Neutral Effect on Markers of Heart Failure, Inflammation, Endothelial Activation and Function, and Vagal Tone After High-Dose HMG-CoA Reductase Inhibition in Non-Diabetic Patients With Non-Ischemic Cardiomyopathy and Average Low-Density Lipoprotein Level

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OBJECTIVES

This study sought to determine the effect of aggressive 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) therapy on surrogate markers in non-ischemic cardiomyopathy (NICM) patients and average low-density lipoprotein (LDL) concentrations.

BACKGROUND

The effects of statins may well go beyond lipid lowering, and these pleiotropic effects may be of benefit in the treatment of heart failure.

METHODS

Fifteen patients with NICM on standard maximized heart failure medication were enrolled in a randomized, double-blinded, placebo-controlled, crossover trial. Patients received 80 mg atorvastatin (ATV) or matching placebo for a 12-week treatment period with a minimum of an 8-week washout period. The following surrogate markers were evaluated: N-terminal-pro brain natriuretic peptide, high-sensitivity C-reactive protein, oxidized LDL antibody, soluble receptor tumor necrosis factor, tumor necrosis factor-alpha, circulating levels of vascular adhesion molecule-1, intercellular adhesion molecule-1, P-selectin, non-invasive endothelial function studies, and heart rate variability.

RESULTS

After ATV therapy, there was a significant decrease in LDL concentration from 110 ± 27 mg/dl to 55 ± 18 mg/dl (p < 0.05). There were no differences between ATV and placebo with regard to the surrogate markers measured.

CONCLUSIONS

Based on these findings, it seems that the administration of high-dose statins to a heart failure population with modest LDL levels and no other indication for statin therapy was neither beneficial nor detrimental as determined by surrogate marker measures. Further studies are needed to determine whether there is an appropriate patient population and optimal dose (LDL concentration) for the treatment of systolic heart failure with statin therapy. (J Am Coll Cardiol 2006;47:338–41) © 2006 by the American College of Cardiology Foundation

Recent evidence has suggested that inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase may be of benefit in patients with ischemic and non-ischemic cardiomyopathy (1–7). However, there are limited data to suggest that low cholesterol levels in the setting of heart failure may be detrimental (8,9).

It is reasonable to derive that the use of HMG-CoA reductase inhibitors (statins) may be of benefit for the treatment of heart failure. The potential benefits of statin therapy are the findings that in both human and animal models HMG-CoA reductase inhibition can improve nitric oxide availability, endothelial function, and heart rate variability, along with reducing markers of inflammation and cytokine activation. Conversely, it has been postulated that too great a reduction in cholesterol or coenzyme Q10 may worsen heart failure (8–10).

To further our understanding of the role of statins, we studied the effect of aggressive HMG-CoA reductase inhibition in non-diabetic patients with non-ischemic cardiomyopathy (NICM) and average low-density lipoprotein (LDL) concentrations. This cohort of patients was selected to determine whether statins would be of benefit in patients who would otherwise not be considered for statin therapy.

METHODS

A total of 15 non-diabetic patients with NICM completed a randomized, double-blinded, placebo-controlled, crossover trial evaluating the effect of atorvastatin 80 mg once per day for 12 weeks.
day (ATV) on surrogate markers of heart failure. Random-
ization was achieved using a block design (n = 10) and a
random numbers table for a total of 20 patients. Seven
patients received ATV as initial therapy. After approval
from the hospital’s Institutional Review Board and before
study entry, informed consent was obtained. Inclusion
criteria included a history of congestive heart failure >3
months secondary to NICM; ejection fraction <40% within
12 months; patients receiving maximized individual heart
failure therapy; or LDL <160 mg/dl. Exclusion criteria
included a New York Heart Association functional class IV
function; diabetes; or cholesterol-lowering, antioxidant, es-
trogen replacement, or non-steroidal anti-inflammatory
therapy.

Treatment periods for ATV and placebo were 12 weeks.
The washout period between treatments was a minimum of
eight weeks. Patient compliance was determined by tablet
count. Both ATV and matching placebo were provided by
Pfizer Inc. (Ann Arbor, Michigan).

