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Ezetimibe: A novel selective cholesterol absorption inhibitor

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Ezetimibe (Zetia) is a novel selective cholesterol absorption inhibitor that was approved by the FDA in October 2002. Unlike statins (HMG-CoA reductase inhibitors) and bile acid sequestrants, ezetimibe does not inhibit hepatic cholesterol synthesis or increase bile acid secretion. In contrast, ezetimibe selectively inhibits the uptake of dietary cholesterol from enterocytes in the brush border of the intestinal lumen resulting in a decrease in the delivery of dietary cholesterol to the liver and a subsequent decrease in hepatic cholesterol stores and increased cholesterol clearance from the blood.[1] Ezetimibe's unique action has generated interest in its use in combination with other cholesterol-lowering agents. It is indicated for the treatment of primary hypercholesterolemia as monotherapy and in combination with a statin. Ezetimibe is also approved for homozygous familial hypercholesterolemia and homozygous sitosterolemia.

TABLE 1: EZETIMIBE CLINICAL TRIAL SUMMARY

Study / Design	Population	Treatment	% Change LDL	% Change HDL	% Change TG
Bays et al[3] MC, R, DB, PC 12 wk; Phase II	N=432 LDL 130-250mg/dl TG ≤300mg/dl	EZ 5 mg EZ 10 mg P	-15.7 -18.5 10 mg>5mg (p< 0.05)	+2.9 +3.5 (p < 0.05)	NS
Dujovne et al[4] MC, R, DB, PC 12 wk; Phase III	N=892 LDL 130-250mg/dl TG ≤350 mg/dl	EZ 10 mg P	-16.9 0.4	+1.3 -1.6	-5.6 +5.7
Davidson et al[5] R, DB, PC 12 wk; Phase III Simultaneous	N=668 LDL 145-250mg/dl TG ≤350mg/dl	EZ 10 mg SIM 10-80 mg EZ + SIM P	-18.1 -36.1 -49.9* -1.3	+5.1 +6.9 +9.3* +0.9	-8.3 -16.6 -24.1* +2.4
Ballantyne et al[6] MC, R, DB, PC 12 wk; Phase III Simultaneous	N=628 LDL 145-250mg/dl TG ≤350mg/dl	EZ 10 mg ATV 10-80 mg EZ + ATV P	-18.4 -42.4 -54.5† +5.9	+4.2 +4.3 +7.3† +3.7	-3.4 -21.5 -29.5† +4.4
Gagne et al[7] MC, R, DB 12 wk; Add-On	N=50 Homozygous familial hypercholesterolemia	Statin 80 mg Statin 40-80 mg + EZ Statin 80 mg + EZ	-6.7 -20.7¶ -27.5¶	NS	NS
Gagne et al[8] MC, R, DB, PC 8 wk; Add-On	N=769 Receiving stable statin dose ≥ 6wk, not meeting NCEP ATP II goal TG ≤350 mg/dl	Statin Statin + EZ	-3.7 -25.0 (p < 0.001)	1.0 2.7 (p < 0.05)	-2.9 -14.0 (p < 0.001)
Kosoglu et al[9] R, DB, PC 2 wk	N=32 LDL ≥ 130 mg/dl	EZ 10 mg FEN 200 mg EZ + FEN P	-22.3 -13.5 -36.3§ -10.0	-13.3 -6.1 -2.0 -14.1	-4.6 +0.3 -32.4 +19.1

MC=multicenter; R=randomized; DB=double-blind; PC=placebo-controlled; EZ=ezetimibe; SIM=simvastatin; ATV=atorvastatin; FEN=fenofibrate; P=placebo
* P < .03 for pooled EZ + SIM vs. SIM alone; † P < .01 for pooled EZ + ATV vs. ATV alone; ¶ p < .01 vs. statin (ATV or SIM) 80 mg alone; § p < .03 compared to ezetimibe or fenofibrate alone

CLINICAL TRIALS

The safety and efficacy of ezetimibe have been reported in several clinical trials, published primarily in abstract form. Results are summarized in Table 1. In comparisons to placebo, ezetimibe monotherapy produced a 15-20% reduction in LDL cholesterol, had minimal or negligible effects on other lipid parameters such as HDL and TG, and a similar adverse effect profile.[2-4] In a pooled analysis of 1,719 patients with primary hypercholesterolemia, this effect was independent of the level of dietary cholesterol and fat intake.[2] Maximal cholesterol lowering occurred within 2 weeks of drug initiation.

