Objective: Lipid abnormalities are common in patients on continuous ambulatory peritoneal dialysis (CAPD) and they are risk factors for atherosclerosis. In this prospective uncontrolled study, the aim was to evaluate the efficacy and safety of atorvastatin, a new statin, in hypercholesterolemic CAPD patients with or without hypertriglyceridemia who failed to respond to diet control.

Methods: Following a hypolipidemic diet for 2 months, atorvastatin was administered at a dose of 10 mg/day once daily in 24 patients (14 males, 10 females). Mean age was 59.9 years (range, 19–74 years) and average time on CAPD was 16.6 months (range, 4–52 months). The results were evaluated at 0, 1, 3, 6, 12, 18, 24, 30, 36, 42, and 48 months. A total of three patients received atorvastatin for longer than 48 months, eight patients received it for longer than 42 months, 10 patients for longer than 36 months, 17 patients for longer than 24 months, 20 patients for longer than 18 months, and all (24) patients for longer than 12 months.

Results: Highly significant decreases were noted in total cholesterol (from 282 ± 28 to 178 ± 22 mg/dL, 20–50%, mean, 34%; p < 0.001), low-density lipoprotein cholesterol (from 198 ± 25 to 112 ± 20 mg/dL, 21–53%, mean, 37%; p < 0.001), and triglycerides (from 256 ± 116 to 177 ± 40 mg/dL, 12–45%, mean, 28%, p < 0.01) from the sixth month. High-density lipoprotein cholesterol was significantly increased from the sixth month (from 40 ± 9 to 48 ± 9 mg/dL, 11–28%, mean, 19.4%; p < 0.01). These changes remained steady during the study. No liver function abnormalities were observed and serum creatinine kinase levels remained within normal limits during treatment. No complications or other side effects were detected.

Conclusions: Our data indicate that atorvastatin, even at a low dose of 10 mg/day, is an effective, safe, and well-tolerated drug for the long-term treatment of hyperlipidemia in CAPD patients. [Hong Kong J Nephrol 2003;5(2):78–83]

Key words: atorvastatin, CAPD, chronic renal disease, dyslipidemia, HDL-cholesterol, hypercholesterolemia, hypertriglyceridemia, LDL-cholesterol

目的：對於正在接受連續可活動性腹膜透析 (CAPD) 的病人，血脂異常 — 動脈粥狀硬化的危險因子 — 是常見的問題。本研究以前瞻、非對照方式，對一種新的 statin 藥物 — atorvastatin 的功效及安全性作出調查，其對象為患有高膽固醇血症 (部分亦合併有高三酸甘油脂血症) 的 CAPD 接受者，均對飲食控制缺乏反應。

方法：在經過兩個月的低脂飲食後，病人 (n = 24，14 男 10 女) 開始接受 atorvastatin 一天一次 10 mg 治療。病人的平均年齡為59.9歲 (範圍 19–74 歲)，平均接受 CAPD 達 16.6 個月 (4–52 個月)。療效的評估於治療開始前，及後 1、3、6、12、18、24、30、36、42，與 48 個月進行。所有病人均持續接受治療達 12 個月以上，達 18 個月以上者有 20 人，24 個月以上有 17 人，36 個月以上有 10 人，42 個月以上有 8 人，達 48 個月以上者則有 3 人。