**Endothelial function.** The method has been previously
published (11).

**Heart rate variability.** Patients were evaluated for 24 h by
a Holter monitor. The data were processed using the
standard Delmar-Reynolds program incorporating a fast
Fourier transform. The time domain analysis of heart rate
variability included standard deviation of all normal-to-
normal intervals (ms), standard deviation of the averages
of normal-to-normal intervals in all 5-min segments (ms), and
the square root of the sum of the squares of differences
between adjacent normal-to-normal intervals.

**Biological markers.** Plasma samples were obtained from
patients at the start and end of each phase for analysis of
biological markers for heart failure (N-terminal-pro brain
natriuretic peptide [BNP]), inflammation (high-sensitivity
C-reactive protein [hsCRP], oxidized LDL-antibody [ox-
LDL], soluble receptor tumor necrosis factor [sTNF-R],
tumor necrosis factor-alpha [TNF-α]), and endothelial
activation (circulating levels of soluble vascular adhesion
molecule [sVCAM]-1, soluble intercellular adhesion mole-
cule [sICAM]-1, soluble P-selectin). Analysis of samples
was performed using an enzyme-linked immunosorbent
assay.

**Statistics.** Comparisons were made using general linear
model repeated-measures analysis of variance (SPSS for
Windows, version 11.5, SPSS Inc., Chicago, Illinois). The
data are expressed as mean ± standard deviation. A value of
p < 0.05 was considered statistically significant. The study
was estimated to have a power to determine a 25% difference
in ~10 to 14 patients for the primary end points: TNF-α,
sICAM, sVCAM, and endothelial function.

**RESULTS**

A total of 18 patients were entered in the study, and 15
completed all phases. One patient died of sudden cardiac
death at the end of the 12-week placebo phase, and two
withdrew unrelated to study drug. Baseline parameters are
shown in Table 1.

Results for surrogate markers are shown in Table 2. No
significant differences were seen for any parameter except
for LDL. No differences were observed between the two
baseline measurements for any parameter (either analysis of
variance or paired t test). When the data were log trans-
formed or when post-therapy (ATV/placebo) values were
evaluated by a paired t test, no significant differences were
found for any variable (except LDL). Patients had non-
detectable levels at some time points for hsCRP (n = 2) and
P-selectin (n = 4). Statistical analysis was similar when
these patients were excluded or the assay’s lowest sensitivity
value was entered as the non-detectable value. The ATV
group had improvement in the markers for heart rate
variability, but this was not statistically significant. Unfor-
nately, because of technical difficulties, only 10 patients
had a complete set of tapes.

There was greater reduction in hsCRP and oxLDL, as
would be expected for the ATV group. A total of 9 of 15
patients had a decrease in hsCRP in the ATV group, and 5
of 15 for the placebo group. A total of 9 of 15 patients also
had a decrease in oxLDL, as compared with 6 of 15 for the
placebo group.

**Table 1. Patient Demographics**

| Age (yrs) | 56 ± 11 |
| Male/female | 9/6 |
| Heart rate (beats/min) | 74 ± 8 |
| NYHA functional class I/II/III | 1/12/2 |
| 6-min walk test (feet) | 1,627 ± 212 |
| LVEF (%) | 25 ± 9 |
| SBP (mm Hg) | 130 ± 23 |
| DBP (mm Hg) | 70 ± 8 |
| Creatinine (mg/dl) | 1.1 ± 0.2 |
| Sodium (mEq/l) | 141 ± 3.8 |
| Hemoglobin (g/dl) | 13.8 ± 1.1 |
| ACE inhibitors/ARB (n) | 13/15 |
| Hydralazine/nitrates (n) | 1/15 |
| Beta-blockers (n) | 12/15 |
| Aldosterone antagonists (n) | 9/15 |
| Digoxin | 10/15 |
| Loop diuretic | 13/15 |

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; DBP = diastolic blood pressure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SBP = systolic blood pressure.
**DISCUSSION**

Studies evaluating statin therapy in left ventricular dysfunction have shown benefit (1–7). The current study, which investigated the use of high-dose statin therapy in a patient population with modest LDL levels and no other indication for statin therapy, showed neutral effects on surrogate markers of heart failure. A significant decrease in LDL was found, and there was an appropriate trend in hsCRP reduction. However, no clear benefit was seen after the administration of 80 mg ATV in this cohort of patients. Conversely, no detrimental effects were observed after aggressive lipid-lowering therapy and resultant low LDL concentrations.

