Atherosclerosis in the HIV and non-HIV setting: detecting and modifying cardiovascular risk

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Ezetimibe/Simvastatin (Inegy™) in the Treatment of Hyperlipidemia

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Summary

Ezetimibe/simvastatin (Inegy™), a dual inhibitor of both cholesterol production and absorption, is a new approach to the management of hyperlipidemia. Recent studies have shown that it produces greater reductions in low-density lipoprotein (LDL) cholesterol than the single inhibition of statin therapy, enabling many more patients to achieve their LDL cholesterol treatment goals. With ezetimibe/simvastatin therapy, reductions of up to 61% from baseline have been seen in LDL cholesterol, with clear improvements in other associated lipid fractions. It has been well tolerated across all studies, with a safety profile similar to that of statin therapy. This paper will review clinical experience to date with ezetimibe/simvastatin, commenting upon its place and potential value in the prevention of cardiovascular disease.
Introduction

Despite the clear risks of hyperlipidemia and the proven benefits of lipid lowering therapies, only a minority of patients currently achieve recommended low-density lipoprotein (LDL) cholesterol treatment goals in clinical practice (1-5). More patients are being treated for lipid reduction than ever before, but there still remains a substantial degree of under treatment. Although this may be due to a number of reasons (e.g. patient noncompliance, tolerability issues, variable physician follow-up), the most likely explanation is that patients are not receiving adequate dosages of the lipid lowering drugs available, or that the drugs themselves are not optimal. Either way, a more aggressive approach to LDL cholesterol reduction is warranted.

Until recently, clinicians had only been able to inhibit one source of cholesterol with drug therapy, that of cholesterol production. Ezetimibe/simvastatin (Inegy™), provides Dual Inhibition of both cholesterol production and absorption, representing a a new approach to lipid management. Recent large-scale, randomized, controlled clinical trials have shown that ezetimibe/simvastatin produces substantially greater reductions in LDL cholesterol than statin therapy, while maintaining a similar safety and tolerability profile to statin therapy (6-11). As such, it may be a viable alternative to traditional statin therapy.

This paper will review the data to consider the use of ezetimibe/simvastatin in the treatment of hyperlipidemia.

Ezetimibe/simvastatin: components with complementary actions

Simvastatin is a competitive inhibitor of hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, the last regulated step in the synthesis of cholesterol. By lowering serum LDL cholesterol levels (through a combination of LDL receptor up-regulation and reduced entry of LDL cholesterol into the circulation), statins as a class have been shown to reduce the incidence of coronary artery disease by 25-60% and the risk of death from any cause by an approximate 30% (12). Simvastatin was one of the first statins to be associated with substantial improvements in morbidity and mortality in this respect (13), and has since shown benefit across a wide range of at-risk individuals (14).

Ezetimibe is the first in a new class of cholesterol absorption inhibitors that blocks the intestinal absorption of dietary and biliary cholesterol, without affecting the uptake of triglycerides or fat soluble vitamins (15, 16). As would be expected from its mode of action, ezetimibe has demonstrated significant reductions in LDL cholesterol in patients with primary hypercholesterolemia (p < 0.01 versus placebo), with favorable effects on associated lipid variables such as triglycerides and high-density lipoprotein (HDL) cholesterol (17, 18).
As blood cholesterol levels are maintained through both endogenous synthesis and intestinal absorption, an agent that inhibits both sources of cholesterol would be expected to lower LDL cholesterol levels to a greater extent than one that acts through either mechanism alone (Figure 1). This theory has proven correct in the laboratory and in the clinic. In a hypercholesterolemic dog model, for example, ezetimibe was seen to synergistically reduce plasma cholesterol levels in the presence of HMG-CoA reductase inhibitors (19). Early clinical pharmacology studies also demonstrated that simvastatin and ezetimibe had incremental benefit on LDL cholesterol reduction, and without any adverse drug-drug interactions (20). Subsequent clinical studies have since shown repeatedly that ezetimibe/simvastatin provides reductions in LDL cholesterol over and above those achieved with statin therapy. Key data in this respect are detailed below.

