Effects of atorvastatin on dyslipidaemia in uraemic patients on peritoneal dialysis

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Abstract

**Background.** Our purpose was to evaluate the efficacy and safety of atorvastatin, a potent cholesterol- and triglyceride-lowering agent, in peritoneal dialysis patients with dyslipidaemia.

**Methods.** Peritoneal dialysis patients with hypercholesterolaemia were treated for 4 months with atorvastatin at a starting dose of 10 mg. The dose could be increased to 20 or 40 mg in order to achieve the following targets: plasma LDL-cholesterol of 130 mg/dl for primary prevention of coronary heart disease, plasma LDL-cholesterol of 100 mg/dl for secondary prevention, and plasma triglycerides of 200 mg/dl. Plasma lipid profile and liver and muscle enzyme levels were assessed at baseline and then monthly during treatment.

**Results.** Thirty-one patients with hypercholesterolaemia were included (16 males and 15 females; mean age 57±16 years; mean duration of peritoneal dialysis 27±17 months). Nineteen of the patients also had hypertriglyceridaemia and seven had diabetes. Twenty patients had no coronary history (primary prevention), whereas nine had experienced a coronary event (secondary prevention). In the primary and the secondary prevention patients, mean LDL-cholesterol levels (mg/dl) decreased significantly by 42 and 46% from 204±23 to 119±27 (P<0.001) and 198±37 to 104±21 (P<0.001), and mean triglyceride levels (mg/dl) decreased by 37 and 26% from 289±132 to 186±92 (P<0.001) and 201±62 to 150±54 (P<0.001 respectively). Nineteen primary prevention and seven secondary prevention patients achieved the LDL-cholesterol target. The triglyceride target was achieved by 15 of the 19 hypertriglyceridaemic patients. Two patients stopped treatment (one because of gastrointestinal disturbances, the other because of an allergic skin reaction). After 4 months, there were no changes in enzyme levels.

**Conclusion.** Atorvastatin is an effective and safe lipid-lowering agent for peritoneal dialysis patients with mixed dyslipidaemia.

**Keywords:** atorvastatin; hypercholesterolaemia; hyper-triglyceridaemia; mixed dyslipidaemia; peritoneal dialysis

Introduction

Disturbances of lipid metabolism in chronic renal failure patients, especially those on dialysis, are a major concern. Depending on the series, 30–70% of dialysis patients exhibit hypertriglyceridaemia [1,2]. Moreover, peritoneal dialysis (PD) patients additionally are at greater risk of developing hypercholesterolaemia, primarily because of lipoprotein overproduction resulting from both the absorption of dialysate glucose and the loss of proteins into the peritoneal effluent [3–5]. According to a recent meta-analysis, 24% of PD patients have a total plasma cholesterol (TC) level above 240 mg/dl and 45%, a plasma LDL cholesterol (LDL-C) level above 130 mg/dl [6]. These patients’ lipid profiles are also characterized by increased plasma apolipoprotein B (Apo-B) and lipoprotein (a) (Lp(a)) levels [7].

Along with other factors, these anomalies certainly contribute to the accelerated atherosclerosis observed in these patients. This is true for hypercholesterolaemia, which has clearly been shown to be a risk factor for the development of coronary heart disease among the general population. It is also true as concerns hypertriglyceridaemia, which acts synergistically with decreased HDL-cholesterol (HDL-C) levels to raise the coronary risk [8]. Recent studies, however, suggest that hypertriglyceridaemia might even be an independent coronary risk factor [9,10].

The higher than average incidence of potential cardiovascular complications as the leading cause of death among uraemic patients on PD argues strongly in favour of treating lipid disturbances. Caution is no longer acceptable as in the past, when the safety of...
effective hypolipidaemic agents in these patients remained questionable [11].

Hydroxymethylglutaryl-CoA reductase (HMG-CoA reductase) inhibitors that act mainly by lowering cholesterol levels are currently recommended for first-line drug treatment of lipid disturbances in PD patients [6], despite the small number of studies in this population [12,13].

Atorvastatin is a novel synthetic HMG-CoA reductase inhibitor that lowers both cholesterol [14,15] and triglyceride (TG) levels [16]. Because of its potent, twofold action this lipid lowering agent might be of value for the treatment of dyslipidaemic PD patients. We therefore carried out a prospective study to determine the efficacy and safety of this new agent in this patient population.