結果：從第 6 個月開始，各血清脂質均已出現顯著的下降，包括總膽固醇 (從 282 ± 28 至 178 ± 22 mg/dL，20–50%，平均 34%；p < 0.001)，低密度脂蛋白膽固醇 (從 198 ± 25 至 112 ± 20 mg/dL，21–53%，平均 37%；p < 0.001) 及三酸甘油脂 (從 256 ± 116 至 177 ± 40 mg/dL，12–45%，平均 28%；p < 0.01)；同一期間，高密度脂蛋白膽固醇則出現顯著的上升 (從 40 ± 9 至 48 ± 20 mg/dL，21–53%，平均 37%；p < 0.001)，及三酸甘油脂 (從 256 ± 116 至 177 ± 40 mg/dL，12–45%，平均 28%；p < 0.01)；同一期間，高密度脂蛋白膽固醇則出現顯著的上升 (從 40 ± 9 至 48 ± 20 mg/dL，21–53%，平均 37%；p < 0.001)，及三酸甘油脂 (從 256 ± 116 至 177 ± 40 mg/dL，12–45%，平均 28%；p < 0.01)；同一期間，高密度脂蛋白膽固醇則出現顯著的上升 (從 40 ± 9 至 48 ± 20 mg/dL，21–53%，平均 37%；p < 0.001)，及三酸甘油脂 (從 256 ± 116 至 177 ± 40 mg/dL，12–45%，平均 28%；p < 0.01)；同一期間，高密度脂蛋白膽固醇則出現顯著的上升 (從 40 ± 9 至 48 ± 20 mg/dL，21–53%，平均 37%；p < 0.001)，及三酸甘油脂 (從 256 ± 116 至 177 ± 40 mg/dL，12–45%，平均 28%；p < 0.01)；同一期間，高密度脂蛋白膽固醇則出現顯著的上升 (從 40 ± 9 至 48 ± 20 mg/dL，21–53%，平均 37%；p < 0.001)，及三酸甘油脂 (從 256 ± 116 至 177 ± 40 mg/dL，12–45%，平均 28%；p < 0.01)；同一期間，高密度脂蛋白膽固醇則出現顯著的上升 (從 40 ± 9 至 48 ± 20 mg/dL，21–53%，平均 37%；p < 0.001)，及三酸甘油脂 (從 256 ± 116 至 177 ± 40 mg/dL，12–45%，平均 28%；p < 0.01)；同一期間，高密度脂蛋白膽固醇則出現顯著的上升 (從 40 ± 9 至 48 ± 20 mg/dL，21–53%，平均 37%；p < 0.001)，及三酸甘油脂 (從 256 ± 116 至 177 ± 40 mg/dL，12–45%，平均 28%；p < 0.01)。
INTRODUCTION

The most common cause of death in patients with end-stage renal disease (ESRD) on maintenance dialysis is cardiovascular disease [1]. Lipid abnormalities are major risk factors for cardiovascular disease and are frequently observed among patients with ESRD, especially those on dialysis [2]. The dyslipidemia of ESRD is characterized by hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C), and elevated low-density lipoprotein cholesterol (LDL-C), with a marked predominance of highly atherogenic, small and dense LDL particles [3–5]. In various studies, 30% to 70% of dialysis patients exhibit hypertriglyceridemia [3]. Moreover, peritoneal dialysis (PD) patients are at greater risk of developing hypercholesterolemia, primarily because of lipoprotein overproduction resulting from both the absorption of dialysate glucose and the loss of proteins into the peritoneal effluent [6–9]. These patients’ lipid profiles are also characterized by increased plasma apolipoprotein B (Apo-B) and lipoprotein (a) (Lp(a)) levels, and according to a meta-analysis, 24% of PD patients have total cholesterol (TC) levels that are greater than 240 mg/dL, and 45% have plasma LDL-C levels that are greater than 130 mg/dL [8–11].

The combination of dyslipidemia and other coexistent risk factors such as hypertension, diabetes, and obesity is likely to contribute to the marked increase in the risk of cardiovascular morbidity and mortality in patients undergoing dialysis relative to the general population [12–14]. This is true for hypercholesterolemia and also hypertriglyceridemia, which acts synergistically with decreased HDL-C [15], although some studies suggest that hypertriglyceridemia might even be an independent coronary risk factor [16,17].

In order to improve the prevention of cardiovascular disease in clinical practice, many recommendations have been produced, based on data from clinical, epidemiologic and observational studies [18,19]. Central to such recommendations is TC level reduction, in particular the lowering of LDL-C. The higher than average incidence of potential cardiovascular complications as the leading cause of death in PD patients argues strongly in favor of treating lipid disturbances. Caution is no longer acceptable, as in the past, when the safety of effective hypolipidemic agents in these patients remained questionable [20]. Despite the effect of lipid-lowering dietary recommendations on nutritional intake and lipid profiles, the vast majority of dyslipidemic dialysis patients require pharmacologic therapy to improve their lipid profiles [21].

