Objective: The aim of our study was to compare the efficacy and safety of atorvastatin versus pravastatin, in dyslipidemic patients on continuous ambulatory peritoneal dialysis (CAPD).

Material and methods: Fifty-five hyperlipidemic CAPD patients were randomized to either atorvastatin (n=27) or pravastatin (n=28) treatment and prospectively followed for nine months. Hyperlipidemia was defined as TC ≥200 mg/dl (5.2 mmol/L) and LDL-C ≥135 mg/dl (3.5 mmol/L). Both drugs were initiated at a dose of 10 mg/day and the doses were increased if LDL-C was >135 mg/dl at visits done every three months. The blood glucose, serum albumin total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglyceride (TG), AST, ALT, GGT, uric acid, CPK, HbA1C were measured in the fasting blood samples taken at baseline, and at 3rd, 6th and 9th months of the treatment.

Results: Both agents resulted in a marked reduction in the TC, LDL-C and TG levels; but no change was observed for VLDL-C and HDL-C in either of the treatment arms. The proportional decrease of TC and LDL-C was more marked in the atorvastatin group, compared to pravastatin group. No major side effects were observed with either of the statins in these patient groups.

Conclusion: The results of our study demonstrated that although both statins improved the lipid profiles and both are safe for use in dyslipidemic CAPD patients, and higher starting doses (20 mg) may be required for pravastatin in patients on CAPD treatment.

Key Words: Dyslipidemia, Atorvastatin, Pravastatin, Continuous ambulatory peritoneal dialysis (CAPD)

INTRODUCTION

Coronary artery disease (CAD) is the main cause of morbidity and mortality in patients with chronic renal failure (CRF), and deaths from CAD account for approximately 40% of total deaths observed among patients with chronic renal failure (CRF) (1). Dyslipidemia is a major risk factor for the development of CAD in patients with CRF as well as in the general population (1,2). The lipoprotein lipase activity begins to decrease when the glomerular filtration rate (GFR) is reduced to 50 ml/min or less while triglyceride (TG) levels begin to increase when GFR falls to a range of 15 to 30 ml/min. (2).
Therefore dyslipidemia is more frequent in patients with CRF than in the general population (2-7). In addition, increased glucose absorption through the peritoneal membrane further augments the hyperlipidemic state (8).

Several studies have demonstrated that the lipid levels at the start of CAPD therapy were predicting survival—During CAPD therapy, the levels of total cholesterol (TC), TG, and the TC/HDL-C ratio continue to increase (9). Therefore, the increased number of cardiovascular events that are associated with CRF requires a close monitoring and treatment of the serum cholesterol levels. Although the results of the any prospective, randomized, controlled study has not yet been available on the effects of the lipid-lowering therapy on cardiovascular morbidity and mortality in patients with CRF, several primary and secondary prevention trials have shown the important role of lipid-lowering therapy in preventing cardiovascular events and mortality in the general population (10,11). 3-Hydroxy-3 methyl glaryl coenzyme-A (HMG-CoA) reductase inhibitors are highly effective in reducing the total (TC) and LDL cholesterol (LDL-C) levels which are also currently used in patients with CRF (12,13). The statins are partly eliminated by the kidneys, for which reason reduced dosages may be needed in patients with CRF. These drugs can reduce TC and LDL-C levels as well as the TG levels, although to a lesser extent. The aim of our study was to compare the efficacy and safety of atorvastatin and pravastatin, which have different pharmacokinetics in dyslipidemic patients on CAPD (14).

**MATERIALS AND METHODS**

Fifty-five dyslipidemic patients over 18 years old who had been treated with CAPD and home peritoneal dialysis for at least 6 months in the Division of Peritoneal Dialysis Unit, the Sub-department of Nephrology, Department of Internal Medicine, Marmara University Hospital were included in the study. Dyslipidemia was defined as TC ≥ 200mg/dl (5.2 mmol/L) and LDL-C ≥ 135 mg/dl (3.5 mmol/L). A target-based treatment method was used in which the dosages were increased if the targeted LDL-C levels were not achieved at follow-up visits every four weeks. The patients who had received lipid-lowering therapy within the last 3 months (n=38), those who had an active hepatic disease (n=3) or whose serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) levels were three-fold greater than the upper normal limit (n=5) or had a creatinine phosphokinase (CPK) level three-fold greater than the upper normal limit (n=3), or those who were hypersensitive to statins or were receiving medications which might affect the lipoprotein metabolism (cyclosporin, erythromycin, azole antifungals) (n=2) were excluded from the study. No patient was taking sevalamer hydrochloride and no patient received a dialysis solution containing 3.86% glucose more than three times per week. The CAPD treatment prescription was not changed during the study in any of the patients. Patients continued to have their previous diets of 35 kcal/kg throughout the study; 50% of the total calories were provided from carbohydrates, 25% from proteins and 25% from lipids. The amount of protein in the diet was 1.3 g/kg. Patients participated in a diet-training program at our clinic once a year.