Clinical efficacy of ezetimibe/simvastatin

Reductions in LDL Cholesterol

Recently published findings from a 12-week treatment study enrolling 887 patients with primary hypercholesterolemia (LDL cholesterol 145-250 mg/dl; triglycerides ≤350 mg/dl) showed ezetimibe/simvastatin to be significantly (p < 0.001) more effective than simvastatin alone in reducing LDL cholesterol levels (8). In the study, patients were randomized to one of four different treatment regimens: ezetimibe 10 mg; simvastatin 10, 20, 40 or 80 mg; ezetimibe 10 mg plus simvastatin 10, 20, 40 or 80 mg; or placebo. Pooled data across all ezetimibe/simvastatin patients demonstrated a mean 53.2% reduction from baseline in LDL cholesterol compared with a 38.5% reduction for simvastatin alone (p < 0.001). The figure of 53.2% is important, as evidence suggests that a reduction in LDL cholesterol of at least 50% is needed for plaque stabilization and the reduced progression of coronary atherosclerosis (21). The differential between the treatment groups could be seen at each dose comparison. Reductions in LDL cholesterol of up to 61% from baseline were reported in patients treated with ezetimibe/simvastatin 10/80 mg (Figure 2). Maximal lowering of LDL cholesterol was evident by 2 weeks, and efficacy maintained throughout the study. In addition to the beneficial effects on LDL cholesterol, there were clear improvements in a number of other lipid fractions and inflammatory markers, with significance between the treatment groups for the majority of variables (Table 1). Of note, the data presented in this review relates to the co-administration of ezetimibe and simvastatin and not the co-formulation of the drugs. However, a recent study by Bays et al clearly demonstrated the bioequivalence of the ezetimibe/simvastatin (eze/simva) combination tablet to co-administration of the 2 individual drugs (22). In this study administration of eze/simva 10/10 mg, 10/20 mg, 10/40 mg and 10/80 mg reduced mean LDL-C levels with 44.8%, 51.9%, 55.2% and 60.2% respectively, after 12 weeks of treatment.
Inegy in the treatment of hyperlipidemia

Figure 1  Dual inhibition of cholesterol production and absorption with ezetimibe/simvastatin

![Diagram showing cholesterol metabolism and inhibition points with ezetimibe/simvastatin]

Chol = cholesterol; VLDL = very-low-density lipoprotein; LDL = low-density lipoprotein; LDL-R = LDL receptor; HDL = high-density lipoprotein; CoA = coenzyme A; SR-BI = class B type 1 scavenger receptor

**LDL Cholesterol Goal Attainment**

Of important clinical consequence is that ezetimibe/simvastatin has been shown to allow more patients to reach their LDL cholesterol goal at a lower dose of simvastatin and with fewer dose titrations than simvastatin alone. In a 23-week study of 710 randomized, high-risk patients (men and women with LDL cholesterol ≥ 130 mg/dl meeting NCEP Adult Treatment Panel III criteria for coronary heart disease [CHD] or CHD risk equivalent), ezetimibe/simvastatin 10/10, 10/20 or 10/40 mg produced greater reductions in LDL cholesterol and allowed more patients to reach an LDL cholesterol treatment goal of < 100 mg/dl than simvastatin monotherapy (20 mg) (6) (Figure 3). After 5 weeks of treatment, 75% patients treated with ezetimibe/simvastatin 10/10 mg achieved LDL-C levels < 100 mg/dl compared to only 46% of patients treated with simvastatin 20 mg. Essentially, patients treated with ezetimibe/simvastatin10/10 mg had approximately 3.6 times greater odds of reaching their treatment goal than patients treated with simvastatin 20 mg. The corresponding odds for patients in the ezetimibe/simvastatin 10/20 and 10/40 mg groups were 6.0 and 8.4 times, respectively. In addition, relatively few patients in the ezetimibe/simvastatin groups required up-titration of the simvastatin dose. For example, 75% of patients receiving ezetimibe/simvastatin 10/10 mg reached their LDL cholesterol goal without a simvastatin dose titration, compared with fewer than half of patients receiving simvastatin 20 mg.
Figure 2  Percent reduction in LDL cholesterol levels from baseline to study endpoint: ezetimibe/simvastatin vs simvastatin monotherapy (8)