The introduction of the well-tolerated and safe 3-hydroxy-3-methylgluylaryl-Coenzyme A (HMG-CoA) reductase inhibitors, or statins, despite limited evidence of their effectiveness in dialysis patients, has made them the most widely used class of drug in the treatment of hyperlipidemia complicating chronic renal disease, including in hemodialysis and PD patients [8,22–26]. Atorvastatin, an established member of the statins drug class, lowers both cholesterol and triglyceride (TG) levels [27–34]. It has been shown to provide statistically significantly greater reductions in LDL-C and TC than milligram-equivalent doses of simvastatin, pravastatin, lovastatin, and fluvastatin [27]. Atorvastatin, at its maximum dose of 80 mg/day, reduces LDL-C levels by up to 61% and TG levels by up to 45% [28], with no serious compromise to its safety profile [29]. As reported in recent studies, atorvastatin was effective and safe in dyslipidemic PD patients after a period of 4 months’ administration [35,36].

In this prospective uncontrolled study, we assessed the long-term efficacy and safety of atorvastatin in dyslipidemic patients with chronic renal failure undergoing continuous ambulatory peritoneal dialysis (CAPD) and receiving a single daily dose of 10 mg.

PATIENTS AND METHODS

This prospective uncontrolled study took place from March 1998 to June 2002, and included 24 patients and was planned to have a follow-up duration of at least 12 months for all patients. Atorvastatin was already a drug in use and patients knew that it was a lipid-lowering drug. The study was approved by our hospital’s Ethics Committee and all the patients gave informed consent.

All patients who had been on PD for more than 3 months in our unit were considered for entry into the study if they were 18 years of age or older. To be eligible for inclusion, patients at screening were required to have dyslipidemia documented by at least two plasma determinations (TC ≥ 200 mg/dL and LDL-C ≥ 135 mg/dL with or without hypertriglyceridemia), and no hypolipidemic treatment in the previous 3 months.
or dyslipidemia uncontrolled by treatment with maximally tolerated doses of other lipid-lowering agents taken for a minimum period of 4 weeks.

Exclusion criteria included age of less than 18 years or greater than 80 years, history of hypersensitivity to HMG-CoA reductase inhibitors, hypothyroidism, severe progressing disease, cachexia, women who were pregnant or breastfeeding, active liver disease or hepatic dysfunction defined as plasma transaminases (alanine transaminase and aspartate transaminase) greater than three times the upper limit of normal, creatinine kinase greater than three times the upper limit of normal, history of alcohol abuse, concurrent treatment with long-term immunosuppressants, medication affecting lipoprotein metabolism, drugs associated with rhabdomyolysis in combination with statins (such as cyclosporine, erythromycin, azole antifungals), and fibrate therapy. Patients with myocardial infarction, transient ischemic attack, percutaneous transluminal coronary angioplasty or coronary artery bypass graft within 3 months of study entry were also excluded, as were those with unstable diabetes mellitus, participation in another clinical trial within 1 month prior to study entry, and clinical evidence of inflammatory muscle disease.

TC, HDL-C, LDL-C, and TG levels were measured before initiating the study treatment. The same parameters were measured monthly during the study. Following a hypolipidemic diet for 2 months, all the patients received a single daily dose of atorvastatin 10 mg at bedtime. This dose remained unchanged during the first 3 months of the study, after which it could be increased to 20 mg if the target LDL-C level of 130 mg/dL or less and the target TG level of 200 mg/dL or less for all patients were not achieved. Safety was assessed by clinical and laboratory monitoring before treatment, then once per month until the end of the study (liver and muscle enzyme level determinations: alanine aminotransferase [ALT], aspartate aminotransferase [AST], gamma-glutamyltransferase [GGT], creatine phosphokinase, and aldolase).

Student’s t test for paired variables and Wilcoxon’s non-parametric test were used to compare the differences between lipid parameters at baseline and on treatment (repeated measures). Results are expressed as mean ± standard deviation and as mean percentage decrease.