**Subjects and methods**

Between February and July 1998, all the patients who had been on PD for more than 3 months in our unit were considered for entry into the study. To be eligible for inclusion, patients had to meet the following criteria: hypercholesterolaemia documented by at least two plasma determinations, indication for hypolipidaemic treatment as defined by current guidelines [17,18] (primary prevention for patients with a plasma LDL-C level above 160 mg/dl and two other risk factors; secondary prevention for patients with a plasma LDL-C level ≥130 mg/dl and coronary event), no hypolipidaemic treatment in the previous 3 months, age below 80 years, no history of allergy to statins, no liver disease, no alcohol abuse, no hypothyroidism, no severe progressing disease, no cachexia.

The patients finally included in the study were followed prospectively for 4 months. TC, HDL-C, LDL-C, TG, Apo-A1, Apo-B, and Lp(a) levels were measured before initiating the study treatment. The same parameters were again measured monthly for 4 months. All the patients received a single daily dose of atorvastatin 10 mg at bedtime, starting on the first day of the study and for 1 month. Depending on the response to treatment, the dose could be increased to 20, 40, and 80 mg daily, after 1 and 2 months of treatment, in order to achieve a target LDL-C level of 130 mg/dl in patients receiving primary prevention, or of 100 mg/dl for patients receiving secondary prevention and a target TG level of 200 mg/dl for all patients, as defined in the above-mentioned guidelines [18]. Safety was assessed by clinical and laboratory monitoring before treatment, then once a month (liver and muscle enzyme level determinations: aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transferase, creatine phosphokinase, and aldolase).

Blood samples for lipid determination were drawn after a 12-h fast, and spun. The plasma was divided into three aliquots processed separately. Direct enzymatic determination of TC, HDL-C, and TG was performed on the first aliquot using a fully automated Kone analyser (KoneLab, Finland). The second aliquot was ultracentrifuged to separate out the VLDL fraction from the HDL and LDL fractions. The recovered HDL and LDL fractions were then used for enzymatic determination of cholesterol on a Kone analyser. LDL-C level was determined by subtracting the value for HDL-C obtained by enzymatic assay in the first aliquot from the value for cholesterol in the HDL and LDL fractions obtained by enzymatic assay in the second aliquot. Apo-A1 and Apo-B levels were determined by nephelometry. Lp(a) levels were determined by radial diffusion electrophoresis.

Student’s t-test for paired variables or Wilcoxon’s non-parametric test were used to compare the differences between lipid parameters at baseline and on treatment. Results are expressed as means with the standard deviations and as mean percentage decrease.

**Results**

One hundred and three patients were evaluated during the screening period. Of these, 61 (59%) were eligible for inclusion because their cholesterol level met the inclusion criteria, and 29 (28%) had triglyceride levels greater than 200 mg/dl.

Thirty of the eligible patients were not included for the following reasons: previously treated dyslipidaemia (11 patients), age 80 years or more (10 patients), concomitant progressing disease (8 patients), statin allergy (1 patient).

Thirty-one patients were finally included: 16 males and 15 females. Mean age was 57 ± 16 years and mean duration of PD treatment was 27 ± 17 months. Twenty-two patients warranted primary prevention and nine, secondary prevention. Nineteen patients had plasma triglyceride levels above 200 mg/dl, and nine were diabetic.

Twenty-nine of the 31 included patients were treated and followed for at least 4 months. The PD protocol remained unchanged throughout the study. Two primary prevention patients were withdrawn from treatment within 1 month, because of treatment-related adverse effects. The study treatment dosage was limited to a maximum of 40 mg because of transient adverse effects in the only patient who received atorvastatin at a dosage of 80 mg.

In the 29 patients who received treatment for 4 months, a significant decrease with respect to baseline was observed for TC, LDL-C, TG, and Apo-B after 1 month of treatment with atorvastatin 10 mg daily (Table 1), whereas no significant change was observed in HDL-C, Apo-A1, and Lp(a) levels.

At the end of 4 months, nine patients were receiving

<table>
<thead>
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<th>Day 0</th>
<th>Month 1</th>
<th>Δ (%)</th>
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<tbody>
<tr>
<td>CT</td>
<td>296 ± 29</td>
<td>211 ± 33</td>
<td>-29</td>
</tr>
<tr>
<td>HDL-C</td>
<td>45 ± 11</td>
<td>44 ± 12</td>
<td>-2.5</td>
</tr>
<tr>
<td>LDL-C</td>
<td>202 ± 28</td>
<td>129 ± 30</td>
<td>-36</td>
</tr>
<tr>
<td>TG</td>
<td>262 ± 121</td>
<td>196 ± 72</td>
<td>-22</td>
</tr>
<tr>
<td>Apo-A1</td>
<td>143 ± 24</td>
<td>132 ± 19</td>
<td>-6</td>
</tr>
<tr>
<td>Apo-B</td>
<td>154 ± 25</td>
<td>118 ± 28</td>
<td>-23</td>
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<tr>
<td>Lp(a)</td>
<td>56 ± 47</td>
<td>66 ± 62</td>
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Values are means ± SD (mg/dl). *p* < 0.001 with respect to baseline values.