Table 1  Mean percent change from baseline to study end point (last available LDL cholesterol measurement) in lipid variables and inflammatory markers: ezetimibe/simvastatin vs simvastatin monotherapy (8)

<table>
<thead>
<tr>
<th></th>
<th>Pooled simvastatin data</th>
<th>Pooled ezetimibe/simvastatin data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean % change from baseline (SD)</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>345</td>
<td>-38.5 (14.2)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>345</td>
<td>-26.4 (11.3)</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>345</td>
<td>7.6 (11.9)</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>345</td>
<td>-34.1 (13.8)</td>
</tr>
<tr>
<td>Triglycerides (median)</td>
<td>345</td>
<td>-15.2 (34.1)</td>
</tr>
<tr>
<td>Apo B</td>
<td>328</td>
<td>-29.2 (14.3)</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>328</td>
<td>6.3 (13.8)</td>
</tr>
<tr>
<td>Apo A-II</td>
<td>199</td>
<td>2.8 (11.5)</td>
</tr>
<tr>
<td>Apo E</td>
<td>328</td>
<td>-19.4 (22.8)</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>199</td>
<td>-9.6 (39.3)</td>
</tr>
<tr>
<td>LDL: HDL cholesterol</td>
<td>345</td>
<td>-42.0 (15.2)</td>
</tr>
<tr>
<td>Total cholesterol: HDL cholesterol</td>
<td>345</td>
<td>-30.8 (13.0)</td>
</tr>
<tr>
<td>CRP (median)</td>
<td>204</td>
<td>-8.7 (61.7)</td>
</tr>
<tr>
<td>Fibrinogen (median)</td>
<td>198</td>
<td>4.4 (20.0)</td>
</tr>
</tbody>
</table>

*p < 0.001 versus pooled simvastatin; LDL = low-density lipoprotein; HDL = high-density lipoprotein; Apo = apolipoprotein; Lp = lipoprotein; CRP = C-reactive protein
Other Patient Populations

Preliminary data also suggest a broader clinical role for ezetimibe/simvastatin for patients where greater LDL cholesterol reduction is necessary, the compound demonstrating notable efficacy in groups of patients at high risk of cardiovascular disease. In patients with type II diabetes mellitus, for example, ezetimibe/simvastatin 10/20 mg was more effective in reducing LDL cholesterol than doubling the dose of statin therapy, and enabled the majority of patients to meet their LDL cholesterol treatment goals (23, 24). It also improved levels of C-reactive protein, a sensitive marker for cardiovascular risk in these patients (25).

Safety and tolerability of ezetimibe/simvastatin

Ezetimibe/simvastatin has been evaluated for safety in more than 3200 patients in clinical trials. Studies reported to date have shown ezetimibe/simvastatin to be well tolerated, with a safety profile similar to that of statin monotherapy. No clinically meaningful differences have been seen between ezetimibe/simvastatin and either simvastatin or atorvastatin as single agents in terms of overall adverse events (drug-related or not), or clinical/laboratory adverse events leading to discontinuation of treatment (6-8) (Table 2). Importantly, there were no reported cases of rhabdomyolysis in clinical trials. Nevertheless, vigilance is required as there have been some case reports of patients experiencing myopathy/tendinopathy both with and without increased serum creatine kinase activity after adding ezetimibe to a statin (26).
Table 2  Summary of adverse events across three randomized, controlled studies comparing ezetimibe/simvastatin with statin monotherapy (6-8)