Twenty-seven patients were randomized to the atorvastatin group (GA), and 28 patients to the pravastatin group (GP). The primary underlying renal disease leading to end-stage renal failure (ESRF) was similar in both groups and was shown in Table I.

<table>
<thead>
<tr>
<th>Primary Causes Underlying Renal Disease Leading to End-Stage Renal Failure in Both Groups</th>
<th>Pravastatin Group (n:28)</th>
<th>Atorvastatin Group (n:27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic nephropathy (n)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Hypertensive nephropathy (n)</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Chronic glomerulonephritis (n)</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Chr. interstitial glomerulonephritis (n)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Unknown reasons (n)</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

Atorvastatin and pravastatin were initiated at a dose of 10 mg/day. The doses of the two drugs were increased to 20 mg/day and 40 mg/day respectively if LDL-C was >135 mg/dl at visits done every three months. Counting the tablets during the monthly checks assessed patients'
compliance to the study drugs. Patients who had used less than 80% of the prescribed tablets were not included in the final analysis.

In the fasting blood samples taken at baseline, and at 3rd, 6th and 9th months of the treatment, the blood glucose and serum albumin levels, and the levels of TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), TG, AST, ALT, GGT, uric acid, CPK, HbA1C were measured. Serum TC, LDL-C, HDL-C, TG values were measured by calorimetric methods.

Statistical Analysis

Descriptive statistics were used to summarize the data as mean ± standard deviation. Continuous random variables, unpaired t-test (chosen according to Levene’s test criteria) was used to compare the two treatment groups.

In each treatment, repeated measures of ANOVA were used to determine the differences in measurement at each time point. When p < 0.05, student Newman Keuls multiple comparison tests were used for comparisons.

Percent of change was calculated for the variables between baseline and 6th month measurements and the unpaired t-test was used to compare these changes between the two groups. For analyzing discrete random variable Fisher’s exact test was used and p<0.05 was considered as significant. SPSS for windows 10.0 was used for all statistical analysis.

RESULTS

Of the 55 patients randomized to the study groups, 50 completed the study (atorvastatin: 24, pravastatin: 26). The reasons for the five-drop outs were transplantation (1) (GP), moving to another center (1), death (1) (GA), and noncompliance to the treatment in two patients (1 GA, 1 GP). These five patients were excluded from the statistical analysis. Both treatment groups were similar in terms of age, sex, duration of CAPD treatment, BMI, serum albumin level, Kt/V and residual renal function at the beginning of the treatment (Table II). Both groups were also similar for the baseline lipid profiles, fasting blood sugar, liver function tests, CPK, and the uric acid levels (Table II).

Following the assessments at month 1, the treatment dose was increased to 20 mg in 14 patients in the GP, and 4 patients in the GA. After the assessments at month 3, the dose of pravastatin was increased to 40 mg in 8 patients already taking 20 mg and to 20 mg in 6 patients taking 10 mg previously, while the dose of atorvastatin was increased to 40 mg in 1 patient already taking 20 mg. When the study was completed at month 9, LDL-C was found at the targeted level (LDL-C ≤ 135 mg/dl) in 42 patients. Although a marked reduction in the serum LDL-C was observed in the remaining 8 patients, the decrease failed to reach the targeted level. At the end of the study, of the 26 patients in the GP, n: 1 (3.8%) was on 10 mg, n: 17 (65.4%) were on 20 mg and n: 8 (30.7 %) were on 40 mg of pravastatin. Although there were marked reductions in one patient receiving 40 mg and 4 patients receiving 20 mg, the targeted level of

Table II: Distribution by demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin (n=24)</th>
<th>Pravastatin (n=26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>46.8 ± 14.3</td>
<td>50.3 ± 15.7</td>
<td>0.395</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/13</td>
<td>9/17</td>
<td>0.564</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 ± 10</td>
<td>28.8 ± 10.5</td>
<td>0.808</td>
</tr>
<tr>
<td>Duration of CAPD (months)</td>
<td>51.4 ± 19.9</td>
<td>52.6 ± 20.6</td>
<td>0.829</td>
</tr>
<tr>
<td>Kt/V</td>
<td>2.8 ± 0.45</td>
<td>2.2 ± 0.35</td>
<td>0.359</td>
</tr>
<tr>
<td>NPCR (g/kg/day)</td>
<td>1.0 ± 0.36</td>
<td>0.9 ± 0.32</td>
<td>0.187</td>
</tr>
<tr>
<td>RRF (ml/min)</td>
<td>1.6 ± 3.48</td>
<td>1.7 ± 2.27</td>
<td>0.582</td>
</tr>
<tr>
<td>Serum Albumin (g/dl)</td>
<td>3.8 ± 0.44</td>
<td>3.8 ± 0.29</td>
<td>0.888</td>
</tr>
</tbody>
</table>

