Management of complex lipid abnormalities with a fixed dose combination of simvastatin and extended release niacin

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Abstract: ER niacin combined with simvastatin provides an additional option for achieving LDL-C and non-HDL-C goals for cardiovascular prevention, with greater efficacy in those with triglyceride levels >200 mg/dL. ER niacin 1000 mg combined with simvastatin 20 mg reduced LDL-C by 6%, non-HDL-C by 7%, and triglycerides by 13%, and raised HDL-C by 11% compared to simvastatin 20 mg alone. The 2000 mg dose combined with simvastatin 20 to 40 mg raised reduced LDL-C by 7% to 24%, non-HDL-C by 16% to 28%, and triglycerides by 23% to 34%, and increased HDL-C by 18% to 22% compared to similar dose simvastatin therapy. While cardiovascular risk is reduced in proportion to the magnitude of LDL-C lowering, the additive benefit of raising HDL-C and lowering triglycerides remains to be determined. ER niacin-simvastatin is reasonably well tolerated, with a <7% discontinuation rate due to flushing in patients who used aspirin or non-steroidal anti-inflammatory medications as needed. However, drop-out rates were high in both the simvastatin and ER niacin–simvastatin treatment groups in both the 24- and 52-week studies. The safety profile of the combination appears to be similar to that of niacin and simvastatin used as monotherapies. Results of ongoing morbidity/mortality trials of ER niacin added to statin therapy are eagerly awaited.

Keywords: simvastatin, niacin, fixed-dose, dyslipidemia

One extended-release (ER) niacin–simvastatin formulation is available in the US and another formulation has been approved in Europe, with approval pending in the US. Simcor® (Abbott Laboratories, North Chicago, Illinois, USA) is the combination of ER niacin (Niaspan®; Abbott Laboratories, North Chicago, Illinois, USA) and simvastatin (Zocor®, Merck Inc., White House Station, New Jersey) which was approved by the US Food and Drug Administration (FDA) February, 2008. ER niacin–simvastatin is indicated to reduce elevated total cholesterol, low density lipoprotein cholesterol (LDL-C), apolipoprotein (apo) B, non-high density lipoprotein cholesterol (non-HDL-C), or triglycerides, or to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.[1] ER niacin–simvastatin is also indicated to reduce triglycerides in patients with hypertriglyceridemia (Frederickson type IV hyperlipidemia) when treatment with simvastatin monotherapy or niacin ER monotherapy is considered inadequate.

Another combination of ER niacin with simvastatin and laropiprant, a compound that decreases flushing, MK-524A (previously called Cordaptive®) (Merck, Inc., White House Station, New Jersey, USA), was not approved by the FDA in April, 2008 although it was approved in European countries. The reason for non-approval

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have not been reported, although is likely related to the inclusion of laropiprant. Laropiprant is a potent PGD_2 DP-1 receptor antagonist shown to reduce moderate to severe niacin-induced cutaneous vasodilatation without affecting lipid-modifying efficacy.[2] Laropiprant could have harmful off-target effects that may counteract beneficial effects of lipid changes on atherosclerotic disease. Laropiprant is also an antagonist of the thromboxane A_2 receptor although little effect on platelet aggregation assays or bleeding time has been observed.[3] The major metabolite of PGD_2 is a potent endogenous PPARγ activator. Activation of PPARγ via PGD_2 with niacin has been shown to stimulate ABCA1-mediated efflux of cholesterol from macrophages.[4] Whether efforts to minimize cutaneous symptoms will influence these pathways is unresolved. Moreover, the DP-1 receptor is found in numerous tissues and the specificity of laropiprant for epidermal Langherhans also remains to be established. It is not clear whether approval of the Merck product awaits the results of the ongoing Treatment of HDL to Reduce the Incidence of Vascular Events (HPS-2 THRIVE), which is comparing the effect of ER niacin plus laropiprant–simvastatin to simvastatin alone on major cardiovascular events in 20,000 subjects.[5]

Published data are available only for the ER niacin–simvastatin coformulation so will be the focus of this review. The pharmacology, efficacy and safety of ER niacin with simvastatin will be presented first, followed by a discussion of the clinical context for this drug combination.

Pharmacology

Niacin exposure from ER niacin–simvastatin has the same pharmacologic properties as ER niacin used as monotherapy.[1] Simvastatin levels were 23% to 41% higher from ER niacin–simvastatin than from simvastatin as monotherapy. Mechanisms of action, metabolism, and excretion are otherwise comparable to those for each drug used as monotherapy. Adverse effects of niacin and simvastatin therapy are discussed below.

Simvastatin undergoes extensive first pass metabolism and is hydrolyzed to the corresponding active β-hydroxyacid form, a potent inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase, the rate-limiting step in cholesterol synthesis.[6] HMG-CoA reductase inhibition reduces tissue and plasma cholesterol levels, which results in upregulation of the expression of LDL receptors in the liver and extrahepatic tissues, thereby enhancing removal of the cholesterol-rich apolipoproteins LDL-C, very low density lipoprotein cholesterol (VLDL-C), and VLDL remnants from plasma. Simvastatin is predominantly metabolized by the cytochrome P450 isoform (CYP) 3A4, and to a lesser degree CYP3A5, CYP2C8, and by glucuronidation. Hepatic uptake of simvastatin is facilitated by organic ion transporting polypeptide 1B1, polymorphisms of which have been associated with increases plasma simvastatin levels and propensity to myopathy.[7] Simvastatin has 13% urinary excretion and 60% biliary excretion. Drug interactions and adverse effects of simvastatin are discussed below.

Niacin is a form of vitamin B3 that in pharmacologic doses has beneficial effects on multiple lipid parameters. Niacin undergoes extensive first pass metabolism in the liver where it is rapidly converted to the active form nicotinamide adenine dinucleotide (NAD) in the NAD coenzyme system.[1] Niacin is not metabolized through the same pathways as statins, and is excreted in urine. Niacin has few important drug interactions although it is extensively bound to cholestyramine.