Our findings were unexpected based on previous studies (6,7,12). One explanation may be the patient population that ended up completing the study. Our patient population was young with a relatively high blood pressure for heart failure patients and a mean LDL of 114 mg/dl. In addition, 9 of 15 patients had a BNP <200 fmol/ml and 8 of 15 patients had an hsCRP <2.6 mg/ml. In addition, the baseline values for a number of our surrogate markers seem to be lower compared with other studies in the literature (13,14). In fact, these markers for the most part were in the range that according to the assay's manufacturer were considered normal. These findings, taken together, suggest a relatively healthy patient group. In relatively healthy patients already on therapies known to reduce morbidity and mortality, it is unlikely for additional therapy to show large changes in surrogate markers, especially for markers that are already in a normal range.

As previously mentioned, studies specifically in patients with hypercholesterolemia or heart failure have shown benefit in the type of surrogate markers we measured (6,7,12). Obviously, in patients with hypercholesterolemia there is generally an elevated inflammatory state that allows for greater drug effect. In regard to studies in heart failure patients, there are two prospective studies that show a benefit in NICM patients (6,7). The first study compared 10 mg/day of simvastatin (n = 24) with placebo (n = 27) for 14 weeks (6). The results showed improvement in ejection fraction, BNP, and TNF-α. Important differences between this study and the current study include higher LDL (154 ± 18 mg/dl, standard error of the mean), TNF-α, and lower blood pressure. Given these differences, this group of patients is perhaps less healthy, has a higher inflammatory state, and is more likely to respond to statin therapy as compared with our patients. The other study evaluated eight NICM patients receiving 0.4 mg cerivastatin compared with seven patients receiving placebo for 20 weeks (7). The mean LDL was 136.9 ± 15.67 mg/dl (standard error of the mean). Significant effects were observed in the statin group regarding reduction in hsCRP and TNF-α, but no difference in sICAM or LDL. Similar to the other study, patients in this study had higher LDL levels.

A concern regarding the use of cholesterol-lowering agents is that significantly decreasing LDL may be detrimental in the setting of heart failure. Reducing the number of lipoproteins too low may prevent significant binding and detoxification of endotoxins, resulting in further activation of proinflammatory mediators and progression of heart failure (10). Another concern specific to statin therapy is the hypothesis that statins may reduce coenzyme Q10 concentrations, which may decrease adenosine triphosphate and lead to the progression of heart failure. This is debatable, and the majority of the evidence at this time does not support this concept (1–7,15–17). The results from our study do not support either of these hypotheses. This is the

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**Table 2. LDL and Markers for Heart Failure, Inflammation, Endothelial Activation, Endothelial Function, and Vagal Tone**

<table>
<thead>
<tr>
<th>Parameters (Baseline Ranges)</th>
<th>ATV-B</th>
<th>ATV</th>
<th>PBO-B</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (55–161 mg/dl)</td>
<td>110 ± 27</td>
<td>55 ± 18*</td>
<td>112 ± 29</td>
<td>115 ± 38</td>
</tr>
<tr>
<td>BNP (50–625 fmol/ml)</td>
<td>242 ± 191</td>
<td>228 ± 197</td>
<td>246 ± 182</td>
<td>247 ± 206</td>
</tr>
<tr>
<td>hsCRP (ND–11.7 ng/ml)</td>
<td>4.5 ± 3.7</td>
<td>3.9 ± 3.1</td>
<td>5.1 ± 4.0</td>
<td>5.8 ± 3.2</td>
</tr>
<tr>
<td>oxLDL (18–117 u/l)</td>
<td>64 ± 29</td>
<td>55 ± 30</td>
<td>60 ± 28</td>
<td>61 ± 28</td>
</tr>
<tr>
<td>sTNF-R1 (587–2,377 pg/ml)</td>
<td>1,286 ± 511</td>
<td>1,361 ± 447</td>
<td>1,216 ± 368</td>
<td>1,271 ± 388</td>
</tr>
<tr>
<td>TNF-α (0.91–3.23 pg/ml)</td>
<td>1.66 ± 0.6</td>
<td>1.73 ± 0.5</td>
<td>1.97 ± 0.8</td>
<td>1.82 ± 0.4</td>
</tr>
<tr>
<td>P-selectin (ND–110 ng/ml)</td>
<td>30 ± 19</td>
<td>23 ± 20</td>
<td>34 ± 33</td>
<td>31 ± 22</td>
</tr>
<tr>
<td>sICAM (208–414 ng/ml)</td>
<td>276 ± 37</td>
<td>277 ± 46</td>
<td>280 ± 48</td>
<td>276 ± 63</td>
</tr>
<tr>
<td>sVCAM (238–1,017 ng/ml)</td>
<td>506 ± 120</td>
<td>514 ± 144</td>
<td>494 ± 172</td>
<td>519 ± 183</td>
</tr>
<tr>
<td>FMD (%)</td>
<td>4.9 ± 4.4</td>
<td>3.3 ± 3.8</td>
<td>4.2 ± 2.9</td>
<td>2.4 ± 2.9</td>
</tr>
<tr>
<td>NMD (%)</td>
<td>14.8 ± 6.1</td>
<td>13.2 ± 6.2</td>
<td>12.8 ± 5.2</td>
<td>16.6 ± 9.7</td>
</tr>
<tr>
<td>SDNN (ms)</td>
<td>116 ± 37</td>
<td>133 ± 66</td>
<td>131 ± 40</td>
<td>112 ± 25</td>
</tr>
<tr>
<td>SDANNS (ms)</td>
<td>102 ± 27</td>
<td>117 ± 50</td>
<td>117 ± 32</td>
<td>98 ± 19</td>
</tr>
<tr>
<td>RMSSD (ms)</td>
<td>52 ± 47</td>
<td>59 ± 70</td>
<td>53 ± 52</td>
<td>50 ± 33</td>
</tr>
</tbody>
</table>

