Combined Treatment with Fibrates and Small Doses of Atorvastatin in Patients with Mixed Hyperlipidemia

George Liamis¹, Anna Kakafika¹, Eleni Bairaktari², George Miltiadous¹, Vasilios Tsimihodimos¹, John Goudevenos¹, Apostolos Achimastos³ and Moses Elisaf⁴

¹Department of Internal Medicine, University of Ioannina, Greece
²Laboratory of Biochemistry, Medical School, University of Ioannina, Greece
³Third Department of Medicine, University of Athens, Greece

Address for correspondence: Prof. Moses Elisaf, Professor of Medicine, Department of Internal Medicine, University of Ioannina, 451 10 Ioannina, Greece. Tel. 06510-097509; Fax 06510-097016

Key words: Atorvastatin – Fibrates – Combination therapy – Mixed hyperlipidemia

SUMMARY

Combined statin and fibrate therapy is often imperative for the improvement of the serum lipid profile in patients with mixed hyperlipidemia. However, the potential risk of myopathy has limited the widespread use of such therapy. Preferably this treatment should involve low optimally tolerable doses of hypolipidemic drugs. Thus, we undertook a study to determine the safety and efficacy of combination therapy with fibrates and small doses of atorvastatin. Twenty-two patients with mixed hyperlipidemia were started on a fibrate regimen (micronised fenofibrate 200 mg/day or ciprofibrate 100 mg/day). Because after 12 weeks of therapy the fibrate failed to normalise the serum lipid profile, small doses of atorvastatin (5 mg/day) were added for a further 12 weeks.

Introduction

Mixed hyperlipidemia with elevations of both LDL-cholesterol and triglycerides is commonly encountered in patients with premature coronary heart disease (CHD)¹. Patients with mixed lipid disorders are often refractory to lipid-lowering monotherapy and warrant a more aggressive treatment through combination regimens². However, an increased risk of side-effects, mainly myopathy and/or rhabdomyolysis, has been reported after such combination regimens³,⁴. Ideally, combination therapy requires the careful administration of low optimally tolerable doses of hypolipidemic drugs⁵.

The most potent triglyceride-lowering agents available – fibrates – are the drugs of choice in patients with raised triglycerides⁶,⁷. However, LDL-cholesterol levels often remain inappropriately high after their administration⁸,⁹. There are limited data concerning the combination of atorvastatin with
fibrates. In all these studies, conventional doses of atorvastatin (10–40 mg/day) were used. We undertook the present study to assess the safety and efficacy of combination treatment with fibrates and small doses of atorvastatin (5 mg/day) in patients with primary mixed hyperlipidemia.

Materials and Methods

Twenty-two patients with primary mixed hyperlipidemia, consisting of elevated total and LDL-cholesterol levels (> 240 mg/dl (6.22 mmol/l) and > 160 mg/dl (4.14 mmol/l), respectively) and triglycerides (> 250 mg/dl (2.82 mmol/l)) after a 3-month hypolipidemic diet, were included in our study. Patients with diabetes mellitus (fasting glucose > 126 mg/dl (6.93 mmol/l)), renal failure (serum creatine > 1.6 mg/dl (142 μmol/l)), liver disease (increased serum liver enzymes more than twice the upper limit of normal), hypothyroidism (TSH > 4.8 μU/ml (4.8 mU/l)), increased levels of creatinim kinase (CK) (more than twice the upper normal limits), as well as patients on drugs that could affect serum lipid parameters, were excluded.

Because of the marked increase in serum triglycerides, patients were started on a fibrate (micronised fenofibrate 200 mg/day, n = 11 or ciprofibrate 100 mg/day, n = 11). As after 12 weeks of therapy the fibrate failed to achieve the desired end-point (LDL-cholesterol < 130 mg/dl (3.37 mmol/l)), small doses of atorvastatin (5 mg/day) were added for a further 12 weeks. Fibrate was given in the morning, while atorvastatin was given in the evening. Before treatment, as well as after 12 and 24 weeks of therapy, blood samples were obtained after a 14 h overnight fast for the determination of the serum lipid profile, as well as liver and muscle enzymes. Hepatic toxicity was defined as the marked elevation of the transaminase levels to more than three times the upper limit of normal. Myopathy was defined as symptomatic myositis associated with a CK elevation greater than ten times the upper limits of normal.

