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Published in:
Heart

DOI:
10.1136/heart.88.3.234

Link to publication

Citation for published version (APA):
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*Heart* 2002;88:234-238
doi:10.1136/heart.88.3.234

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Long term efficacy and safety of atorvastatin in the treatment of severe type III and combined dyslipidaemia

M van Dam, M Zwart, F de Beer, A H M Smelt, M H Prins, M D Trip, L M Havekes, P J Lansberg, J J P Kastelein

Background: Fibric acid derivatives and HMG-CoA reductase inhibitors are effective in combination for treating patients with familial dysbetalipoproteinaemia and severe combined dyslipidaemia, but combination therapy affects compliance and increases the risk of side effects.

Aim: To evaluate the efficacy and safety of monotherapy with atorvastatin, an HMG-CoA reductase inhibitor with superior efficacy in lowering low density lipoprotein cholesterol and triglyceride concentrations, in patients with dysbetalipoproteinaemia and severe combined dyslipidaemia.

Methods: Atorvastatin was tested as single drug treatment in 36 patients with familial dysbetalipoproteinaemia and 23 patients with severe combined dyslipidaemia.

Results: After 40 weeks of 40 mg atorvastatin treatment decreases in total cholesterol, triglycerides, and apolipoprotein B of 40%, 43%, and 41%, respectively, were observed in the combined dyslipidaemia group, and of 46%, 40%, and 43% in the dysbetalipoproteinaemic patients. Target concentrations of total cholesterol (<5 mmol/l) were reached by 63% of the patients, and target concentrations of triglycerides (<3.0 mmol/l) by 66%. Treatment with atorvastatin was well tolerated and no serious side effects were reported.

Conclusions: Atorvastatin is very effective as monotherapy in the treatment of familial dysbetalipoproteinaemia and severe combined dyslipidaemia.
METHODS

Patients

We recruited consecutive patients with a tentative diagnosis of dysbetalipoproteinaemia at the lipid research clinic of the University of Amsterdam (Academic Medical Centre and Slotervaart Training Hospital) by retrieving patient records from our clinical database. Eligible patients were men and women between 18 and 80 years of age with a diagnosis of probable dysbetalipoproteinaemia. This diagnosis was made when a patient presented with severe combined dyslipidaemia (both total cholesterol and triglyceride concentrations significantly above the 95th percentile for age and sex), occasionally typical xanthomas, and in many cases atherosclerotic vascular disease. All eligible patients were informed about atorvastatin and asked to participate in the study. Patients with poorly controlled diabetes mellitus, hypothyroidism, and hepatic or renal dysfunction were excluded. Pregnant or breast feeding women were also excluded.

Before entry to the study and at its completion, all patients underwent a complete physical examination and were counselled on the use of a lipid lowering diet, according to the Dutch national guidelines. Written informed consent was obtained from all patients.

Study design

At the start of the study all lipid lowering drugs were discontinued for eight weeks. After this, baseline lipids, apolipoproteins, and apo E genotyping were undertaken in all patients, together with routine biochemistry. Upon confirmation of homozygosity for apo E2 (arg 158→cys) (E2/E2) or the apo E2 variant (lys 146→gln), lipoprotein ultracentrifugation was performed. Subsequently, atorvastatin was prescribed, and patients were examined at regular 12 week intervals, concluding at week 40.

At all visits, the patients were questioned about adherence to the diet and possible side effects of the drug treatment. They were counselled on the use of a lipid lowering diet, according to the Dutch national guidelines. Written informed consent was obtained from all patients.

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
</tr>
<tr>
<td>Age (years) [range]</td>
</tr>
<tr>
<td>Male/female (%)</td>
</tr>
<tr>
<td>Postmenopausal status (%)</td>
</tr>
</tbody>
</table>

Vital signs

| Body mass index (kg/m²)*                                                     | 27.2 (4.6)                               |
| Systolic blood pressure [mm Hg]*                                            | 128 (10.5)                               |
| Diastolic blood pressure [mm Hg]*                                          | 81.5 (5.4)                               |

Apolipoprotein E genotype†

<table>
<thead>
<tr>
<th>Apo E genotype‡</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>E2/E2</td>
<td>34</td>
</tr>
<tr>
<td>E2/lys146→cys</td>
<td>2</td>
</tr>
<tr>
<td>E2/lys146→gln</td>
<td>16</td>
</tr>
<tr>
<td>E2/E4</td>
<td>7</td>
</tr>
</tbody>
</table>

*Values are given as mean (SD); †apo E genotypes are given in absolute numbers.