Niacin lowers the level of very low density lipoprotein cholesterol (VLDL-C), the precursor to LDL-C, through a variety of mechanisms, only some of which have been elucidated.[8,9] Activation of adipocyte G protein-coupled nicotinic acid receptor GPR109A (HM74A in humans) results in inhibition of hormone-sensitive lipase, reduced triglyceride hydrolysis, and reduced flux of free fatty acids from adipose to the liver. Decreased fatty acid synthesis and esterification reduces triglyceride synthesis. Increased lipoprotein lipase activity may increase the rate of chylomicron triglyceride removal from plasma. Reductions in intrahepatic triglyceride availability taken together with increased catabolism of apolipoprotein B, results in decreased assembly of apolipoprotein (apo)-B containing proteins VLDL and LDL.[10] Increased catabolism of VLDL-C also lowers LDL-C levels. Reduced large triglyceride-rich VLDL-C levels result in lower levels of small dense LDL-C. Niacin raises HDL-C by increasing apo A-I synthesis and decreasing HDL-C uptake and removal via the ATP synthase β-chain, an HDL/ApoA-I receptor for HDL endocytosis in liver cells.[10,11] Decreased triglyceride synthesis may also increase HDL-C levels. Niacin does not affect the reverse cholesterol transport pathway.

Efficacy

Three shorter-term efficacy and safety trials comparing ER niacin–simvastatin to simvastatin monotherapy have been published, SEACOAST I and II (24 weeks) and OCEANS (52 weeks) (Table 1).[12–14] Subjects were selected on the basis of having a non-HDL-C above the goal defined in the third National Cholesterol Education Program Adult Treatment

Panel (ATP III). About half of subjects were women and most were middle aged (median age 58–60 years). On a lead-in of either simvastatin 20 mg or 40 mg, median non-HDL-C levels were 131 to 165 mg/dL (3.39–4.27 mmol/L), LDL-C levels were 99 to 118 mg/dL (2.56–3.06 mmol/L), HDL-C levels were 41 to 47 mg/dL (1.06–1.22 mmol/L), triglyceride levels were 141 to 214 mg/dL (1.59–2.42 mmol/L), and Apo B levels were 89 to 103 mg/dL. Adherence rates were 96% to 98% in the 24-week SEACOAST studies and 82% in the 52-week OCEANS study. Drop-out rates were substantial and unusually high for this type of shorter-term efficacy safety trial. However, the rates in the ER niacin – simvastatin groups (28%–31% for the 1000 mg doses, 22%–29% for the 2000 mg doses) did not differ greatly from the simvastatin monotherapy groups (26%–27%) in the SEACOAST studies.

In SEACOAST I, the addition of ER niacin 1000 mg to simvastatin 20 mg reduced non-HDL-C by another 7% compared to simvastatin 20 mg plus 50 mg of immediate-release (IR) niacin added with the intention of maintaining the blind but without lipid-lowering efficacy. LDL-C was reduced by 6%, triglycerides by 13%, and Apo B by 10%, and increased HDL-C by 11% (Table 1).[13] (Note: efficacy comparisons in the text were calculated as difference from the simvastatin comparator arm at the end of the treatment period). The addition of ER niacin 2000 mg to simvastatin 20 mg decreased non-HDL-C by another 16%, LDL-C by 7%, triglycerides by 23%, and Apo B by 14%, and increased HDL-C by 18%. Greater reductions in non-HDL-C were observed in those with triglycerides ≥200 mg/dL (−9% on ER niacin 1000 mg and −19% compared to simvastatin monotherapy) than those with triglycerides <200 mg/dL (−5% for ER niacin 1000 mg and −7% for ER niacin 2000 mg). A similar blunting of efficacy with lower triglyceride levels was also observed for triglycerides (−14% and −29% vs −9% and −14%), and Apo B (−11% and −20% vs −3% and −6%) but not for HDL-C (+9% and +17% vs +14% and +20%). ER niacin–simvastatin appeared to have similar efficacy in women as in men.

In SEACOAST II, when ER niacin 1000 mg was added to simvastatin 40 mg there was no difference in non-HDL-C or LDL-C compared to simvastatin 80 mg (with 50 mg IR niacin), although HDL-C increased by 14% and triglycerides were reduced by 23%.[12] However, ER niacin 2000 mg added to simvastatin 40 mg had greater efficacy for all lipid parameters when compared to simvastatin 80 mg. When compared to simvastatin 80 mg, non-HDL-C was reduced by an additional 7%, triglycerides by 32%, and Apo B by 10%, and HDL-C was increased by 21%, although LDL-C did not differ.[12]

In the OCEANS study, after a lead-in on simvastatin 40 mg, subjects were randomized to receive an 8- or 12-week titration of ER niacin to 2000 mg combined with simvastatin 40 mg.[14] No difference in tolerability, safety, or efficacy was found and results were pooled for analysis. Compared to baseline after 4 weeks of simvastatin 40 mg therapy, at 24 weeks the addition of ER niacin 2000 mg to simvastatin 40 mg reduced non-HDL-C by an additional 22%, LDL-C by 21%, triglycerides by 30%, and apo B by 20%, and increased HDL-C by 21% (Table 1). A little more than half of subjects completed 52 weeks of follow-up and slightly greater efficacy for all lipid parameters was observed. The greater efficacy observed in OCEANS was similar to that observed in the SEACOAST studies when the on-treatment lipid levels on 2000 mg ER niacin were compared to baseline levels.