Statistical Analysis

Descriptive statistics were performed and all data were expressed as mean ± standard deviation (SD). Treatment effects were tested with a paired t-test for normally distributed data or with the Wilcoxon signed-rank test for non-normally distributed data, which included serum triglycerides, alanine aminotransferase (SGPT), aspartate aminotransferase (SGOT), gamma-glutamyl transpeptidase (γ-GT) and alkaline phosphatase.

Laboratory Determinations

Concentrations of total cholesterol and triglycerides were determined enzymatically on the Olympus AU600 clinical chemistry analyser (Olympus Diagnostica, Hamburg, Germany). High-density lipoprotein (HDL)-cholesterol was determined in the supernatant, after precipitation of the ApoB-containing lipoproteins with dextran sulphate–Mg2+ (Sigma Diagnostics, St. Louis, Mo, USA). Low-density lipoprotein (LDL)-cholesterol was calculated using the Friedewald formula. Apolipoproteins A1, B and E were measured with a Behring Nephelometer BN100, and reagents (antibodies and calibrators) from Dade Behring Holding GmbH (Liederbach, Germany). The ApoA1 and ApoB assays were calibrated according to the International Federation of Clinical Chemistry (IFCC) standards. Lipoprotein(a) (Lp(a)) levels were determined by the enzyme immunoassay Macra Lp(a) (Trinity Biotech, Jamestown, NY, USA). The lower limit of detectability was 0.8 mg/dl (0.008 g/l). Liver and muscle enzymes were measured using conventional methods.

Results

The administration of fibrates was followed by a small, though significant, decrease in total and LDL-cholesterol levels (11.6% and 8%, respectively), a considerable decrease in serum triglycerides (43%), and a marked increase in HDL-cholesterol levels (19.4%). Furthermore, a significant decrease in serum alkaline phosphatase was evident, though the other liver or muscle enzymes were unchanged. No significant differences in the changes of serum lipid parameters were observed between the two fibrates used (fenofibrate and ciprofibrate).

The addition of atorvastatin (5 mg/day) resulted in a significant further decrease in total cholesterol (by 21.5%) and LDL-cholesterol (by 21.9%). A small decrease in serum triglycerides was also observed (by 8.8%).

Fifteen out of the 22 patients achieved the desired LDL-cholesterol levels (< 130 mg/dl (3.37 mmol/l)) according to the recently published NCEP ATP III guidelines.

Combination therapy was well tolerated. No episodes of myopathy or profound aminotransferases elevation of more than three times the upper limit of normal occurred. Furthermore, small insignificant increases in the activity of muscle and liver enzymes was observed. The results are summarised in Table 1.

Unlike ciprofibrate administration, fenofibrate administration caused a significant decrease in serum uric acid levels (6.4 ± 1.6 mg/dl vs. 4.5 ± 1.2 mg/dl)
The addition of atorvastatin was followed by a small insignificant decrease in serum uric acid levels (5.3 ± 1.3 mg/dl vs. 5.0 ± 0.9 mg/dl, p = 0.005). The addition of atorvastatin was followed by a small insignificant decrease in serum uric acid levels (5.3 ± 1.3 mg/dl vs. 5.0 ± 0.9 mg/dl, p = 0.005). The small further decrease in serum triglycerides after atorvastatin administration could be related to the low dose of the drug used, since the triglyceride-lowering effect of statins is dose dependent. However, it could also be ascribed to the co-administration of fibrates, which may limit the ability of atorvastatin to further affect the metabolism of triglyceride-rich lipoproteins. Further studies are needed to clarify this issue better. It is worth mentioning that low-dose combination therapy in patients with normal renal function, who are not given medications that could increase the circulating levels of either the statin or the fibrate, is in agreement with the recent NCEP ATP III guidelines.

We conclude that many patients with dyslipidemia, who do not achieve target level with monotherapy, may benefit from combination regimens. In this setting, the careful administration of small doses of atorvastatin, in patients with mixed dyslipidemia receiving fibrates, is associated with a combination regimens reported in the literature. The small further decrease in serum triglycerides after atorvastatin administration could be related to the low dose of the drug used, since the triglyceride-lowering effect of statins is dose dependent.