Figure 1 Lipoprotein and apolipoprotein concentrations before and after atorvastatin treatment in patients with combined dyslipidaemia. Mean values are given; triglyceride values were log transformed before statistical analysis.

40 weeks of treatment) and were analysed at TNO-PG, Gaubius Laboratory, Leiden. After completion of the study we compared our results with those of other pharmacological studies already performed in patients with FD and to previous lipid results in our patient cohort.

Lipid and apolipoprotein measurements

Total plasma cholesterol was determined by an enzymatic polarimetric procedure using cholesterol esterase and cholesterol oxidase (CHOD-PAP Boehringer Mannheim, Mannheim, Germany). HDL cholesterol was determined after precipitation of apo B containing lipoproteins, using phosphotungstic acid and magnesium ions. Triglycerides were quantified by an enzymatic colorimetric procedure using lipase, glycerokinase, and glycerol-3-phosphate oxidase. Apo A1 and apo B were measured by immunonephelometry.

Lipoprotein analysis

Blood samples were collected in EDTA tubes and placed on melting ice. Plasma was obtained by centrifugation at 1500 g for 10 minutes at 4°C within four hours after sampling. Plasma samples were then brought to a final concentration of 10% (wt/vol) sucrose, capped under nitrogen, snap frozen in liquid nitrogen, and stored at −80°C until further analysis. Under these conditions, lipoprotein size and biological properties have been shown to remain intact for months. Separation of lipoproteins was done by density gradient ultracentrifugation according to Zhao and colleagues, with slight modifications. Briefly, the gradient consisted of 2 ml plasma (adjusted to d = 1.21 g/ml by adding 0.65 g KBr), overlaid by 5 ml of d = 1.03 g/ml, 3.5 ml of d = 1.006 g/ml, and 1.5 ml of d = 1.00 g/ml solutions. The gradient was centrifuged at 285 000 ×g in a SW-40 swingout rotor (Beckman, Geneva, Switzerland) for 18 hours at 4°C. The gradient was then divided into fractions of 0.5 ml. In each fraction, cholesterol and triglyceride concentrations were measured with enzymatic assay kits (Boehringer Mannheim).

Apolipoprotein E phenotyping and genotyping

Homozygosity for the apo E2 (arg 158→cys) isoform was determined by isoelectric focusing of delipidated serum samples followed by immunoblotting with a polyclonal anti-apo E antiserum, and confirmed by apo E genotyping as previously described by Reymer and colleagues. Identification of the apo E2 variant (lys 146→gln) was by polymerase chain reaction using a mutagenic amplification primer assay followed by digestion with restriction enzyme Pvu II as described previously.

Statistical analysis

The analyses, which were done using SAS 6.1.2, addressed the change in lipid and apolipoprotein variables and lipoprotein
subfractions before and after atorvastatin treatment. Before analysis, triglyceride, VLDL-C, VLDL-TG, and IDL-TG values were logarithmically transformed. Untransformed concentrations are reported in the tables. Significance was assessed at the 5% level of probability.

RESULTS
Patient characteristics
Fifty nine patients (43 men and 16 women) were included in the study. Clinical and biochemical baseline characteristics are summarised in table 1. The mean age of the patients was 51.5 years (range 28–79 years) and mean (SD) body mass index

**Table 2** Lipoprotein subfractions before and after atorvastatin treatment in patients with dysbetalipoproteinaemia

<table>
<thead>
<tr>
<th>Subfraction</th>
<th>Baseline (n=28)</th>
<th>Atorvastatin 40 mg (n=28)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL-C* (mmol/l)</td>
<td>4.24 (3.39)</td>
<td>1.72 (2.11)</td>
<td>0.0001</td>
</tr>
<tr>
<td>IDLC (mmol/l)</td>
<td>1.80 (0.80)</td>
<td>0.89 (0.38)</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDLC (mmol/l)</td>
<td>1.87 (0.56)</td>
<td>1.16 (0.47)</td>
<td>0.0001</td>
</tr>
<tr>
<td>VLDL-TG* (mmol/l)</td>
<td>1.08 (0.28)</td>
<td>1.19 (0.32)</td>
<td>0.06</td>
</tr>
<tr>
<td>IDLTG* (mmol/l)</td>
<td>4.08 (4.00)</td>
<td>2.21 (1.70)</td>
<td>0.0014</td>
</tr>
<tr>
<td>VLDL/C-TG (ratio)</td>
<td>0.59 (0.24)</td>
<td>0.32 (0.14)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Values are mean (SD).