The values are given as mean ± SD.
BMI: body mass index, nPCR: protein catabolism rate, RRF: residual renal function.
### Table III: Distribution of patients in the atorvastatin and pravastatin groups according to their biochemical values

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin group</th>
<th>Pravastatin group</th>
<th>P</th>
<th>P(B)</th>
<th>P(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Month 3</td>
<td>Month 6</td>
<td>Month 9</td>
<td>P</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>241 ± 37</td>
<td>191 ± 32</td>
<td>176 ± 28</td>
<td>170 ± 27</td>
<td>0.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>163 ± 30</td>
<td>119 ± 35</td>
<td>101 ± 30</td>
<td>104 ± 29</td>
<td>0.001</td>
</tr>
<tr>
<td>VLDL</td>
<td>43 ± 15</td>
<td>31 ± 12</td>
<td>35 ± 11</td>
<td>33 ± 14</td>
<td>0.097</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44 ± 12</td>
<td>45 ± 13</td>
<td>48 ± 11</td>
<td>41 ± 13</td>
<td>0.139</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>202 ± 68</td>
<td>168 ± 59</td>
<td>145 ± 57</td>
<td>143 ± 77</td>
<td>0.001</td>
</tr>
<tr>
<td>Glucose</td>
<td>100 ± 30</td>
<td>109 ± 33</td>
<td>106 ± 26</td>
<td>102 ± 26</td>
<td>0.506</td>
</tr>
<tr>
<td>HbA1c</td>
<td>5.6 ± 0.8</td>
<td>5.7 ± 0.7</td>
<td>6.3 ± 1.4</td>
<td>5.4 ± 0.9</td>
<td>0.084</td>
</tr>
<tr>
<td>Uric acid</td>
<td>6.2 ± 1.7</td>
<td>6.0 ± 1.6</td>
<td>6.4 ± 1.5</td>
<td>6.4 ± 1.4</td>
<td>0.581</td>
</tr>
<tr>
<td>CPK</td>
<td>42 ± 18</td>
<td>71 ± 46</td>
<td>83 ± 55</td>
<td>93 ± 74</td>
<td>0.095</td>
</tr>
<tr>
<td>GGT</td>
<td>26 ± 13</td>
<td>39 ± 45</td>
<td>35 ± 39</td>
<td>27 ± 22</td>
<td>0.710</td>
</tr>
<tr>
<td>AST</td>
<td>19 ± 7</td>
<td>20 ± 9</td>
<td>22 ± 8</td>
<td>18 ± 6</td>
<td>0.182</td>
</tr>
<tr>
<td>ALT</td>
<td>22 ± 10</td>
<td>19 ± 10</td>
<td>20 ± 11</td>
<td>20 ± 14</td>
<td>0.725</td>
</tr>
</tbody>
</table>

The values are given as mean ± SD.

$*$: Statistically greater significance vs. baseline values.
P(B): Comparison for the atorvastatin and pravastatin groups by baseline values.

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LDL-C could not be achieved. As for the 24 patients in the GA, n: 17 (71%) were on 10 mg, n: 6 (25%) were on 20 mg and n:1 (4%) was on 40 mg of atorvastatin at the completion of the study. Although 3 patients receiving 20 mg of atorvastatin showed marked reductions, the targeted level of LDL-C could not be achieved.

In the analysis of changes in lipid profiles, the levels of TC, LDL-C and TG were significantly reduced in both groups ($p<0.001$), while no change was observed in the levels of VLDL-C and HDL-C in either of the groups (Table III).

When the proportional changes in the levels of TC and LDL-C were compared between two treatment groups, there was a significantly greater reduction in the GA compared to GP (Fig.1).

No patient experienced atorvastatin and pravastatin induced hepatotoxicity at the doses of 10, 20 and 40 mg. Although none of the patients suffered from myalgia and malaise, an increase in the CPK level (maximum three times) at month 3 was observed in 3 patients (11.5%) in the GP and in 4 patients (16.6 %) (maximum

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**Fig. 1:** Atv: Atorvastatin, Prv: Pravastatin, TC: Total Cholesterol, TG: Triglyceride, LDL-C: Light density Lipoprotein-Cholesterol.
three times the upper level of normal) at month 1 in the GA. In the GA, there were no other side effects except constipation in one patient (4.1%) and dyspepsia in another patient (4.1%) while there was no such side effect in the GP group.

