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**Notes**
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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.

Type III dyslipidaemia or familial dysbetalipoproteinaemia (FD) is a severe disturbance of plasma lipoprotein metabolism associated with premature vascular disease. FD is associated with raised concentrations of both cholesterol and triglycerides because of an accumulation of cholesterol ester enriched chylomicron and very low density lipoprotein (VLDL) remnants (IDL cholesterol).1 FD has a recessive mode of inheritance, a frequency of approximately 1:10 000, and is usually manifested in adulthood. The disease is far more prevalent in men than in women, who usually only present with this disorder after the menopause.1

Almost half the patients with FD have symptoms of premature cardiovascular disease. The distribution of vascular disease differs from that in other genetic lipoprotein disorders, as peripheral vascular disease is as prevalent as coronary artery disease.1,2 The metabolic basis of the accumulation of IDL lies in the impaired clearance of these particles by hepatic lipoprotein receptors. Apolipoprotein E (apo E) is the major ligand for these receptors and mediates chylomicron and VLDL remnant uptake.3 Apo E is a 299 amino acid protein and a major constituent of plasma lipoproteins such as chylomicrons, chylomicron remnants, VLDL, IDL, and high density lipoprotein (HDL).4 Apo E has three major isoforms (E2, E3, and E4). These are all products of alleles at a single gene locus on chromosome 19.5 Apo E3/E3 is the most common genotype and therefore E2 and E4 are considered variants. The apo E3 isoform shows normal binding to the low density lipoprotein (LDL) receptor, while apo E4 binds with a somewhat higher affinity and the apo E2 isoform shows very low affinity.6,7 FD occurs most commonly in association with the apo E2/E2 genotype (> 90%).5–7 However, several rare apo E mutants also lead to dysbetalipoproteinaemia, but usually with a dominant expression (for example, apo E3-Leiden, apo E2 (Lys146→Gln)).8–10

There is a large discrepancy between the occurrence of homozygous apo E2 (1:100) in the general population and the prevalence of FD (1:10 000). Most E2/E2 carriers are either normolipidaemic or even slightly hypocholesterolaemic.1 Other genetic or environmental factors such as a high alcohol intake, obesity, or concomitant diseases (for example, diabetes mellitus or thyroid dysfunction) may be required for the development of the FD phenotype.

Patients with FD have a high risk of premature cardiovascular disease and should thus be treated aggressively.1,3 Fortunately, FD often shows a favourable response to lipid lowering treatment.1 First line treatment is dietary control and weight reduction. However, drugs are often required to control raised concentrations of plasma lipoproteins. Several lipid lowering agents can be given to FD patients, including fibric acid derivatives and HMG-CoA reductase inhibitors.11–14 Often, a combination of these drugs is necessary to normalise both cholesterol and triglyceride concentrations.

Although the use of HMG-CoA reductase inhibitors has mainly been directed at decreasing LDL cholesterol, over the last few years the triglyceride lowering effect of these agents has aroused interest. Recently, it has been shown that statins reduce triglycerides by almost the same percentage as they do LDL cholesterol in hypertriglyceridaemic subjects.15–17 Atorvastatin, an established third generation statin with proven effectiveness in reducing plasma LDL cholesterol and triglyceride concentrations, could thus be well suited to treating patients with FD.18–22

In this study we evaluated the efficacy and safety of atorvastatin monotherapy in outpatients with severe combined dyslipidaemia, among whom a subset had molecularly diagnosed dysbetalipoproteinaemia.

Abbreviations: apo E, apolipoprotein E; C, cholesterol; FD, familial dysbetalipoproteinaemia; HDL, high density lipoprotein; IDL, intermediate density lipoprotein; VLDL, very low density lipoprotein; TG, triglyceride; VLDL, very low density lipoprotein.
women were also excluded. Renal dysfunction were excluded. Pregnant or breast feeding controlled diabetes mellitus, hypothyroidism, and hepatic or disease. All eligible patients were informed about atorvastatin xanthomas, and in many cases atherosclerotic vascular above the 95% centile for age and sex), occasionally typical total cholesterol and triglyceride concentrations significantly patient presented with severe combined dyslipidaemia (both total cholesterol and triglyceride concentrations significantly above the 95% centile 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 disease. Mean values are given; triglyceride values were log transformed before statistical analysis.

40 weeks of treatment) and were analysed at TNO-PG, Gauhus 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.

**METHODS**

**Patients**

We recruited consecutive patients with a tentative diagnosis of dysbetalipoproteinemia 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 dysbetalipoproteinemia. This diagnosis was made when a patient presented with severe combined dyslipidaemia (both total cholesterol and triglyceride concentrations significantly above the 95% centile 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 undertook 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 presence of 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 then had a physical examination. At each visit, blood samples were taken after an overnight fast for the determination of plasma lipids, apolipoproteins, and safety indices. These measurements were done at the central laboratory of both hospitals in Amsterdam. Extra blood samples were drawn from apo E2/E2 subjects or heterozygous carriers of the apo E2 (lys 146→gln) variant to assess the efficacy of atorvastatin towards VLDL, IDL, LDL, and HDL cholesterol and towards VLDL and LDL triglycerides. These ultracentrifugation samples were taken at baseline and at the end of the study (after
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 was 27.2 (4.6) kg/m². Most patients included in the study were of north European descent (97%).

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Thirty four patients were homozygous for the apo E2 genotype and two patients were heterozygous carriers of the apo E2 (lys 146 → gln) variant. The remaining 23 patients either had an apo E2/E3 or an apo E2/E4 genotype. Baseline lipoprotein subfractions of the two groups are shown in figs 1 and 2. Mean plasma lipid concentrations in both groups were Log transformed before statistical analysis.

Mean values are given; triglyceride values were log transformed after statistical analysis.

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

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

<table>
<thead>
<tr>
<th>Lipoprotein 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>IDL-TG* (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>
<tr>
<td>Values are mean (SD).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*VLDL-C, VLDL-TG, and IDL-TG values were log transformed before statistical analysis.</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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 dysbetalipoproteinemia (fig 2). Target concentrations of total cholesterol (< 5 mmol/l) were reached by 63% of patients, and target concentrations of triglycerides (< 2 mmol/l) by 66%.

Lipoprotein subfractions
 In patients with homozygosity for apo E2 and heterozygous carriers of the apo E2 (lys 146 → gln) 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 dysbetalipoproteinemia, 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 dysbetalipoproteinemia and combined dyslipidaemia

<table>
<thead>
<tr>
<th>Safety indices</th>
<th>Baseline (n=28)</th>
<th>Atorvastatin 40 mg (n=28)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALAT (U/l)</td>
<td>54 [23 (16)]</td>
<td>19 [11 (8)]</td>
<td></td>
</tr>
<tr>
<td>ASAT (U/l)</td>
<td>54 [23 (16)]</td>
<td>24 [19 (10)]</td>
<td></td>
</tr>
<tr>
<td>CPK (U/l)</td>
<td>50 [19 (11)]</td>
<td>56 [20 (14)]</td>
<td></td>
</tr>
<tr>
<td>Values are mean (SD). ALAT, alanine aminotransferase; ASAT, aspartic aminotransferase; CPK, creatine phosphokinase.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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, aspartagine 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 dysbetalipoproteinaemia. 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 fibrin 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 dyslipidaemia. In this study, we addressed the question of whether atorvastatin might also be a good candidate as monotherapy in 23 patients with severe combined dyslipidaemia and 36 patients with molecularly diagnosed dysbetalipoproteinaemia. 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 dysbetalipoproteinaemia 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 dysbetalipoproteinaemia.

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