**Figure 2** Lipoprotein and apolipoprotein concentrations before and after atorvastatin treatment in patients with dysbetalipoproteinaemia. Mean values are given; triglyceride values were log transformed before statistical analysis.

known to be taking one or more drugs that might affect lipid metabolism, including β blocking agents (n = 18), diuretics (n = 6), and oral contraceptives (n = 7). These drugs were prescribed continuously during the course of the study. None of the postmenopausal women who were participating were taking hormone replacement therapy.

Fifty patients completed the study. Five patients dropped out because of adverse events: three patients had gastric complaints (all E2/E3 or E2/E4), one suffered from psychological problems (E2/E2), and one developed viral hepatitis (E2/E2).

Four patients (all E2/E3 or E2/E4) dropped out because of non-compliance.

Efficacy
Lipids and lipoproteins
At 40 weeks of treatment, the efficacy of atorvastatin 40 mg was examined in both patient groups (figs 1 and 2). A significant decrease in total cholesterol, triglycerides, and apo B (by 40%, 43%, and 41%, respectively) was observed in the combined dyslipidaemia group (fig 1); all reductions were highly significant (p < 0.0002). Reductions were also seen for total cholesterol, triglycerides, and apo B concentrations (by 46%, 40%, and 43%, respectively; p = 0.0001) in patients with dysbetalipoproteinaemia (fig 2). Target concentrations of total cholesterol (< 5 mmol/l) were reached by 63% of patients, and target concentrations of triglycerides (< 3 mmol/l) by 66%.

Lipoprotein subfractions
In patients with homozygosity for apo E2 and heterozygous carriers of the apo E2 (lys 146→glu) variant, the efficacy of atorvastatin on lipoprotein subfractions was examined at baseline and after 40 weeks. A significant decrease was observed in almost all lipoprotein subfractions (table 2). For LDL-C, VLDL-C, and IDL-C these reductions were 38%, 59%, and 51%, respectively (p = 0.0001). The VLDL-C to triglycerides ratio, an important marker of dysbetalipoproteinaemia, decreased from 1.15 at baseline to 0.79 after 40 weeks of atorvastatin treatment.

**Table 3** Safety indices before and after atorvastatin treatment in patients with dysbetalipoproteinaemia and combined dyslipidaemia

<table>
<thead>
<tr>
<th>Safety indices</th>
<th>Baseline</th>
<th>Atorvastatin 40 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALAT (U/l)</td>
<td>54 (23)</td>
<td>23 (16)</td>
</tr>
<tr>
<td>ASAT (U/l)</td>
<td>19 (11)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>CPK (U/l)</td>
<td>197 (73)</td>
<td>124 (19)</td>
</tr>
</tbody>
</table>

Values are mean (SD).

ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; CPK, creatinine phosphokinase.
Side effects and tolerance

Treatment with atorvastatin was well tolerated. Eleven of the 59 patients reported side effects that could possibly be related to the treatment. Three suffered from gastric complaints, another four had joint or muscle complaints, and two had a rash, though in one of these it was probably related to moisturising products. One patient suffered from impotence. The three patients with gastric complaints all dropped out, as did the patient with psychological problems and the patient with viral hepatitis.

Other reported side effects, all occurring during the first eight weeks of treatment, disappeared during the course of the study. Clinical laboratory changes were minimal in both study groups. There was no clinically significant increase in creatinine phosphokinase activity (that is, to more than three times the upper limit of normal (193 U/l)). Only γ-glutamyl transferase (γ-GT) showed mild increases in four patients after the first eight weeks of treatment. These disappeared during the study. In one subject the γ-GT value exceeded three times the upper limit of normal (58 U/l) and remained high, most probably because of a high alcohol intake. Mean baseline and 40 week concentrations of alanine aminotransferase, asparagine aminotransferase, and creatine phosphokinase are given in table 3. None of the differences reached significance.

DISCUSSION

We have studied the efficacy and safety of atorvastatin in patients with severe combined dyslipidaemia and dysbetalipoproteinemia. Our findings show that this drug is a very effective cholesterol and triglyceride lowering agent in the treatment of both groups of patients. Target concentrations of total cholesterol (< 5 mmol/l) were reached in 63% of patients, and of triglycerides (< 3 mmol/l) in 66% of patients.