**DISCUSSION**

Treating lipid abnormalities has a vital importance in all patients with ESRF including patients on CAPD due to the well-recognized risk of cardiovascular disease. It has been repeatedly reported that the HMG-CoA reductase inhibitors are the best antihyperlipidemic agents for reducing the levels of TC and LDL-C in the general population (13,15,16). Although there are many studies showing the efficacy and safety of the agents in hyperlipidemic patients without ESRF, data on the use of statins in patients on CAPD is limited (17). In the present study, comparing the efficacy and safety of atorvastatin and pravastatin in CAPD patients, both agents resulted in a marked reduction in the TC, LDL-C and TG levels reaching the highest significance by the sixth month of the treatment; but no change was observed for serum VLDL-C and HDL-C in either of the treatment groups. The proportional decrease of TC and LDL-C was more marked in the GA, compared to the GP, whereas the reductions in TG levels were similar in both groups.

Our results suggest that the starting dose for the treatment of dyslipidemia with pravastatin should be 20 mg in patients on CAPD. Our finding is different from the results obtained in the studies carried out in the general population in this respect (18,19). However, in the CURVES study, atorvastatin administered at a dosage of 10 mg/day has been shown to reduce the LDL-C level at a similar rate or even more markedly compared to the other HMG-CoA reductase inhibitors (simvastatin, pravastatin, lovastatin and fluvastatin) administered at a dosage of 40 mg/day (19).

The reduction in TG levels was similarly significant in both treatment groups. Contrary to our results, some studies in the general population have demonstrated the superiority of atorvastatin when compared to other statins in this respect (10,14). The hypertriglyceridemia frequently encountered in CAPD patients has been associated with the frequent use of hypertonic glucose solutions. We have observed that when the use of solutions containing 3.86% glucose was increased, the TG level rose compared to the previous period despite the statin treatment. Although our patients used three solutions per week at most, this rise was still observed.

We could not obtain any significant reduction in the VLDL-C level or any significant elevation in the HDL-C level in either of the treatment groups. This finding was also not consistent with the results reported in the general population and CAPD patients (10, 19-25).

Data on the use of statins in patients on CAPD are limited, and some side effects have also been reported in CAPD patients (22).

The patients on CAPD metabolically resemble diabetic patients, because of their glucose absorption of approximately 75-300 g/day from the dialyze resulting in an iatrogenic hyperglycemic state (26). Furthermore, insulin resistance has been demonstrated in a vast majority of patients on CAPD treatment. Therefore, statins, which have been shown to be effective for the treatment of hyperlipidemia in type-2 diabetes, may be theoretically a better choice for the treatment of patients on CAPD. In a placebo-controlled study in which simvastatin, pravastatin, lovastatin and atorvastatin were compared in patients with type-2 diabetes and, the levels of TC, LDL-C, TG and HDL-C were significantly more reduced in the patients treated with atorvastatin compared to those treated with other statins (27). In their study, Hufnagel et al. have reported that atorvastatin reduced the levels of TC, LDL-C, and TG on CAPD patients by 33%, 42%, and 37%, respectively (21). In another placebo-controlled study, atorvastatin significantly improved the lipid profiles in patients on CAPD (20). However, these studies have not prospectively compared statins in terms of the efficacy and side effect profile. On the other hand, in a cross-sectional study assessing the patients on antihyperlipidemic therapy with atorvastatin versus simvastatin, while an improvement has been observed on the lipid profiles in favor of atorvastatin, the difference
failed to reach statistical significance (24). However, the percentage of diabetic patients was 38% in the simvastatin group, and 22% in the atorvastatin group in the latter study, whereas the percentage of diabetic patients is much less (16%) in our study.

Although the efficacy of antihyperlipidemic therapy has not been reported for patients on CAPD by the prospective, randomized studies, it is suggested that lowering the level of LDL-C may decrease the morbidity and mortality. (2,15,28).

Statins are generally well tolerated among the general population. Serious side effects such as rhabdomyolysis and hepatotoxicity are rarely seen. We did not observe any significant increase in the levels of uric acid, CPK, AST, ALT, and GGT consistent with hepatotoxicity or rhabdomyolysis throughout the nine-month follow-up in any of the treatment groups. Only two patients experienced constipation and dyspepsia in the GA and no such side effect was observed in the GP. Gastrointestinal side effects including dyspepsia and constipation have not exceeded 2% in the general population with the use of atorvastatin (29) while it was found to be 4.1% in our study. However, these side effects were only temporary and did not require discontinuation of the medication. No dose reduction has been necessary in our study. Our results confirm that both agents are safe for use in patients on CAPD.

In conclusion, the results of our study demonstrated that although both atorvastatin and pravastatin improved the lipid profiles, atorvastatin was significantly more efficacious in lowering TC and LDL-C than pravastatin and higher starting doses may be required for pravastatin in patients on CAPD treatment. Atorvastatin and pravastatin seem to be equally safe for use in treating hyperlipidemia in CAPD patients.

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