All 3 trials evaluated lipoprotein (a) [Lp(a)]. As shown in Table 1, baseline Lp(a) levels ranged from 9 to 24 mg/dL (0.32–0.86 μmol/L). Compared to simvastatin 20 or 40 mg with 50 mg of immediate-release niacin, the addition of ER niacin 1000 mg reduced Lp(a) levels by 9% to 17%, and the addition of ER niacin 2000 mg reduced Lp(a) levels by an additional 17% to 21%. When compared to the simvastatin 20 to 40 mg lead-in, Lp(a) reductions of 21% to 29% were observed. Ratios of Apo A-I to Apo B increased by 4% to 16% for the ER niacin 1000 mg groups and by 10% to 30% for the ER niacin 2000 mg groups compared to simvastatin with 50 mg immediate-release niacin groups. Compared to the simvastatin monotherapy lead-in, the ER niacin 2000 mg dose increased the Apo A-I/B ratio by 22% to 43%. Commensurate declines of 25% to 33% in the total to HDL-C ratio compared to baseline were observed.

The addition of ER niacin 1000 or 2000 mg to simvastatin 20 or 40 mg did not increase the proportion of subjects achieving their NCEP-defined non-HDL-C and LDL-C goals compared to simvastatin 20 or 80 mg monotherapy.[12,13] Although not a goal established by ATP III,[15] subjects receiving ER niacin 1000 or 2000 mg with simvastatin 40 mg, or ER niacin 2000 mg with simvastatin 20 mg (65%, 75%, and 70% respectively) were more likely to achieve an HDL-C ≥ 40 mg/dL (1.04 mmol/L) compared to simvastatin 20 or 80 mg (45% and 25%, respectively). Achievement of a triglyceride level < 150 mg/dL (1.69 mmol/L), again not a goal established by ATP III, occurred with greater frequently with ER niacin 1000 or 2000 mg with simvastatin 40 mg, or ER niacin 2000 mg with simvastatin 20 mg, (45%, 65%, and 50%, respectively) than with simvastatin 20 or 80 mg (30% and 15%, respectively).

Table 1 ER niacin–simvastatin trials

	Study population	Treatment duration	Treatment	N	Adherence
				N randomized (N end of study)	
SEACOAST I[13]	LDL-C ≤ target + Non-HDL-C above goal on simva 20 mg Median age 58 Men 49 (–58%	24 weeks	Simvastatin 20 mg + IR niacin 50 mg	121 (90)	99%
			Simvastatin 20 mg + ER niacin 1000 mg	108 (78)	96%
			Simvastatin 20 mg + ER niacin 2000 mg	56 (40)	97%
SEACOAST II[12]	Non-HDL-C above goal on simva 40 mg Median age 60 Men 51%–61%	24 weeks	Simvastatin 80 mg + IR niacin 50 mg	123 (90)	98%
			Simvastatin 40 mg + ER niacin 1000 mg	118 (82)	98%
			Simvastatin 40 mg + ER niacin 2000 mg	102 (80)	98%
				N randomized (N wk 24; end of study)	
OCEANS[14]	Non-HDL-C above goal on simva 40 mg Mean age 59–60 Men 55%–58%	52 weeks	8 week titration to ER niacin 2000 mg	231 (142; 87)	82%
			12 week titration to ER niacin 2000 mg	232 (126; 74)	82%
				N end of study	
ARBITER 2[68]	CHD 7 HDL-C < 45 mg/dL Mean age 67 Men 91%	12 months	Simvastatin ≥ 20 mg§ + placebo	80	90%–95%
			Simvastatin ≥ 20 mg§ + ER niacin 1000 mg	87	90%–95%

§93.4% received simvastatin.

No trials comparing ER niacin–simvastatin to placebo are available to gauge absolute lipid benefits. It is somewhat unclear from the limited data in the 3 trials above whether the addition of ER niacin to simvastatin retains the full effect of both agents on LDL-C. ER niacin 2000 mg lowered LDL-C by 14% in the ER niacin clinical database, and this reduction was preserved when added to lovastatin 40 mg (Advicor®, Abbott Laboratories, North Chicago, Illinois).[25] It does appear that in patients with non-HDL-C above goals on statin therapy, most of the benefit should be expected in non-HDL-C rather than LDL-C levels, as was observed in the study populations of these 3 ER niacin–simvastatin trials.

Adverse effects
Flushing
Niacin-induced flushing of the face and upper body is characterized by redness, warmth, tingling, or itching, and usually lasts an hour or less. Flushing is related to peak serum levels of niacin. ER niacin is absorbed over 8 to 12 hours and peak levels are lower than for immediate release niacin.[16]

Although the proportion of patients who flushed was about the same for ER niacin as for immediate-release niacin, the number of flushing episodes was much lower (9 vs 2 flushing events) over a 4 week period after 4 weeks on the 1500 mg dose.[17] In the 2 trials of the ER niacin and simvastatin 20 or 40 mg, ER niacin–simvastin, about 55% of subjects experienced any flushing with the 1000 mg ER niacin, and up to about 65% experienced any flushing with the 2000 mg ER niacin dose (Table 2). Serious flushing and flushing resulting in discontinuation occurred in only 4 to 7% of those receiving 1000 mg ER niacin and 6% to 11% of those receiving the 2000 mg dose.