Table 1. Change in lipid parameters after 4 weeks of atorvastatin 10 mg (n = 29)
atorvastatin 10 mg daily; their TC levels had dropped by 34%, LDL-c levels had dropped by 44%, TG levels by 38%, and Apo B levels by 36%.

Of the 20 patients in the two prevention groups who did not achieve their respective targets with the 10-mg starting dose, six were receiving 20 mg and 14 were receiving 40 mg at the end of the study (seven primary prevention patients and seven secondary prevention patients). Figure 1 shows the response to treatment expressed as a percentage of reduction in lipid parameters at 1 and 4 months, with respect to baseline, in the 14 patients who were receiving 40 mg.

Table 2 shows the results after 4 months of treatment in each prevention group, with respect to baseline lipid parameters and as percentage of reduction.

Figure 2 shows the response to treatment in terms of reduction in plasma TG levels in the 19 hypertriglyceridaemic patients. In 16 of these patients the plasma TG level dropped by 27–52%; in three patients the reduction in plasma TG levels was ≤12%.

At the end of the fourth month, 19 of the 20 patients in the primary prevention group and seven of the nine patients in the secondary prevention group had achieved the target LDL-C reduction. In the primary prevention group, 16 patients achieved the target after just 1 month of atorvastatin 10 mg, two patients achieved the target with the 20-mg dose, and a third achieved it with the 40-mg dose. In this group, the only patient who did not achieve the target level with a 40-mg dose did achieve it with the 80-mg dose. In the secondary prevention group, one patient achieved his target with the 10-mg dose, one patient with the 20-mg dose, and five patients with the 40-mg dose.

In the primary prevention group, 16 patients had elevated TG levels before treatment. Six achieved the targeted TG reduction with a 10-mg dose; seven patients achieved the target with a 40-mg dose. Three patients, including one diabetic, failed to achieve their targets with this dose. Three patients in the secondary prevention group had elevated TG levels. One of them achieved the target with the 10-mg dose. Two of them, including one diabetic, failed to achieve their targets with a 40-mg dose.

One patient experienced diarrhoea after only a few days of treatment. Diarrhoea regressed after atorvastatin was withdrawn, but recurred upon rechallenge. The patient was therefore withdrawn from the study. Another patient was excluded because of an allergic skin reaction that occurred 10 days after the beginning of the study. Muscle weakness and abnormal elevation of CPK levels to 753 IU/l (normal <195 IU/l) were observed in one patient after 1 month of atorvastatin treatment at a dosage of 80 mg daily. These anomalies regressed after dosage was reduced to 40 mg. No other clinical or laboratory adverse event was observed during the study.

Table 2. Change in lipid parameters in the primary and secondary prevention groups

<table>
<thead>
<tr>
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<th>Primary prevention (n=20)</th>
<th>Secondary prevention (n=9)</th>
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<tbody>
<tr>
<td></td>
<td>Day 0</td>
<td>Month 4</td>
</tr>
<tr>
<td>TC</td>
<td>302 ± 24</td>
<td>201 ± 35</td>
</tr>
<tr>
<td>LDL-C</td>
<td>204 ± 23</td>
<td>119 ± 27*</td>
</tr>
<tr>
<td>TG</td>
<td>289 ± 132</td>
<td>186 ± 92*</td>
</tr>
<tr>
<td>Apo-B</td>
<td>152 ± 25</td>
<td>107 ± 27*</td>
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Values are means ± SD (mg/dl). *P <0.001 with respect to baseline values.
Discussion

The results of a preliminary efficacy study carried out in primary hypercholesterolaemic patients with normal renal function showed that atorvastatin was one of the most potent HMG-CoA reductase inhibitors, in terms of the reduction in TC, LDL-C and Apo-B levels [14]. According to the CURVES study, reductions of 30, 46 and 51% in LDL-C can be achieved with dosages of 10, 20 and 40 mg respectively. Such reductions are greater than those achieved with equivalent doses of simvastatin, pravastatin, lovastatin, and fluvastatin [15]. The same study also showed that atorvastatin, given at a dose of 10 mg, led to a comparable or greater reduction in LDL-C than 40 mg of the foregoing compounds. Also, atorvastatin 80 mg reduced LDL-C levels by 54%, a reduction which is not significantly different from the response observed with an equivalent dose of lovastatin (48%).