<table>
<thead>
<tr>
<th></th>
<th>Simvastatin</th>
<th>Atorvastatin</th>
<th>Ezetimibe/simvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg</td>
<td>10 mg</td>
<td>10/10 mg</td>
</tr>
<tr>
<td>Any clinical adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>168 (66%)</td>
<td>-</td>
<td>140 (56%)</td>
</tr>
<tr>
<td>Study 2</td>
<td>-</td>
<td>-</td>
<td>187 (71%)</td>
</tr>
<tr>
<td>Study 3</td>
<td>-</td>
<td>219 (63%)</td>
<td>-</td>
</tr>
<tr>
<td>Treatment-related adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>19 (8%)</td>
<td>-</td>
<td>24 (10%)</td>
</tr>
<tr>
<td>Study 2</td>
<td>-</td>
<td>-</td>
<td>42 (16%)</td>
</tr>
<tr>
<td>Study 3</td>
<td>-</td>
<td>46 (13%)</td>
<td>-</td>
</tr>
<tr>
<td>Discontinuation due to any adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>14 (6%)</td>
<td>-</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Study 2</td>
<td>-</td>
<td>-</td>
<td>10 (4%)</td>
</tr>
<tr>
<td>Study 3</td>
<td>-</td>
<td>7 (2%)</td>
<td>-</td>
</tr>
<tr>
<td>Creatine kinase ≥10 times ULN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>2 (1%)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Study 2</td>
<td>-</td>
<td>-</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Study 3</td>
<td>-</td>
<td>1 (0.3%)</td>
<td>-</td>
</tr>
<tr>
<td>Alanine aminotransferase and/or aspartate aminotransferase ≥3 times ULN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>0</td>
<td>-</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Study 2</td>
<td>-</td>
<td>-</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Study 3</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

† Simvastatin 10, 20, 40 or 80 mg; ULN = upper limit of normal; study 1 = Feldman et al 2004 (6); study 2 = Ballantyne et al 2004 (7); study 3 = Goldberg et al 2004 (8)

**Efficacy comparisons with other statins**

**Ezetimibe/Simvastatin vs Atorvastatin**

In addition to comparisons of ezetimibe/simvastatin versus simvastatin alone, the published literature also provides evidence for the superior efficacy of ezetimibe/simvastatin versus atorvastatin in the treatment of hypercholesterolemia. A recently reported forced-titration study compared the efficacy of ezetimibe/simvastatin with atorvastatin in 788 patients randomized to i) atorvastatin (10 mg titrated to 20, 40 and 80 mg at 6-week intervals); ii) ezetimibe/simvastatin (10/10 mg titrated to 10/20, 10/40 and 10/80 mg at 6-week intervals); and iii) ezetimibe/simvastatin (10/20 mg titrated to 10/40 mg after 6 weeks and 10/80 mg after 18 weeks) (7). All patients were 18 years or older, with baseline LDL cholesterol levels at or above the drug treatment threshold detailed in the National Cholesterol Education Program (NCEP) Adult Treatment Panel III guidelines (27). After the first 6 weeks of treatment (primary endpoint), ezetimibe/simvastatin (10/10 and 10/20 mg) produced significantly greater reductions in LDL cholesterol (-46% and -50%, respectively) than atorvastatin 10 mg (-37%; p ≤ 0.05). In fact, at all time/dose points throughout the study, ezetimibe/simvastatin showed greater efficacy than...
atorvastatin in decreasing LDL cholesterol (Figure 4), as well as non-HDL cholesterol, apolipoprotein B, and total cholesterol. Similarly, ezetimibe/simvastatin was significantly (p ≤ 0.05) more effective than atorvastatin in increasing levels of HDL cholesterol from baseline.