Niacin binds to adipocyte and macrophage GPR109A (HM74A) to induce release of prostaglandin D_2 (PGD_2) by epidermal Langherhans cells.[18] PGD_2 acts locally on capillary smooth muscle cells via the PGD_2 receptor (DP1) to induce cutaneous capillary vasdilation. Niacin may also increase prostaglandin E_2, thromboxane B_2, and leukotriene synthesis. Pretreatment with aspirin 325 mg or other non-steroidal ant-inflammatory agents that inhibit prostaglandin release

Table 1 (*Continued*)

Non-HDL-C	LDL-C	HDL-C	Triglyceride	Lp(a)	Apo B	Apo A-I/ B ratio	Total/ HDL-C ratio
Baseline after 4 week simvastatin 20 mg lead-in in mg/dL (Median change from simvastatin 20 mg lead-in – ITT)							
157 (–7%)	115 (–7%)	43 (7%)	209 (–15%)	15 (–8%)	101 (–4%)	1.2 (11%)	5 (–10%)
165 (–14%)	118 (–13%)	41 (18%)	210 (–27%)	12 (–17%)	103 (–14%)	1.3 (27%)	5 (–21%)
160 (–23%)	112 (–14%)	41 (25%)	214 (–38%)	9 (–25%)	96 (–18%)	1.3 (41%)	5 (31%)
Baseline after 4-week simvastatin 40 mg lead-in in mg/dL (Median change from simvastatin 40 mg lead-in)							
131 (–10%)	99 (–13%)	47 (–1%)	141 0%	19 0%	89 (–9%)	1.5 (12%)	3.8 (–5%)
136 (–11%)	105 (–9%)	44 (15%)	147 (–23%)	20 (–17%)	90 (–10%)	1.5 (16%)	4.1 (–16%)
143 (–17%)	109 (–12%)	46 (22%)	156 (–32%)	23 (–21%)	92 (–14%)	1.4 (22%)	4.2 (–25%)
Baseline after 4 week simvastatin 40 mg lead-in in mg/dL (Median change from simvastatin 40 mg lead-in – ITT at 24 weeks [only subjects completing 52 weeks])							
141 (–23%) [–25%]	111 (–22%) [–20%]	45 (22%) [27%]	145 (–33%) [–40%]	24 (–25%) [–29%]	94 (–22%) [–25%]	1.4 (36%) [43%]	4.2 (–28%) [–30%]
141 (–21%) [–28%]	110 (–20%) [–24%]	45 (20%) [25%]	152 (–27%) [–34%]	21 (–21%) [–25%]	94 (–17%) [–26%]	1.4 (36%) [43%]	4.2 (–27%) [–33%]
Baseline in mg/dL (Change from baseline in mg/dL)							
121 (–5%)	91 (–6%)	40 (0%)	172 (–5%)				4.0 (–3%)
115 (–7%)	87 (–2%)	39 (21%)	154 (–13%)				3.95 (–17%)

Non-HDL-C = total cholesterol – HDL-C.
Abbreviations: CHD, coronary heart disease; ER, extended release; IQR, interquartile range; IR, immediate release; ITT, intent to treat; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); Non-HDL-C, non-high-density lipoprotein cholesterol; SR, slow release.

taken 30 to 60 minutes prior to niacin can reduce flushing incidence and intensity by 30% to 40%.[19,20] Tachyphylaxis to PGD$_2$ secretion begins to occur after 1 week of consistent dosing and most patients experience a marked diminution of flushing after 4 weeks and by 1 year most patients report very infrequent or no flushing.[16] Niacin less commonly causes maculopapular rash and urticaria. Rarely, acanthosis nigricans, hyperpigmentation, and dermopathies may occur.

Liver

Persistent elevations in hepatic alanine aminotransferase >3 times the upper limit of normal, the best index of drug-related hepatotoxicty, were not reported in the 912 subjects who received ER niacin up to 2000 mg concomitantly with simvastatin 20 to 40 mg over a period of up to 52 weeks. In the ER niacin clinical trial database, none of the 245 subjects receiving doses of 500 to 3000 mg over 17 weeks and 1% of 1028 subjects receiving ER niacin coformulated with lovastatin had persistent transaminase elevations >3 times

the upper limit of normal.[17] Serum alanine aminotransferase should be monitored every 6 to 12 weeks during the first 6 to 12 months of niacin treatment, and every 6 months thereafter. The dose of ER niacin should not exceed 2 g/day since serious hepatoxicity and fulminant liver failure have been reported with doses of slow or sustained-release niacin ≥1.5 g/day.[16]

No safety data are available for ER niacin used with the highest dose (80 mg) of simvastatin. Slightly higher rates of persistent transaminases elevations occur at the highest dose of simvastatin, with 0.9% having persistent transaminase elevations with 40 mg and 2.1% with 80 mg over 12 months of treatment.[21] In long-term morbidity/mortality studies, persistent transaminase elevations for simvastatin monotherapy are uncommon but dose-related. Moderate dose simvastatin (20–40 mg) has a rate of <0.5% over a 5-year period, while simvastatin 80 mg has a rate closer to 1%.[22] Excessive alcohol intake or a past history of liver disease may also increase the risk of transaminase elevations with simvastatin. Randomized trials have not

Table 2 Percent of patients experiencing treatment-related adverse events (AE)

