, fenofibric acid monotherapy reduced those meeting diagnostic criteria by 26%. Predictably, dual therapy had the largest impact in decreasing the number of patients meeting the specific criteria of hypertriglyceridemia and decreased HDL-C, although small improvements in blood pressure and fasting blood glucose were also seen.

Safety Profile

The previously mentioned studies have resulted in fenofibric acid becoming the sole fibrate FDA approved for use with low and moderate statins in the treatment of patients with mixed dyslipidemia and CHD.[15] Historically, the combination of fibrates and statins has been avoided due to safety concerns.[16,27] One of the original fibrate medications, gemfibrozil, was found to inhibit glucuronidation and thereby decrease the elimination of statins, resulting in increased toxicity. The second generation fenofibrate is a much weaker inhibitor of glucuronidation, resulting in fewer reports of toxicity.[28] Fenofibric acid's safety profile with low and moderate dose statin therapy is well documented. Myalgias were reported in 3.3% of patients on fenofibric acid monotherapy and 3.1 and 3.5% in patients on low and moderate dose dual statin therapy, respectively. Myalgias occurred in 4.7 and 6.1% of patients on low and moderate dose statin monotherapy.[11] No significant effect on liver function tests or CPK levels have been noted. The number of patients developing an increase in CPK to greater than five times normal on dual therapy was low and did not differ between dual therapy groups and statin monotherapy groups. No patients receiving fenofibric acid monotherapy reported an increase in CPK to greater than five times normal.[11,26] A small trial evaluating potential interactions of fenofibric acid with 40 mg of rosuvastatin did not reveal significant interaction with high dose statin therapy in

Table 1. Simvastatin monotherapy effect on LDL was not evaluated in the study. Fenofibric acid monotherapy effect on HDL and triglycerides was not evaluated in the study.

Mean % change	Fenofibric acid (n = 107)	Simvastatin 20 (n = 14)	Simvastatin 20 + fenofibric acid (n = 104)	*P*	Simvastatin 40 (n = 103)	Simvastatin 40 + fenofibric acid (n = 104)	*P*
LDL	–4		–24	<0.001		–25.3	<0.001
HDL		+7.2	+17.8	<0.001	+8.5	+18.9	<0.001
Trig		–14.2	–37.4	<0.001	22.7	–42.7	<0.001

Data derived from Mohiuddin S, Pepone C, Kelly M, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combinations with simvastatin in patients with mixed dyslipidemia: a phase 3 randomized controlled study. *Am J cardiol*. 2005;45:1649–53.

Table 2. Rosuvastatin monotherapy effect on LDL was not evaluated in the study. Fenofibric acid monotherapy effect on HDL and triglycerides was not evaluated in the study.

Mean % change	Fenofibric acid (n = 242)	Rosuvastatin 10 (n = 252)	Rosuva 10 + fenofibric acid (n = 252)	*P*	Rosuvastatin 20 (n = 255)	Rosuva 20 + fenofibric acid (n = 249)	*P*
LDL	–6.5	–37.2		<0.001	–38.8		<0.001
HDL		+8.5	+20.3	<0.001	+10.3	+19	<0.001
Trig		–24.4	–47.1	<0.001	–25.6	–42.9	<0.001

Data derived from Jones P, Davidson M, Kashyap M, 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;204:208–15.

healthy young volunteers.[29] However, the combination of high dose statin and fenofibric acid has not adequately been evaluated and should be avoided.

Common adverse effects are nausea, myalgia, headache and back pain. These rarely result in medication discontinuation however. The risk of rhabdomyolysis has been shown to be very low, and equal to that of statin monotherapy. By increasing cholesterol excretion into bile, fibrates potentiate cholelithiasis.

Dosing

In addition to its FDA approval for use with low and moderate dose statin therapy, it is approved as monotherapy for severe hypertriglyceridemia and mixed dyslipidemia. The adult starting dose in combination with statin therapy or monotherapy for primary hyperlipidemia or mixed dyslipidemia is 135 mg once daily and may be taken at the same time as statin therapy. For the treatment of severe hypertriglyceridemia, the starting dose is 45 to 135 mg once daily and may be adjusted at 4–8 week intervals to a maximum of 135 mg daily.[15] Patients with mild to moderate renal impairment (creatinine clearance 30–80 ml/min) should be started at 45 mg once daily and be closely monitored. Fenofibric acid is contraindicated in those with severe renal impairment (including those on dialysis), those with active liver disease, preexisting gallbladder disease and nursing mothers.

Effectiveness

Fenofibric acid is potent in improving triglyceride and HDL-C levels, both alone and in combination with low and moderate dose statin therapy. With monotherapy, fenofibric acid has been shown to result in a 16.3% increase in HDL-C.[11] One study showed a greater increase in HDL-C levels compared to prior studies of fenofibrate.[24] Dual therapy with statins resulted in an 18% increase in HDL-C. Triglycerides were reduced approximately 31% with monotherapy and 42%–43% with combination therapy. Combination therapy resulted in more of a decrease in VLDL when compared to fenofibric acid or statin monotherapy. While the combination of fenofibric acid with low or moderate dose statin improved non-HDL and apoB levels, the effect was not significantly higher than that achieved with statin monotherapy.[11]

Place in Therapy

Fenofibric acid offers several appealing characteristics that make it an attractive therapy in the treatment of

Table 3. Atorvastatin monotherapy effect on LDL was not evaluated in the study. Fenofibric acid monotherapy effect on HDL and triglycerides was not evaluated in the study.