FD comprises a separate nosological entity in the spectrum of severe combined dyslipidaemia, with an extremely atherogenic lipoprotein profile and therefore a high risk of premature atherosclerosis. It should be managed aggressively with lipid lowering treatment and is usually responsive to such interventions. First line treatment should be diet and lifestyle adjustments, followed by the correction of pre-existing metabolic disorders. In the majority of FD patients, however, lipid lowering drugs are required to control dyslipidaemia. Drugs with proven efficacy in FD include nicotinic acid, clofibrate, fenofibrate, gemfibrozil, lovastatin, and simvastatin. Unfortunately, many patients remain hyperlipidaemic on diet and single drug treatment and often require combination treatment with a fibrac acid derivate and a statin. However, it is well established that combination treatment affects compliance and increases the risk of side effects such as liver dysfunction or myopathy.

Atorvastatin is an established and effective HMG-CoA reductase inhibitor. Clinical studies with this agent have shown that LDL cholesterol concentrations may be decreased by up to 61% at doses of 80 mg, and triglycerides may be reduced by 46%. Furthermore, it has been found recently that atorvastatin reduces both VLDL and LDL apo B production and in addition increases the clearance of triglyceride-rich lipoproteins.

McKenny and colleagues recently reported that atorvastatin is very effective as monotherapy in lowering both cholesterol and triglycerides in patients with combined dyslipidemia. In this study, we addressed the question of whether atorvastatin might also be a good candidate as monotherapy in 23 patients with severe combined dysbetalipoproteinaemia and 36 patients with molecularly diagnosed dysbetalipoproteinemia. In keeping with the results of McKenny and colleagues, atorvastatin showed good efficacy and safety in our patient cohort. In the group with severe combined dyslipidaemia, total cholesterol, triglycerides, and apo B decreased by 40%, 43%, and 41%, respectively, while in the patients with dysbetalipoproteinemia the decreases were 46%, 40% and 43%. Furthermore, VLDL-C and VLDL-TG fell by 59% and 46%, respectively, and IDL-C and IDL-TG by 51% and 46% compared with baseline. The VLDL-C/TG ratio fell from 1.15 to 0.79.

Data on the efficacy of lipid lowering drugs in the treatment of FD are only available for small numbers of patients. The confidence intervals in those studies were large, making it difficult to draw firm conclusions about differences in various therapeutic regimens (table 4). Treatment of FD patients with fibrates generally results in a decrease in total cholesterol of up to 48%, and an increase in HDL of up to 33%. Triglyceride concentrations were decreased by up to 68%. IDL, as a marker of FD, decreased by 34% when treatment with gemfibrozil was initiated. In the treatment of FD with statins, total cholesterol was decreased by up to 46% and HDL was raised by up to 25%. Triglycerides were decreased by up to 42%. IDL showed a reduction of 50% after treatment with simvastatin 20 mg.

We investigated the efficacy of atorvastatin in 36 FD patients, a substantially larger population than previously reported. Moreover these patients were followed for a longer period of time than in most other studies. However, a definite disadvantage of our study is the lack of a control or placebo group. The use of placebo groups in treatment studies of genetic dyslipidaemia is no longer considered ethical, and the relatively small number of FD patients precluded the use of a formal double blind control comparison. We have, however, compared baseline and 40 week lipid and lipoprotein concentrations and have shown highly significant and impressive reductions on 40 mg atorvastatin monotherapy. Side effects were mild and generally transient, as reported for other studies with this drug.

Conclusions

Atorvastatin proved to be both effective and safe when given as monotherapy in the treatment of severe combined dyslipidaemia and familial dysbetalipoproteinemia.

<table>
<thead>
<tr>
<th>Percentage change with drug treatment</th>
<th>Gemfibrozil22</th>
<th>Fenofibrate19</th>
<th>Lovastatin20</th>
<th>Simvastatin21</th>
<th>Atorvastatin28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>+48</td>
<td>+35</td>
<td>+44</td>
<td>+39</td>
<td>+46</td>
</tr>
<tr>
<td>HDL-C (mmol/l)</td>
<td>+13</td>
<td>+33</td>
<td>+25</td>
<td>+18</td>
<td>+10</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>+68</td>
<td>+56</td>
<td>+42</td>
<td>+41</td>
<td>+40</td>
</tr>
<tr>
<td>VLDL-C (mmol/l)</td>
<td>+72</td>
<td>+63</td>
<td>+53</td>
<td>+44</td>
<td>+59</td>
</tr>
</tbody>
</table>

HDL-C, high density lipoprotein cholesterol; VLDL-C, very low density lipoprotein cholesterol.

ACKNOWLEDGEMENTS

We wish to thank R Buyenbek, S Kamerling, M Muller, O Ternede, I. van Vark and T Vroom for their expert technical assistance.

Table 4: Published reports on lipid lowering treatment in familial dysbetalipoproteinemia
REFERENCES