Event	Simvastatin 20 mg/ IR niacin 50 mg* (n = 114)	Simvastatin 80 mg/ IR niacin 50 mg** (n = 119)	Simvastatin 20 mg/ ER niacin 1000 mg* (n = 123)	Simvastatin 20 mg/ ER niacin 2000 mg* (n = 64)	Simvastatin 40 mg/ ER niacin 1000 mg** (n = 116)	Simvastatin 40 mg/ ER niacin 2000 mg**† (n = 100**/n = 509†)
Any AE	17.5%	29.4%	25.2%	35.9%	29.3%	34%/48.7%
Any serious AE	0%	0.8%	0.8%	0%	0%	0%/0.6%
Gastric ulcer hemorrhage						/0.2%
Drug toxicity						/0.2%
Vasovagal syncope						/0.2%
Discontinuation due to AE	5.3%	4.2%	12.2%	15.6%	11.2%	12.0%/0.0%
Any flushing	45%	49.6%	54%	60%	57.0%	67%/71%
Flushing – serious or leading to discontinuation	0%	2.5%	7.3%	10.9%	4.3%	6.0%/7.1%
Discontinuation due to flushing	0%	0.8%	6.5%	9.4%	4.3%	5.0%/7.1%
Pruritis		0%			4.3%	5.0%
Rash		0.8%			0.9%	3.0%/2.4%
Headache	0.9%	1.7%	2.4%	4.7%	3.4%	0%/2.6%
Dizziness	1.8%	1.7%	0%	0%	0.9%	2.0%
Hyperglycemia (increased HbA1c)	0%		1.6%	3.1%		0%/3.1% (4.1%)
Vomiting	0.9%		0%	3.1%		/2.6%
Gastritis	1.8%	0.8%	0%	3.1%	0.9%	2.0%
Abdominal pain	2.6%	0.8%	0.8%	0%	0.9%	2.0%
Nausea	0.9%	5.0%	2.4%	1.6%	1.7%	3.0%/4.1%
Myalgia (arthralgia)	0%	0%	0%	0%	0.9%	2.0%/1.6% (1.8%)
Myopathy/rhabdomyolysis	0%	0%	0%	0%	0%	0%/0%
Gout	0%	0%	0%	0%	0%	1.0%/0% (0%)
ALT > 3 times ULN	0%	0%	0%	0%	0%	0%
CK > 3 times and <10 times ULN	0%	2.5%			0.9%	3.0%/2.2%
CK > 10 times ULN	0%	0%	0%	0%	0%	0%/0%

*SEACOAST I
**SEACOAST II
†OCEANS
Abbreviations: ALT, alanine amino transferase; CK, creatine kinase; HbA1c, hemoglobin A1c; ULN, upper limit of normal.

reported any difference in rates of clinical hepatitis (jaundice or other symptoms), hepatic failure, or other evidence of hypersensitivity with simvastatin or any other statin compared to placebo.[23]

Muscle

The most common form of myotoxicity related to lipid-modifying drugs is myalgia (muscle pain, weakness, or cramps) with normal creatine phosphokinase (CK) levels. Clinically important myopathy is characterized by muscle symptoms and evidence of muscle damage (elevated CK levels), which in its most severe form, rhabdomyolysis, has more extensive muscle damage and is usually associated with renal impairment.[24] In the 912 subjects in the ER niacin–simvastatin Simcor® clinical trial database, no cases of myopathy, rhabdomyolysis, or CK elevations >10 times the upper limit of normal were reported over a period as long as 52 weeks (Table 2). Myalgias were slightly more likely in those receiving simvastatin 40 mg combined with ER niacin 2000 mg with (2%) than with ER niacin 1000 mg (0.9%). No cases of rhabdomyolysis and 1 case of myopathy were reported in 1079 subjects treated with ER niacin and lovastatin 40 mg over a period of up to 2 years.[25] Rare cases of rhabdomyolysis have been associated with statins used concomitantly with niacin ≥1 g in the Food and Drug Administration Adverse Event Reporting Database.[26] Indeed, the safety of ER niacin and a statin appears comparable with the safety of each drug used alone.

In the over 20,000 subjects in the 5-year Heart Protection Study (HPS), about 6% of subjects reported muscle symptoms at a given visit in both the simvastatin and placebo groups.[27] However, this rate may be lower than experienced in clinical practice since 30% of subjects did not proceed to randomization following a 5-week active run-in period. Myopathy and rhabdomyolysis are very rare with simvastatin monotherapy. In the clinical trial database for simvastatin, 41,050 subjects were treated with simvastatin, of which 26,747 (60%) were treated more than 4 years. Although very uncommon, dose-related increases in the risk of myopathy and rhabdomyolysis occurred at a rate of 0.02% for 20 mg, 0.08% for 40 mg, and 0.53% for 80 mg.[21] There were 10 cases of myopathy/rhabdomyolysis in the 10,269 subjects allocated to simvastatin (0.1%) in HPS, 4 of whom were >65 years; 4 cases of myopathy occurred in the placebo group (0.04%).[27] It should be emphasized that participants in clinical trials are carefully selected to minimize the potential for toxicity. Much higher rates of rhabdomyolysis have been found when simvastatin has been used in patients with multiple risk factors for myopathy, including concomitant use with gemfibrozil, advanced age, impaired renal function, and serious comorbid conditions.[28]

Inhibitors of CYP3A4 shown to increase serum simvastatin levels include itraconazole, fluconazole, erythromycin, clarithromycin, cyclosporine, danazol, diltiazem, verapamil, amiodarone, grapefruit juice, HIV protease inhibitors, and some antidepressants. In 25,248 patients treated with simvastatin and verapamil, the incidence of myopathy was 0.63% compared to 0.061% in those taking simvastatin with another calcium channel blocker.[21] The fibrate gemfibrozil (Lopid®, Pfizer, New York, NY; generic, Watson Pharamceutical, Corona, CA) inhibits the glucuronidation of statins to inactive forms.[29] Gemfibrozil increases the blood levels of all statins, with the exception of atorvastatin.[30,31] Fenofibrate (Tricor®, Abbott, North Chicago, IL; Lofibra®, Gate, Sellerville, PA; Triglide®, Sciele, Atlanta, GA) is a weaker inhibitor of glucuronidation and appears to have a lower rate of serious muscle effects when used concomitantly with a statin.

Other adverse effects of ER niacin

Niacin may worsen insulin resistance, especially in those with impaired fasting glucose or abnormal glucose tolerance.[16] Patients with fasting glucose levels 100 to 125 mg/dL may be at increased risk of developing diabetes on niacin and should be encouraged to adhere to healthy lifestyle pattern and undergo careful monitoring. However, since idiosyncratic elevations of glucose may occur in those with normal glucose levels, fasting glucose should be monitored after each dose titration and annually thereafter. Niacin at a dose of approximately 2000 mg has been shown to reduce coronary heart disease (CHD) events in patients with diabetes but may require intensification of diabetic therapy if glucose control worsens.[32,33] This dose of niacin has also been shown to reduce CHD in those with metabolic syndrome, although diabetes incidence was not reported.[34] It is of concern that earlier onset of diabetes may increase long-term cardiovascular risk and so long-term trials are needed to evaluate the cost versus benefit in insulin resistant subjects.