Mean % change	Fenofibric acid (n = 112)	Atorvastatin 20 (n = 113)	Atorvastatin 20 + fenofibric acid (n = 110)	*P*	Atorvastatin 40 (n = 109)	Atorvastatin 40 + fenofibric acid (n = 110)	*P*
LDL	–3.4		–33.2	<0.001		–35.4	<0.001
HDL		+6.3	+14	<0.005	+5.3	+12.6	0.01
Trig		–16.5	–45.6	<0.001	–23.2	–42.1	<0.001

Data derived from Goldberg A, Bays H, Ballantyne C, et al. Efficacy and safety of ABT-335 (fenofibric acid) in combination with atorvastatin in patients with mixed dyslipidemia. *Am J Cardio*. 2009;2:426–35.

lipid disorders. It can be taken once daily and without consideration to oral intake. There are relatively few interactions with other commonly prescribed drugs, and its safety with low and moderate dose statin therapy is well established. There is currently a combination pill with rosuvastatin in development which may improve compliance in patients in need of dual therapy.

While fenofibric acid clearly provides an additional and favorable option in the treatment of lipid disorders, it is important to acknowledge that studies are lacking which demonstate a morbidity or mortality benefit. This is in contrast to the numerous studies demonstrating such benefit with statin therapy. However, one in five patients who are at goal LDL with statin therapy continue to have events.[30] The underlying causes of this residual risk are not clearly delineated, although previous studies provide clues that lipid parameters beyond LDL may play an important role. Statin trial meta-analyses have shown the highest placebo event rate and greatest absolute reduction in clinical events in patients with the lowest baseline HDL-C.[31,32] Low HDL-C is also the most common lipid abnormality in patients with premature CAD. Prior trials with older fibrate medications suggest the importance of treating low HDL-C and elevated triglycerides. The VA-HIT trial found that gemfibrozil reduced mortality and non fatal MI independent of changes in LDL-C.[33,34] The BECAIT trial found a decrease in disease progression when HDL and triglyceride profiles improved despite no change in LDL-C.[35] Treating to New Targets established that patients with low HDL-C (<42 mg/dl) had a higher event rate even when LDL-C was <70 mg/dl.[36] A secondary prevention trial in patients with acute coronary syndrome, PROVE-IT 22, found the best outcomes occurred when LDL-C was <70 mg/dl and triglycerides were <150 mg/dl.[37] A recent meta-analyses of trials which used IVUS to monitor plaque progression determined that progressors had higher levels of triglycerides, glucose, apoB and smaller increases in HDL-C when compared to non-progressors.[38]

Recent studies evaluating the use of fibrates to improve residual risk have had disappointing results. The FIELD study evaluated the effect of fenofibrate on CV outcomes in patients with type 2 diabetes mellitus.[39] The primary outcome of major coronary events was not reduced. Slight reductions in coronary revascularization and non-fatal MI were noted. Microvascular complications of DM, such as albuminuria and need for laser retinopathy, were reduced. The ACCORD lipid study randomized type 2 diabetic patients to simvastatin plus fenofibrate or placebo.[40] The primary outcome was first non-fatal MI or CVA or death from CV cause. Combination therapy was not found to reduce the event rate for primary outcomes, and the routine use of dual therapy was not recommended. While these trials suggest that fibrates do not contribute to reducing residual risk, they do not sufficiently address the question. The largest criticism of these trials was that the patient population did not adequately represent those who are commonly targeted in clinical practice for fibrate therapy either alone or in combination with statin.[41] The FIELD study included patients with normal lipids and had a high drop in rate of statins. In the ACCORD lipid study, the baseline triglyceride level was 162 mg/dL and baseline HDL was 38.1 mg/dL. While these levels are not quite at goal, they do not reflect the patient seen in clinical practice that is considered for dual therapy. Importantly, a subgroup analysis of the ACCORD lipid study found that fibrate therapy did decrease the event rate in patients with triglycerides >204 mg/dL and HDL-C <34 mg/dL.[40]

Conclusion

While clinical trials are ongoing, substantial evidence exists which suggests an important role for fenofibric acid in the treatment of dyslipidemia, hypertriglyceridemia and hyperlipidemia. Studies of fenofibric acid consistently demonstrate an impressive safety profile, even in conjunction with statin therapy. The improved bioavailability compared to prior fibrate formulations is an additional benefit. The effects on lipid parameters are notable, especially the pronounced decrease in triglyceride levels which can be achieved with dual therapy with statins. Further trials with an appropriate patient population which reflects those seen in clinical practice that are most commonly targeted for dual therapy with a statin could potentially demonstrate the sought after morbidity and mortality benefits that is currently lacking for fibrates.

Abbreviations

LDL-C, low density lipoprotein cholesterol; HMG-CoA, 5-hydroxy-3-methylglutamyl-coenzyme A; HDL-C,

high density lipoproteint cholesterol; PPAR, peroxisome proliferator activated receptor; VCAM-1, vascular cell adhesion molecule; ET-a, endothelin 1; Apo C-III, apolipoprotein C-III; Apo A-I, apolipoprotein A-I; Apo A-II, apolipoprotein A-II; GI, gastrointestinal; CYP 3a4, cytochrome P 3 a4; Hs CRP, high sensitivity c reactive protein; CPK, creatinine phosphokinase; FDA, federal drug administration; CHD, coronary heart disease; VA-HIT, Veterans Affairs cooperative high density lipoprotein intervention trial; BECAIT, bezafibrate coronary atherosclerosis intervention trial; PROVE-IT, Pravastatin or atorvastatin evaluation and infection therapy; IVUS, intravascular ultrasound; FIELD, Fenofibrate intervention and event lowering in diabetes; CV, cardiovascular; MI, Myocardial infarction; DM, Diabetes mellitus; ACCORD, Action to control cardiovascular risk in diabetes; CVA, cerebrovascular accident.

Disclosure

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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