Several studies of short duration have also demonstrated safety and efficacy of ezetimibe in combination with statins, either initiated simultaneously or sequentially as add-on therapy. Ezetimibe - statin combination therapy resulted in additional reductions in LDL by approximately 10 to 20% over statin monotherapy. In studies in which both ezetimibe and atorvastatin or simvastatin were initiated simultaneously, the combination produced a significantly greater reduction in LDL compared to the statin alone.[5, 6] Ezetimibe has demonstrated similar effects when added to ongoing statin therapy.[7, 8] In a pooled analysis, in which the majority of patients were receiving atorvastatin (42%) or simvastatin (30%), the addition of ezetimibe to ongoing statin therapy resulted in a 25% reduction in LDL compared to 4% for placebo (p<.001).[8] Near maximal LDL lowering was observed by week 2 and maintained throughout the study. No significant differences were observed between groups when evaluated according to type of statin or across age, sex, race, NCEP ATP II category, or BMI subgroups. For patients who were above NCEP ATP goals at baseline, 71.5% of the combination group and 18.9% of the statin alone group achieved target LDL goals after 8 weeks (OR 23.7; p < 0.001). Of note is that because of daily biologic variation in fasting cholesterol levels, patients with LDL ≤ 5% below goal were allowed to enroll resulting in ~18% of patients who were at NCEP ATP II targets at baseline. This may allow for a different interpretation of results. Overall, the adverse events were similar across treatment arms (21% for combination therapy and 17% for statin alone) and were similar in between-group comparisons of statins. Gastrointestinal symptoms were the most common and no cases of rhabdomyolysis or hepatitis were reported.

Finally, in a small preliminary analysis, ezetimibe - fibric acid combination therapy was evaluated.[9] In this study, 32 patients with primary hypercholesterolemia were randomized to ezetimibe 10 mg daily, fenofibrate 200 mg daily, ezetimibe plus fenofibrate, or placebo for 14 days. Ezetimibe plus fenofibrate was well tolerated and resulted in a significant reduction in LDL compared to either drug alone or placebo (p< 0.03). HDL decreased in all treatment groups and was proposed to be the result of restricted activity. Additional safety and efficacy data is required to evaluate the potential for

ezetimibe-fibric acid combination therapy. Fenofibrate and gemfibrozil have been shown to increase the bioavailability of ezetimibe; and as such this combination is not yet recommended.

Safety and Administration

In placebo-controlled trials, ezetimibe's safety profile, adverse event rates, and discontinuation rates were similar to placebo. Furthermore, the combinations of ezetimibe and a statin also had similar safety profiles to that of statins alone. Pre-marketing data suggest that ezetimibe does not affect the intestinal absorption of triglycerides or fat-soluble vitamins. However, the studies primarily excluded patients with significantly elevated TG levels (>300-350 mg/dl) at which point statins have been observed to cause further increases in TG. It is unclear if similar effects will be observed in a more diverse population.

Ezetimibe is primarily metabolized in the liver and small intestine and is not recommended in patients with moderate or severe hepatic insufficiency. Significant differences in elevation of serum transaminases have not been observed when compared to placebo; however, the frequency was slightly higher in patients receiving combination ezetimibe-statin therapy (1.3%) than statins alone (0.4%). Therefore, ezetimibe should not be co-administered with a statin in persons with active liver disease or unexplained persistent elevations in serum transaminases. If prescribed in combination with a statin, liver-function tests and a lipid profile should be performed four to six weeks after initiating therapy and again following three to six months of treatment—then repeated every six months after that. Rhabdomyolysis, myopathy, and drug-drug interactions involving the CYP450 enzyme system have not been observed to date. Dosing of ezetimibe should occur more than two hours before or more than four hours after administration of a resin.

The recommended dose of ezetimibe is one 10 mg tablet daily, taken without regard to food or time of day. Doses greater than 10 mg daily have not been evaluated. It is unknown if larger doses will produce additional LDL-lowering and they are therefore, not recommended. No dosage reductions are required in patients with mild hepatic insufficiency, renal insufficiency, or in the elderly. Ezetimibe is pregnancy category C, and has not been studied in children.