Niacin has several other uncommon adverse effects.[16] Niacin raises uric acid 5% to 15%. Gout is a relative contraindication to niacin, although allopurinol can be considered for patients with a history of gout whose serum uric acid levels exceed 10 mg/dL. Niacin more than doubles the risk of atrial fibrillation and should be avoided in patients with intermittent atrial fibrillation or other atrial arrhythmias.

However, niacin is an option for patients with established atrial fibrillation or ventricular arrhythmias. Other adverse effects of niacin include upper gastrointestinal bleeding (niacin is contraindicated only in patients with active peptic ulcer disease), blurred vision (cystoid macular degeneration reported with niacin >3 g), and mildly decreased platelet counts.

Clinical context for ER niacin–simvastatin use

Statins are the lipid-modifying drugs of choice for cardiovascular risk reduction. Extensive clinical trial data from over 90,000 participants in long-term trials has shown that for each 38 mg/dL reduction in low-density lipoprotein cholesterol (LDL-C), statins reduce the risk of CHD by 23% and stroke by 17%.[35] Moreover, statins are quite safe in properly selected patients.[22] Similar magnitudes of CHD risk reduction occur with other therapies that primarily lower LDL-C.[36] What is the potential role of simvastatin–niacin fixed dose formulations within this context?

LDL-C

In order to reach the aggressive LDL-C goals of <100 mg/dL (2.59 mmol/L) or <70 mg/dL (1.81 mmol/L) identified in recent guidelines,[37,38] the majority of patients will require not only a high-dose statin, which may lower LDL-C by up to 50% to 60%, but the addition of intensive lifestyle changes and/or or one or more drugs. In the Treating to New Targets Trial, on atorvastatin 10 mg more than half of subjects had an LDL-C >100 mg/dL and on atorvastatin 80 mg, more than half had an LDL-C >77 mg/dL.[39] Only 2 statins lower LDL-C by ≥50%: atorvastatin 40 to 80 mg/day and rosuvastatin 20 to 40 mg/day.[40,41] Options for achieving an additional approximate 15% reduction in LDL-C include quadrupling the statin dose, or adding niacin 2 g, bile acid sequestrants, or ezetimibe 10 mg.[1,6,17,25,42,43] Fibrates have variable effects on LDL-C, and may increase levels in patients with elevated triglyceride levels.[44–46] In general, fenofibrate appears to more effectively lower LDL-C than gemfibrozil, which also has serious safety concerns when used with a statin.

The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial recently brought into question whether the additional LDL-C reduction from ezetimibe will translate into a reduction in cardiovascular events. In ENHANCE, ezetimibe 10 mg added to high dose simvastatin therapy had no significant effect on carotid intimal medial thickness (CIMT) over a 2-year period in 720 subjects with familial hypercholesterolemia (FH).[47] ENHANCE differed in 2 important ways from the earlier Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) trial which demonstrated regression with atorvastatin 80 mg compared to simvastatin 40 mg in FH subjects.[48] In ASAP, subjects were required to have a baseline CIMT >0.7 mm and few had been treated with aggressive LDL-C-lowering therapy. As would be expected after ASAP, which was conducted by the same investigators, 80% of subjects in ENHANCE received prior statin therapy and were most likely treated with high dose statins if not ezetimibe as well. Long-term statin therapy stabilizes plaque by depleting lipid content without changing plaque volume.[49] In the 20% of ENHANCE subjects who were statin naïve at baseline, there was evidence of less CIMT progression in those receiving ezetimibe. Two major conclusions can be drawn from ENHANCE. First, ENHANCE demonstrated the success of cholesterol-lowering treatment. ENHANCE subjects (mean age 46) had baseline CIMT levels similar to that of an average 32-year-old male with an untreated LDL-C of 134 mg/dL.[50] Second, lowering LDL-C by another 17% over a 2-year period in subjects with stabilized plaque had little effect. The findings in ENHANCE are similar to those in the ASAP trial after 2 additional years of follow-up.[51] For these reasons, Merck cancelled a carotid IMT trial of its ER niacin–simvastatin–laropiprant product.[52]

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial failed to meet its primary endpoint of a reduction aortic valve disease events and major cardiovascular events.[53] Simvastatin 40 mg/ezetimibe 10 mg was compared to placebo over 4 years in 1873 subjects with asymptomatic mild to moderate stenosis who did not have an indication for statin therapy. A 22% reduction in the secondary endpoint of major atherosclerotic events was found with ezetimibe–simvastatin, which lowered LDL-C by 61%. However, more cancers were observed in the ezetimibe-simvastatin (n = 105, 11.1%) than in the placebo group (n = 70, 7.5%; p = 0.01), and more cancer deaths (n = 39, 4.1% vs n = 23, 2.5%; p = 0.05. No particular type of cancer was predominant. A meta-analysis of 2 additional ongoing ezetimibe–simvastatin versus simvastatin monotherapy trials (SHARP and IMPROVE-IT, total N = 20,617) found similar rates of cancer in the 2 groups (n = 313 vs 326, respectively; risk ratio 0.96, 95% CI 0.82–1.12, p = 0.61).[54] The mean follow-up of subjects in these trials is less than in SEAS. In light of the controversies surrounding the efficacy and safety of ezetimibe, ER niacin remains a reasonable choice

for additional LDL-C and non-HDL reduction in patients receiving statin therapy.