### Discussion

Our study showed for the first time that even small doses of atorvastatin (5 mg/day) could significantly improved the serum lipid profile of patients with mixed hyperlipidemia receiving fibrates. The absence of toxicity, possibly related to the low statin dose, permits the use of this combination therapy in patients at high risk of atherosclerotic complications. Even though a number of studies have demonstrated that statin–fibrate regimens markedly ameliorate mixed lipid disorders, atorvastatin was infrequently used in these combinations, and when used, higher doses (20–40 mg) of this statin were administered. In the present study, the low dose combination therapy conferred lipid-altering benefits of a similar magnitude with those reported in the literature after combination therapy with conventional doses of statins and fibrates. Thus, beyond the LDL-cholesterol reduction by approximately 30%, a pronounced increase in HDL-cholesterol by 22% was observed; the latter increase is in turn superior to that observed after most of the combination regimens reported in the literature.

### Table 1. Effect of hypolipidemic drugs on the serum lipid profile and serum liver and muscle enzymes

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline values</th>
<th>After fibrate administration</th>
<th>After combination treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>299 ± 59</td>
<td>264 ± 48&lt;sup&gt;2&lt;/sup&gt;</td>
<td>218 ± 27&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>199 ± 38</td>
<td>183 ± 45&lt;sup&gt;2&lt;/sup&gt;</td>
<td>141 ± 20&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>36 ± 9</td>
<td>43 ± 11&lt;sup&gt;4&lt;/sup&gt;</td>
<td>44 ± 9</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>317 ± 73</td>
<td>181 ± 81&lt;sup&gt;3&lt;/sup&gt;</td>
<td>165 ± 88</td>
</tr>
<tr>
<td>AST (IU/l) {reference range 5–40 IU/l}</td>
<td>23 ± 7</td>
<td>27 ± 6</td>
<td>23 ± 3</td>
</tr>
<tr>
<td>ALT (IU/l) {reference range 5–40 IU/l}</td>
<td>26 ± 11</td>
<td>31 ± 16</td>
<td>26 ± 10</td>
</tr>
<tr>
<td>γ-GT (IU/l) {reference range 10–52 IU/l}</td>
<td>20 ± 7.6</td>
<td>24 ± 14</td>
<td>21 ± 14</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/l)</td>
<td>57 ± 9</td>
<td>49 ± 9&lt;sup&gt;2&lt;/sup&gt;</td>
<td>48 ± 7</td>
</tr>
<tr>
<td>CPK (IU/l) {reference range 90–190 IU/l}</td>
<td>97 ± 4</td>
<td>124 ± 20</td>
<td>151 ± 41</td>
</tr>
</tbody>
</table>

<sup>1</sup>p < 0.001 compared to values obtained after fibrate administration  
<sup>2</sup>p < 0.05,  
<sup>3</sup>p < 0.01,  
<sup>4</sup>p < 0.001 compared to baseline values  
To convert to mmol/l, multiply by 0.0259 for cholesterol and by 0.0113 for triglycerides  
To convert to μkat/l, multiply by 0.01667 for AST, ALT, γ-GT, alkaline phosphatase and CPK
significant amelioration of lipid abnormalities. This low-dose combination therapy is possibly associated with improved safety and tolerability profile in comparison with escalation doses of monotherapy with each compound. However, such treatment should be administered with appropriate caution and combined clinical and laboratory monitoring. Even though combination drug treatment was well tolerated in our study with either of the fibrates used, micronized fenofibrate may be preferable since its half-life is shorter (20–22 h) than ciprofibrate (80 h). This is of special importance taking into account the increased half-life of atorvastatin (12–14 h).

References

16. Smit JW, Jansen GH, de Bruin TW, Erkelens DW. Treatment of combined hyperlipidemia with fluvastatin and gemfibrozil, alone or in combination, does not induce muscle damage. Am J Cardiol 1995;76:126A-128A
20. Tuzol S, Wang LD, Kastelein JJ. Tolerability and efficacy of gemfibrozil and simvastatin combination therapy in 263 dyslipidemic patients attending a lipid clinic. 66th Congress of the European Atherosclerosis Society 1996;Florence, Italy