RESULTS

A total of 24 patients were eligible for inclusion and were finally included: 14 males and 10 females. Mean age was 59.9 ± 20 years (range, 19–74 yr), and the mean duration of CAPD treatment was 16.6 ± 13.4 months (range, 4–52 mo). The primary renal diseases were: diabetes mellitus (nine patients, two of whom had type 1), hypertension (five patients), chronic glomerulonephritis (four patients), polycystic kidney disease (two patients), chronic pyelonephritis (two patients), and unknown cause (two patients). Lipid parameters were measured every month, at the monthly visit of the patients, and the results were evaluated at the start (baseline) and then at 1, 3, 6, 12, 18, 24, 30, 36, 42, and 48 months. From the third month, the reported lipid levels were the average of three consecutive measurements.

A total of three patients received atorvastatin for more than 48 months, eight patients for more than 42 months, 10 patients for more than 36 months, 17 patients for more than 24 months, 20 patients for more than 18 months, and all (24) patients for more than 12 months. Atorvastatin was administered at a dose of 10 mg, once daily, at bedtime, and only in five patients was the dose increased to 20 mg/day because the target level (130 mg/dL) of LDL-C was not achieved at the end of the third month of treatment.

A significant decrease with respect to baseline was observed for TC and LDL-C after 1 month of treatment with atorvastatin 10 mg daily, whereas no significant change was observed in TG and HDL-C levels. At the end of the sixth month of treatment, and after the atorvastatin dose was increased to 20 mg/day in five patients, there was also a significant decrease in TG levels and a significant increase in HDL-C levels (Table 1).

At the end of the study, there were more significant changes from baseline for all the lipid parameters, as shown in the Figure. The results showed the following: highly significant decreases in TC of 20% to 50% (mean, 34%; p < 0.001), in LDL-C of 21% to 53% (mean, 37%; p < 0.001), in TG of 12% to 45% (mean, 28%; p < 0.01), and increase in HDL-C of 11% to 28% (mean, 19.4%; p < 0.01). These changes remained almost steady during the study, as shown in Table 2.

Six patients achieved LDL-C levels of less than 100 mg/dL, and the vast majority of the patients had

| Table 1. Change in lipid parameters after 6 months of atorvastatin 10 mg (n = 19) or 20 mg (n = 5) after the third month. |
|-----------------|-----------------|-----------------|-----------------|
| Day 0           | Month 6         | Change (%)      |
| TC              | LDL-C           | TG              | HDL-C           |
| 282 ± 28        | 190 ± 30        | –32*            | 40 ± 9          |
| 198 ± 25        | 120 ± 29        | –39*            | 256 ± 116       |
| 256 ± 116       | 189 ± 61        | –26*            | 46 ± 11         |

* p < 0.001, † p < 0.01, with respect to baseline values. Values are mean ± SD (mg/dL). TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol.
Atorvastatin in dyslipidemic CAPD patients

LDL-C values between 100 mg/dL and 130 mg/dL. There was no change in the uremic profiles of the patients, nor were there any alterations in medications (antihypertensives, hypoglycemic control), diet, exercise, or CAPD schedule that might have affected lipid profiles during the study. Complete clinical and laboratory evaluations were performed every month. There were no cardiovascular events during the study, no withdrawals from the study, and all the patients remained on CAPD at the end of the study.

No liver function abnormalities were observed and all liver and muscle enzyme levels (ALT, AST, GGT, creatine phosphokinase, and aldolase) remained within normal limits during the study. No complications, side effects or adverse events were detected.

DISCUSSION

The need to treat lipid abnormalities complicating renal disease is unproven. However, it seems likely that the high prevalence of dyslipidemia in dialysis patients contributes to the elevated risk of cardiovascular morbidity and mortality in this patient population [36]. In guidelines for the prevention of coronary heart disease in clinical practice, renal dysfunction is classified together with existing coronary heart disease and type 2 diabetes as diseases that confer a high risk of future coronary events and for which lipid-lowering therapy is recommended for all patients [18]. However, as reported by Harris et al [36], only 16% of dialysis patients were receiving treatment with lipid-lowering drugs, and of those patients on therapy, only 50% had achieved an LDL-C of less than 115 mg/dL. These data suggest that more aggressive treatment of dyslipidemia may be indicated in this patient population.