Non-HDL-C

The ATP III guidelines identified non-HDL-C as the second target of therapy in patients with triglyceride levels between 200 and 500 mg/dL (2.26–5.64 mmol/L). Non-HDL-C is calculated by subtracting HDL-C from total cholesterol and is a measure of circulating atherogenic Apo B-containing apolipoproteins – LDL-C, VLDL-C and intermediate density lipoprotein cholesterol. The non-HDL-C goal is 30 mg/dL (0.78 mmol/L) higher than the LDL-C goal. Non-HDL-C is a more accurate predictor of cardiovascular risk than LDL-C, and closely correlates with Apo B levels in patients receiving statin therapy.[55] Reductions in non-HDL-C from add-on drug therapies to background statin treatment are about 6% from doubling the statin dose, 12% from ezetimibe 10 mg, and highly variable for fibrates (+2% to −18%).[6,42,44,45] Bile acid sequestrants are less effective for lowering non-HDL-C (−5% to 8%) due to their VLDL-C raising effects.[43] In contrast, the addition of ER niacin 2000 mg to simvastatin can decrease non-HDL-C by 16% to 28%, in large part due to the increases in HDL-C.[13,25]

HDL-C and triglycerides <500 mg/dL

An HDL-C level <40 mg/dL (1.04 mmol/L) was defined as a risk factor for cardiovascular disease by ATP III on the basis of epidemiologic data. However, a treatment goal was not identified due to the lack of clinical trial evidence that pharmacologically raising HDL-C results in a reduction in cardiovascular risk. The method by which HDL-C is raised may be important. Development of torcetrapib was discontinued due to an excess of deaths in a large morbidity/mortality trial despite a 72% increase in HDL-C and a 25% decrease in LDL-C with torcetrapib over atorvastatin therapy alone.[56] Adverse off-target effects on the renin-angiotensin system and blood pressure elevations have been implicated, although an adverse effect of cholesteryl ester transfer protein inhibition or other effects cannot be excluded.

Similarly, a triglyceride level <150 mg/dL (1.69 mmol/L) was defined as optimal on the basis of epidemiologic data but a treatment target for drug therapy to prevent cardiovascular disease was not identified. ATP III did define a triglyceride goal of <500 mg/dL (5.64 mmol/L). to prevent pancreatitis and its complications in patients with severe hypertriglyceridemia defined as fasting triglycerides >500 mg/dL. Although triglyceride levels >150 mg/dL have been associated with increased cardiovascular risk,

much of the excess risk disappears after adjustment for low HDL-C and insulin resistance. Clinical trials comparing high- to moderate-dose statin therapy have not found the additional 20% to 25% reduction in triglycerides added to the risk reduction expected from the degree of LDL-C reduction,[35,39,57] nor have trials of fenofibrate and gemfibrozil found a correlation between triglyceride-lowering and cardiovascular event reduction.[58]

"Residual risk" is a term that has been used to describe the fact that patients who have achieved their LDL-C and non-HDL-C goals on statin therapy may still experience a cardiovascular event. These patients often have low HDL-C and elevated levels of triglycerides levels, LDL-C particles, and apo B. While levels of HDL-C and triglycerides remain predictive of cardiovascular risk in patients with LDL-C levels at goal, it is not entirely clear whether the HDL-C increases or triglyceride decreases from drug therapy contribute substantial additional benefit beyond that expected from LDL-C lowering.[36,59] An evidence-based strategy has yet to be determined for these patients. It should be realized, however, that residual lipid abnormalities are also reflective of the inflammatory state of insulin resistance, and thus may be markers rather than causal factors for the increased cardiovascular risk observed in these patients.[60]

Triglycerides >500 mg/dL

In those with triglyceride levels >500 mg/dL, prevention of pancreatitis is the primary objective. Once triglycerides are <500 mg/dL, attention can then turn to addressing cardiovascular prevention by lowering LDL-C and non-HDL-C.[15] In those with severe hypertriglyceridemia, a triglyceride treatment goal of <500 mg/dL has been established for the purpose of preventing pancreatitis. Once it has been determined that the patient fasted for at least 8 hours prior to obtaining the blood sample for triglyceride measurement, secondary causes of hypertriglyceridemia should be evaluated since triglyceride levels usually fall to <500 mg/dL once these conditions have been treated. Particular attention should be paid to detecting undiagnosed or poorly controlled diabetes or hypothyroidism. All patients should see a dietitian for counseling on a diet very low in fat (<15%) and refined carbohydrates, and obese patients should be counseled to lose weight. When triglyceride levels exceed 1000 mg/dL, a triglyceride-lowering drug is usually started simultaneously with diet and lifestyle changes. Fibrates are considered first-line therapy and lower triglycerides by 20% to 50%.[38] Concentrated omega-3 fish oils with 3 to 4 g of eicosopentanoic and docohexanoic acids are an excellent

second-line therapy with a similar efficacy profile to fibrates, and may be safer when combined with higher dose statin therapy.[61] ER niacin can be considered as add-on therapy or in those unable to tolerate fibrates. No efficacy data are available for ER niacin used in patients with triglycerides exceeding 500 mg/dL, but in those with triglyceride levels exceeding 200 mg/dL, 25% to 35% reductions in triglycerides were obtained above those obtained with simvastatin. Statins also lower triglycerides in a dose-dependent manner, with 25% to 30% reductions in triglycerides from atorvastatin 40 to 80 mg and rosuvastatin 20 to 40 mg.[42] Simvastatin, however, has lesser effects on triglycerides, with 15% to 20% reductions with simvastatin 40–80 mg. Ezetimibe has modest triglyceride-lowering effects. Bile acid sequestrants are contraindicated in these patients since marked exacerbation of hypertriglyceridemia may occur. Once triglyceride levels are <500 mg/dL, attention can then turn to achieving LDL-C and non-HDL-C goals to reduce cardiovascular risk, as described above.