Table 2: Drug Selection by Lipoprotein Profile*

	Lipoprotein Profile	Recommended Drug Treatment
Initial Therapy	Elevated LDL only	1) Statin 2) Resin 3) Niacin 4) Ezetimibe
	Elevated LDL, TG	1) Niacin 2) Statin 3) Fenofibrate 4) Ezetimibe
	Elevated TG only	1) Niacin 2) Gemfibrozil 3) Fenofibrate 4) Omega 3 Fatty Acids
Combination Therapy (Patients who fail statin monotherapy)	Elevated LDL	1) Statin + Resin 2) Statin + Niacin 3) Statin + Ezetimibe

* Adapted from Table 2; OR DUR Board Newsletter, V4, N1, March 2002

Place in Therapy

In conclusion, in studies of short duration, ezetimibe has demonstrable efficacy in reducing LDL when administered as monotherapy and in combination with a statin. When used as monotherapy, ezetimibe's LDL-lowering ability is less than that of statins. However, it has been shown to impart additional LDL-lowering when added to baseline statin therapy. The long-term efficacy and safety of ezetimibe alone or in combination with a statin beyond 12 weeks is unknown. Effects on cardiovascular morbidity and mortality are also unknown. Studies of longer duration and with niacin, resins, and fibrates are warranted to more completely assess the safety of ezetimibe in combination therapy.

Statins remain the most potent LDL-lowering drugs and data from large outcome trials support the use of statins as first line therapy for secondary prevention in most patients. The choice of statin should take into consideration the patient's history of tolerance to a particular statin, the percent LDL lowering required to reach goal, the potential for drug interactions as previously described and the cost per LDL lowering. According to Oregon's Health Resource Commission report,[10] all statins in equipotent doses are effective at reducing LDL up to 40%, though only lovastatin, pravastatin and simvastatin had supporting outcome data. The preferred statins on the Practitioner-Managed Prescription Drug Plan are generic lovastatin, Mevacor, and Pravachol. In patients who do not tolerate statins, resins or niacin are the preferred cost-effective alternatives. Ezetimibe monotherapy should be reserved for those who do not tolerate statins or second-line drugs (Table 2).

In patients who fail to achieve goals with maximal doses of monotherapy or are unable to tolerate higher doses of statins, statin-resin or statin-niacin combination therapy should be considered prior to statin-ezetimibe combination therapy taking into consideration a lack of clinical trial data comparing combination therapy regimens and cost (Table 3).

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Table 3: Comparative Cost of Therapy

Monotherapy to achieve 15-26% LDL Reduction				
Brand	**Generic**	**Strength**	**Dose**	**Cost / Month^**
niacin immediate-release	niacin IR	500 mg	1 T TID	$ 1.90
lovastatin*	**lovastatin**	**10 mg**	**1 T QHS**	**$ 14.90**
Lipitor	atorvastatin	10 mg	½ T QHS	$ 29.55
Zocor	simvastatin	10 mg	½ T QHS	$ 32.55
cholestyramine	cholestyramine	4 gm	BID	$ 34.45
Lescol	fluvastatin	20 mg	1 T QHS	$ 42.95
Zocor	simvastatin	5 mg	1 T QHS	$ 47.80
Lipitor	atorvastatin	10 mg	1 T QHS	$ 59.10
Zetia	ezetimibe	10 mg	1 T QD	$ 62.25
Pravachol*	**pravastatin**	**10 mg**	**1 T QHS**	**$ 71.40**
Colestid	colestipol	5 gm	1 T BID	$ 97.30
Welchol	colesevelam	625 mg	3T BID	$126.70
Combination Therapy				
First Line	**Add-on**			
lovastatin 40 mg QHS	niacin IR 500 mg TID			$ 56.70
	gemfibrozil 600 mg BID			$ 67.50
	cholestyramine 4 G BID			$ 89.25
	ezetimibe 10 mg QD			$117.05

* Preferred statins on the Practitioner-Managed Prescription Drug Plan List
^ Lower of Average Wholesale Price – 14% or Oregon Maximum Allowable Cost or Federal Upper Limit as reported by First DataBank 1/03. Prices do not include Medicaid rebate.

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