The reduction in LDL-C and the overall efficacy of atorvastatin observed in our study was similar to that reported in two previous studies in uremic patients on PD [35,36] and in non-uremic patients using the drug [27–34]. In this last group of patients, it was as expected because renal dysfunction has been shown not to alter the pharmacokinetics or LDL-C reduction of atorvastatin [37]. Our study confirms previously reported observations that atorvastatin reduces LDL-C levels significantly more than other statins [22,23,26–29,35,36].

In primary hypertriglyceridemia, the reduction in TG levels achieved with atorvastatin is dose-dependent and greater than with other statins: 26% to 46% for daily doses ranging from 5 mg to 80 mg [30]. A similar reduction was observed in our study; the 12% to 45% reduction in TG with the lowest atorvastatin dose of 10 mg confirms the results of previous studies with atorvastatin in PD patients [35,36], and the reduction is greater than that obtained with other statins in the same patient population, in which TG reduction ranged from 6.2% to 22% [22,23,26].

In our study, there was a significant increase in HDL-C levels after the sixth month of treatment; this observation is in agreement with one previous study [36], but not with another [35]. The ability of atorvastatin to modify TG and HDL-C levels beneficially is important because abnormal concentrations of these lipids characterize the usual

Table 2. Lipid parameters during the study.

<table>
<thead>
<tr>
<th></th>
<th>Day 0 (n = 24)</th>
<th>Month 6 (n = 24)</th>
<th>Month 12 (n = 24)</th>
<th>Month 18 (n = 20)</th>
<th>Month 24 (n = 17)</th>
<th>Month 36 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>282 ± 28</td>
<td>190 ± 30*</td>
<td>185 ± 26*</td>
<td>187 ± 24*</td>
<td>180 ± 25*</td>
<td>178 ± 22*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>198 ± 25</td>
<td>120 ± 29*</td>
<td>115 ± 20*</td>
<td>113 ± 21*</td>
<td>116 ± 18*</td>
<td>112 ± 20*</td>
</tr>
<tr>
<td>TG</td>
<td>256 ± 116</td>
<td>189 ± 61*</td>
<td>190 ± 40*</td>
<td>185 ± 45†</td>
<td>182 ± 38†</td>
<td>177 ± 40†</td>
</tr>
<tr>
<td>HDL-C</td>
<td>40 ± 9</td>
<td>46 ± 11*</td>
<td>45 ± 9†</td>
<td>48 ± 12*</td>
<td>49 ± 10†</td>
<td>48 ± 9†</td>
</tr>
</tbody>
</table>

*p < 0.001, †p < 0.01, with respect to baseline values. Values are mean ± SD (mg/dL). TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; HDL-C = high-density lipoprotein cholesterol.
pattern of dyslipidemia observed in uremic patients and may also contribute to the elevated cardiovascular risk seen in dialysis patients [8].

Atorvastatin was well tolerated in our study. With the lowest dose of 10 mg but the long duration of treatment, there were no liver function abnormalities, muscle enzyme level elevations, cardiovascular events, complications or other side effects. All the studies with atorvastatin have reported that it is well tolerated and better tolerated than other statins, both in subjects with normal renal function and in uremic patients [27–36].

Atorvastatin is effective and safe in reducing the dyslipidemic components (LDL-C and TG) that are observed in uremic patients on PD. Despite these results, there remains a pressing need for large, prospective, randomized, controlled trials with long-term follow-up to determine the effects of lipid-lowering therapy on cardiovascular morbidity and mortality in dialysis and pre-dialysis patients [36].

It seems that statins (their effects on plasma lipid levels notwithstanding) have ancillary actions that may be relevant to nephrology [38]. It is reported that statins may have important effects on the pathophysiology of progressive renal injury, including effects on inflammatory processes, cell proliferation, and intracellular signaling pathways [39,40]. Furthermore, as recent studies have shown, statins may have effects on hemostatic parameters such as platelet aggregation, endothelial function, and fibrinolysis in CAPD patients [41–43]. Therefore, future studies are warranted to investigate the potential role of lipid-lowering therapy in chronic renal disease and in patients on PD.

In conclusion, our data indicate that atorvastatin, even at the lowest dose of 10 mg/day, is an effective, safe, and well-tolerated lipid-lowering drug for the long-term treatment of dyslipidemia in PD patients.

REFERENCES


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