Lp(a)

The addition of ER niacin 200 mg lowered Lp(a) by 17% to 25% more than simvastatin alone. The significance of this is unclear. Very high levels of Lp(a) are associated with increased cardiovascular risk in some but not all populations, nor has not been shown that reducing Lp(a) reduces cardiovascular risk.[62]

Cardiovascular endpoint studies

The addition of niacin or fibrates to statin therapy has been advocated by some to normalize residual HDL-C and triglyceride abnormalities. However, no clinical trial evidence is yet available from long-term morbidity/mortality trials to determine whether pharmacologic strategies directed to these abnormalities are additive to lowering LDL-C and non-HDL-C with statin therapy. Extensive clinical trial evidence has shown that simvastatin and other statins lower the risk of heart attack and stroke in direct proportion to the magnitude of LDL-C reduction.[35] The only randomized, controlled trial, of niacin monotherapy, the Coronary Drug Project, reported a 17% reduction in coronary heart disease events over 6.2 years with approximately 2 g of niacin.[63] It should be noted this relative reduction in risk is about what would be expected from a 15% reduction in LD-C with niacin 2 g, the average dose in the trial.

Several trials have evaluated the effect of ER or sustained-release niacin combined with a statin or colestipol on surrogate endpoints of coronary angiographic progression or carotid IMT. Beneficial effects on angiographic progression or carotid IMT were observed over periods of 2 or more years.[64–67] In the HDL and Atherosclerosis Treatment Trial (HATS), 160 subjects with CHD, low HDL-C, and normal LDL-C were randomized to placebo or a mean dose of simvastatin 13 mg and sustained-release niacin 2.4 g for 3 years.[64] The niacin–simvastatin group had a 42% reduction in LDL-C and a 26% increase in HDL-C and experienced regression on coronary angiography along with a 92% reduction in CHD events.

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER)-2 study was a 12 month carotid IMT study in 149 subjects that compared a statin to a statin with ER niacin 1000 mg added.[68] Simvastatin ≥20 mg was the statin used by 93% of subjects. There were no differences in the non-HDL-C or LDL-C levels between the 2 groups, although HDL-C was increased by 21% and triglycerides were lowered an additional 8% in the niacin group (Table 1). The niacin group had no progression in carotid IMT versus progression in the group on statin monotherapy compared to baseline, although no significant difference between the 2 groups was found at 1 year. A subset of 125 subjects continued into the ARBITER 3 trial and all were treated with ER niacin and a statin for another year.[67] Among the subjects treated with ER niacin for 24 months, regression of carotid IMT was observed.

Few cardiovascular events were reported in these small surrogate endpoint trials, precluding any definitive conclusions regarding the value of niacin-related lipid changes other than LDL-C reduction for reducing cardiovascular risk. Reductions in coronary heart disease risk varied from 17% to 92%, although the 95% confidence intervals were wide and included 1.0.

Several clinical trials are underway to evaluate the benefit of ER niacin added to background statin therapy. Ongoing clinical trials include the AIM-HIGH trial, which will determine whether the addition of ER niacin to simvastatin will result in additional cardiovascular event reduction independent of the degree of LDL-C-lowering in subjects with established cardiovascular disease.[8] The HPS-2 THRIVE trial will randomize 20,000 subjects with cardiovascular disease to aggressive LDL-C-lowering using simvastatin with or without ER niacin coformulated with laropiprant.[5]

Areas for future investigation

The large majority of subjects in the ER niacin–simvastatin database have been middle-aged. Since older individuals

are at the highest absolute risk of a coronary heart disease or stroke event, more studies of efficacy, safety, and tolerability in the elderly are needed.[69] Notably, most first cardiovascular events occur after age 75 in women. Efficacy and safety studies are needed in other populations as well. Those with both diabetes and cardiovascular disease are at very high risk of a cardiovascular event and have the potential for the most absolute benefit from very aggressive lipid management.[70] Those with impaired fasting glucose and metabolic syndrome are also at increased cardiovascular risk, but may also be at increased risk of transitioning to diabetes with niacin. Furthermore, many patients will require the addition of another lipid-lowering agent to high dose statin therapy to achieve very aggressive LDL-C and non-HDL goals.

Conclusions

ER niacin combined with simvastatin provides an additional option for achieving LDL-C and non-HDL-C goals for cardiovascular prevention. The 2000 mg dose of ER niacin has the greatest benefit for lowering LDL-C and non-HDL-C. ER niacin–simvastatin at both the 1000 and 2000 mg doses is effective for raising HDL-C and lowering triglycerides compared simvastatin monotherapy, although the additive benefit of these changes for reducing cardiovascular events remains to be determined. ER niacin–simvastatin is reasonably well-tolerated by most patients. The muscle and liver safety profile of the combination appears to be similar to that of ER niacin and simvastatin used as monotherapy. Combination of ER niacin with simvastatin has the potential to be safer than some statin–fibrate combinations, although no head-to-head comparison have been performed. ER niacin has an increased rate of hyperglycemia, adverse gastrointestinal effects, and atrial arrhythmias that may alter the benefit-risk ration in at-risk populations. Therefore, the efficacy, safety and tolerability in the elderly, women, those with diabetes, and with the highest doses of statins are needed. Results of ongoing ER niacin morbidity/mortality trials are eagerly awaited.

Disclosures

Jennifer G Robinson, MD, MPH has received research grants from Abbott, Aegerion, Astra-Zeneca, Bristol-Myers Squibb, Daiichi-Sankyo, Hoffman la Roche, Merck, Merck Schering Plough, Pfizer, and Takeda. She has received speaker honoraria from Merck Schering Plough and has served as a consultant for Astra-Zeneca and Merck Schering Plough.

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