**Ezetimibe in Combination with Atorvastatin, Pravastatin, Lovastatin and Rosuvastatin**

The beneficial effects of ezetimibe coadministered with a statin are not limited to simvastatin; valuable improvements in clinical efficacy have also been seen in combination with all statins studied, such as atorvastatin (9, 28-30), as well as pravastatin (31), lovastatin (32), and rosuvastatin (33). For example, in a recent pooled analysis of data from a collective 2382 patients with primary hypercholesterolemia, 12 weeks of treatment with ezetimibe plus one of four statins (atorvastatin, lovastatin, pravastatin or simvastatin) produced significantly (p < 0.01) greater reductions in LDL cholesterol, total cholesterol, triglycerides, non-HDL cholesterol and apolipoprotein B compared with statin therapy alone (34). HDL cholesterol levels were also significantly (p < 0.01) increased. At each statin dose, coadministration with ezetimibe led to a greater LDL cholesterol reduction than the next highest statin monotherapy dose. Moreover, the enhanced LDL cholesterol lowering effects of ezetimibe plus statin were independent of the statin type, and were generally consistent across patient subgroups (e.g. age, gender, hypertension, diabetes, baseline lipid level, and family history of CHD). The safety profiles of all ezetimibe/statin combinations were similar to each other and to those of statin therapy alone.

**Figure 4** Percent reduction in LDL cholesterol levels from baseline with ascending doses of ezetimibe/simvastatin vs atorvastatin monotherapy (7)
**Considerations**

There is a wide variation in the response to ezetimibe with some cases reported of patients with hypercholesterolemia who are unresponsive at all to treatment with ezetimibe. It has been suggested that variants in the \( \text{NPC1L1} \) gene, the molecular target for ezetemibe, are responsible for this unresponsive phenotype (35). Also, the additional benefit of adding ezetimibe to a statin in patients with refractory familial hyperlipidemia or patients who are intolerant to statin therapy is modest with an average 11% additional reduction in LDL-C as recently reported by Wierzbicki et al (36). Incidences of ezetimibe-induced hyperlipidemia, both in monotherapy and in combination with statins have also been observed. Apart from biological variation and lesser dietary or drug compliance this could be explained by an ezetimibe-induced increase in hepatic cholesterol synthesis, albeit unlikely.

### Table 3 Ongoing outcomes program for ezetimibe/simvastatin

<table>
<thead>
<tr>
<th>Study</th>
<th>Objective(s)</th>
<th>Measures</th>
<th>Scope</th>
</tr>
</thead>
</table>
| Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) | To evaluate the effects of aggressive lipid lowering on carotid artery intima media thickness: ezetimibe/simvastatin vs statin monotherapy | **Primary:** Mean change in carotid artery intima media thickness  
**Secondary:** Incidence of plaque regression, changes in maximal intima media thickness | 725 patients at 18 international centers treated for 2 years |
| Improved Reduction of Outcomes: VYTORINTM Efficacy International Trial (IMPROVE IT) | To evaluate the risk reduction provided by ezetimibe/simvastatin vs simvastatin in reducing death and major coronary events in patients with acute coronary syndromes | **Primary:** Composite of death, MI, rehospitalization for acute coronary syndromes or revascularization | 10,000 patients followed for at least 2 years |
| Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) Study | To assess whether aggressive cholesterol lowering in patients with moderate AS slows progression of AS, reduces number of valve replacements, and incidence of CVD outcomes: ezetimibe/simvastatin vs placebo | **Primary:** Risk reduction in composite endpoint of MCEs  
**Secondary:** Aortic valve events, echocardiographic progression of AS, safety/tolerability | 1400 patients treated for 4 years |
| Study of Heart and Renal Protection (SHARP) | To assess the effects of ezetimibe/simvastatin vs placebo in patients with chronic kidney disease | **Primary:** Time to 1st major vascular event (nonfatal MI or cardiac death, nonfatal/fatal stroke, revascularization)  
**Secondary:** Progression to ESRD, various causes of death, MCEs, stroke, hospitalization for angina | 9000 patients at >200 hospitals in 10 countries treated for ≥ 4 years |