*p < 0.05 vs. all groups. The range for analysis of variance p values, excluding LDL, was 0.181 to 0.994.

ATV = atorvastatin treatment; ATV-B = atorvastatin baseline; BNP = N-terminal pro brain natriuretic peptide; FMD = flow mediated dilation; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; ND = not detectable; NMD = nitroglycerine mediated dilation; oxLDL = oxidized LDL antibody; PBO = placebo; PBO-B = placebo baseline; RMSSD = square root of the sum of the squares of differences between adjacent normal-to-normal intervals; SDANNS = standard deviation of all normal-to-normal intervals in all 5-min segments; SDNN = standard deviation of all normal-to-normal intervals; sICAM = soluble intracellular adhesion molecule; sTNF-R1 = soluble receptor tumor necrosis factor; sVCAM = soluble vascular adhesion molecule; TNF-α = tumor necrosis factor alpha.
first trial that has evaluated high-dose statin therapy in NICM. Despite having extremely low LDL concentrations, there were no negative outcomes observed.

In contrast to the above argument, it could be rationalized that our neutral effect is in a sense a negative effect. Significant reductions in LDL and coenzyme Q10 levels prevented the study from showing positive results. To directly answer these questions, a dose-response trial is required. However, it is reassuring that if aggressive lipid lowering is required, further activation of inflammatory state or heart failure progression (as measured by BNP) does not occur.

There are a number of limitations in this study, including a small sample size. However, given the findings of our study (small differences and large standard deviations), a reasonable increase in the sample size is unlikely to change the conclusions, with the exception perhaps of heart rate variability and hsCRP. For example, to show a difference of 0.05, 0.2 in BNP or sICAM based on our results, more than 1,000 patients would need to be studied. In contrast, for hsCRP, the number would be <100 patients. Another limitation is that this was not a dose-response trial, and not all of statins' pleiotropic effects were measured (e.g., interleukin-6). Finally, there is the inherent limitation of using surrogate markers in a short-term trial in place of long-term morbidity and mortality endpoints.

Overall, HMG-CoA reductase inhibition does not seem to have a major effect on the markers of heart failure, inflammation, or endothelial activation, and does not improve endothelial function or vagal tone in this cohort of NICM patients. Based on these findings, it seems that the administration of high-dose statins for the treatment of heart failure in this relatively healthy heart failure population may be of limited short-term benefit as determined by the surrogate markers measured. Higher-risk patients, such as patients with ischemic cardiomyopathy or with diabetes and either ischemic or NICM, may show greater benefit with statin therapy. Importantly, no apparent negative consequences were observed after aggressive HMG-CoA reductase inhibition and resultant low LDL concentrations. However, the lack of an apparent benefit may also relate to the resultant low LDL concentrations. Further studies are needed to determine whether there is an appropriate patient population and optimal dose (LDL concentration) for the treatment of systolic heart failure with statin therapy.

References