Our study showed that the overall efficacy of atorvastatin is comparable both in dyslipidaemic patients on PD and in non-uraemic hypercholesterolaemic patients, with the reduction in LDL-C being somewhat higher (44% as compared with 38%) in patients who receive a minimal effective dose of 10 mg as primary prevention but somewhat less (41% as compared with 51%) in patients receiving the highest dose of 40 mg for either primary or secondary prevention.

Two studies have reported lipid reductions in PD patients receiving other statins: reductions of 44 and 41% in LDL-C were observed with simvastatin at a dose of 20–40 mg [12] and equivalent doses of lovastatin [13]. The numbers of patients in these studies, however, was too small (10 patients in each) and the data were not sufficiently detailed to allow an accurate comparison of the dose–effect relationship of each compound, although it does appear that atorvastatin has the most favourable dose–effect relationship. With atorvastatin, the target LDL-C for primary prevention can generally be achieved (95% of the cases), and in most cases with the lowest dose (10 mg). The target for secondary prevention can also generally be achieved, with a few exceptions, at doses of 20 and 40 mg. In our study, we chose the LDL-C target values that are accepted in France [17] and similar to those set forth in the American guidelines [19].

In primary hypertriglyceridaemia, the reduction in TG levels achieved with atorvastatin is dose-dependent and greater than with other statins: 26–46% for daily doses ranging from 5 to 80 mg [16]. A reduction of the same magnitude was observed in our study. It was also dose-dependent and usually proportional to the reduction in LDL-C levels. The reduction in TG level ranged from 38% in patients who achieve their target LDL-C level with a 10 mg dose, to 29% in those who may or may not achieve it with a 40 mg dose. Furthermore, it is greater than that obtained with other statins in uraemic patients on peritoneal dialysis, in whom the reduction ranges from 18% with lovastatin at doses of 20–40 mg [13] to 22% with equivalent doses of simvastatin [12].

In terms of target achievement for all groups considered as a whole, 73% of the patients achieved their target reduction in TG levels. We chose the TG target value that is defined by the European guidelines for the prevention of coronary heart disease [18].

Atorvastatin has no effect on HDL-C levels, like most statins, with the exception of simvastatin which, when administered at a dose of 40 mg, may increase HDL-C levels in nearly 10% of primary hypercholesterolaemic patients [20]. Lovastatin is thought to have a similar effect at equivalent doses in PD patients [13]. As could be expected, atorvastatin had no effect on Lp(a).

Atorvastatin was well tolerated. Twenty-nine out of the 31 patients completed the study. One case of diarrhea and one of skin allergy were considered treatment-related and required withdrawal of treatment. Atorvastatin is metabolized in the liver and excreted in the bile. Renal function impairment therefore does not affect plasma atorvastatin concentrations and does not require dosage adjustment [21]. No dose-dependent adverse effect was observed at atorvastatin dosages below 40 mg daily. Transient elevation in CPK levels was observed in one patient receiving the 80 mg dose; enzyme levels, however, remained below 10-times the upper normal limit. This led us to reduce dosage to 40 mg in this patient and to limit maximum atorvastatin to 40 mg in our study, to avoid any risk of rhabdomyolysis. Two cases of moderately increased CPK levels in DP patients after 2 months of lovastatin were reported by Li et al. [13]. No change in transaminase levels was observed in our study, in contrast to what has been described with statins, both in subjects with normal renal function and in uraemic patients. Two cases of elevated transaminase levels were observed in PD patients receiving lovastatin [13]. When given at a dosage not exceeding 40 mg, atorvastatin is well tolerated in PD patients. However, the safety of atorvastatin requires confirmation by long-term follow-up.

As previously described in non-uraemic dyslipidaemic patients, atorvastatin has a greater cholesterol- and triglyceride-lowering effect than other agents belonging to the same drug category.

In the past, efficacy of this magnitude could only be achieved by combining a statin with another hypo-lipidaemic, generally, however, at the price of poor tolerance in patients with impaired renal function, especially if the hypolipidaemic was a fibrate. In contrast, atorvastatin is effective and safe in reducing both dyslipidaemic components observed in uraemic patients on PD.

Results of large-scale prevention studies among the general population have clearly demonstrated that treatment with HMG-CoA reductase inhibitors could reduce the risk of myocardial infarction and cardiovascular mortality in hypercholesterolaemic patients [20,22,23]. Moreover, there is now strong evidence that drug treatment also has a preventive effect when hypertriglyceridaemia is a concomitant risk factor [24,25]. According to our experience, two out of three
PD patients have hypercholesterolaemia and half of them have concomitant hypertriglyceridaemia. There is every reason to think that treating both dyslipidaemic components in these patients would be beneficial despite the difficulties of evaluating the impact because of the multiple risk factors to which they are exposed.

References

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