MI = myocardial infarction; ESRD = end-stage renal disease; AS = aortic stenosis; CVD = cardiovascular disease; VYTORIN = INEGY

1 MCEs = cardiovascular death, aortic valve replacement surgery, CHF as a result of progression of AS, nonfatal MI, CABG, PCI, hospitalized unstable angina, nonhemorrhagic stroke; 2 MCEs (major cardiovascular events) = nonfatal MI or cardiac death
Conclusions: perspectives and expectations

In recent years, lipid lowering therapy has been directed towards the inhibition of cholesterol production through the use of statins. For many patients, however, clinical efficacy can only be achieved through a strategy of dual inhibition of both the production and absorption of cholesterol. As such, ezetimibe/simvastatin would appear to present the clinician and patient with a number of advantages over existing therapy. First, the impressive efficacy seen with ezetimibe/statin therapy should offer patients an increased likelihood of LDL cholesterol goal attainment. As large proportions of patients with hyperlipidemia currently remain under treated, an intervention that increases the chances of goal realization has to be viewed as positive. In fact, some might contend that even patients who comfortably achieve LDL cholesterol goals on existing therapy might benefit from more aggressive lipid lowering. There is much to support the ‘lower is better’ argument. Every major primary prevention trial of statin therapy to date has demonstrated that lower LDL cholesterol levels are associated with a reduced risk of atherosclerotic disease (37). Those that have analyzed event rates in relation to LDL cholesterol have shown that lower LDL cholesterol tertiles are associated with a reduced occurrence of major coronary events (38), and that aggressive lipid lowering can produce more favorable outcomes than conservative approaches (39-42). This has led some to propose that target LDL cholesterol levels should be as low as < 70 mg/dl, and not 100-115 mg/dl as recommended by current guidelines (43). As a matter of fact, the recently revised NCEP guidelines have already moved towards this new LDL-C target of < 70 mg/dl in (very) high-risk patients (44). A similar pattern can be noticed in the Joint British Societies guidelines II/ British Hypertension Society guidelines IV (45). These changes were brought about by the beneficial results of intensive lipid-lowering therapy beyond current targets observed in the PROVE-IT and Heart Protection Study (14, 41). From a clinical practice standpoint, multiple (upward) dose adjustments with ezetimibe/simvastatin therapy should not be necessary, and many more patients should be able to achieve their LDL cholesterol goals with low doses. In contrast, initial doses of statins are very often insufficient to enable patients to achieve their goals. Clinical evidence shows that when initial doses of statins are doubled, this only provides an additional 6% reduction in LDL cholesterol (12).

Future studies will need to address the potential clinical benefits of ezetimibe/statin therapy over and above those of improving LDL cholesterol levels. The body of evidence for simvastatin is clear in this respect, there being a strong patient outcomes base in the form of the Scandinavian Simvastatin Survival Study and Medical Research Council/British Heart Foundation Heart Protection Study (13, 14, 46). As a single agent, ezetimibe has been shown to reduce atherosclerotic progression in an animal model (47), but clinical evidence of the effectiveness of ezetimibe/simvastatin in the prevention of the complications of atherosclerosis is not yet available. An active outcomes program for ezetimibe/simvastatin is ongoing (Table 3) (48-50). These studies, which include over 21,000 patients across a number of countries worldwide,
will confirm whether the greater LDL cholesterol lowering effects of Dual Inhibition translate in the clinic into beneficial modifications of cardiovascular endpoints. Clearly, it would be an advancement in clinical practice to offer appropriate patients with hyperlipidemia the greater effectiveness of dual cholesterol inhibition with ezetimibe/simvastatin.

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References


