

Efficacy and Safety of Ezetimibe and Low-Dose Simvastatin as Primary Treatment for Dyslipidemia in Peritoneal Dialysis Patients

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We previously reported that the level of low-density lipoprotein cholesterol (LDL-C) was higher in patients receiving continuous ambulatory peritoneal dialysis (CAPD) than in patients on hemodialysis (HD). One of the problems associated with reaching the LDL-C target during statin treatment of patients on CAPD is the emergence of laboratory or clinical side effects. The present study evaluated the efficacy and tolerability of daily combined treatment with ezetimibe 10 mg and simvastatin 10 mg in patients receiving CAPD.

Our study enrolled 12 CAPD patients who were experiencing adverse effects from statin therapy. Their existing statin therapy was suspended for 1 month ("washout period"), and the patients were then shifted to treatment with the ezetimibe-simvastatin combination. The patients were again monitored for adverse events such as asthenia and myalgia during the subsequent 12 months. Body mass index and levels of glycated hemoglobin, fasting plasma glucose, total cholesterol, LDL-C, triglycerides, alanine amino-transferase, aspartate aminotransferase, and creatinine phosphokinase were also assessed.

The combination of ezetimibe and low-dose simvastatin significantly reduced levels of total cholesterol (by a mean of 27%), triglycerides (by 9%), and LDL-C (by 33%) and increased levels of high-density lipoprotein cholesterol (by 15%). In 11 patients (92%), the target LDL-C level of less than 100 mg/dL was reached. No significant change in weekly creatinine clearance occurred, and no serious adverse effects were observed.

patient developed muscle pain or weakness, and no increase in creatinine kinase was found. Residual renal function declined, although not significantly when compared with initial values.

In conclusion, the present study suggests that combined ezetimibe and low-dose statin treatment is a promising approach for safe and effective primary treatment of dyslipidemia in CAPD patients.

Key words

Dyslipidemia, statins, ezetimibe

Introduction

Disturbances in plasma lipoprotein (Lp) metabolism are frequently observed among patients on continuous ambulatory peritoneal dialysis (CAPD). The most common lipid and Lp profile in peritoneal dialysis shows elevated levels of total cholesterol, low-density Lp cholesterol (LDL-C), triglycerides, Lp(a), and apolipoprotein B. High-density Lp cholesterol (HDL-C) and apolipoprotein A1 levels are usually low. These abnormalities are not all seen in all patients (1), and among all these atherogenic factors, LDL-C values are the ones most commonly used in clinical practice as an index of atherosclerosis.

In the general population, guidelines have been published for the treatment of patients with high LDL-C and low HDL-C levels, because certain levels have been established as risk factors for cardiovascular disease (2). However, the guidelines have not been validated in the dialysis population. This lack of concrete evidence for therapeutic efficacy and the paradoxical relationship between cholesterol level and clinical outcome in observational studies may be responsible for the small percentage of peritoneal dialysis patients being treated with lipid-modifying medications, as seen in previous studies (3).

Recently, Goldfarb–Rumyantzev *et al.* (4) reported that therapy with lipid-modifying medication may be associated with improved clinical outcomes in peritoneal dialysis patients. In spite of those supportive data, statins produce several adverse effects, including serious complications such as rhabdomyolysis. Adverse events have not been regularly reported, and many trial protocols do not specify standard methods for ascertaining harmful statin effects. Uncertainty therefore exists about the safety of statins in patients on CAPD. The present study evaluated the efficacy and tolerability of daily treatment with a combination of 10 mg ezetimibe and 10 mg simvastatin in patients receiving CAPD.

Patients and methods

Patients undergoing CAPD complicated with hyperlipidemia were eligible for inclusion in the study. All patients were required to have been diagnosed with hyperlipidemia (defined as LDL-C above 140 mg/dL). Eligible patients were fully informed about the aims of the study, and written informed consent was obtained from each patient.

The following exclusion criteria were used:

- Myocardial infarction within the preceding 6 months
- Clinically significant valvular disease
- Familial hypercholesteremia
- History of cerebrovascular accident within the preceding 6 months
- Any condition that may have precluded a patient from remaining in the study, such as alcohol or drug abuse, chronic liver disease, malignant disease, or psychiatric disorder

The study protocol was approved by the ethics committee of the Saitama Medical School Hospital. The trial was performed in accordance with the principles of the World Medical Association's Declaration of Helsinki and was conducted at the Kidney Disease Center in Saitama Medical School Hospital, Saitama, Japan.

The study enrolled 12 CAPD patients (9 women, 3 men; average age: 63.5 ± 2.5 years; causes of end-stage renal disease: 6 diabetic nephropathy, 3 immunoglobulin A nephropathy; 3 nephrosclerosis) who had experienced adverse effects such as myalgia, asthenia, and elevation of alanine aminotransferase,

aspartate aminotransferase, and creatinine phosphokinase while on statin therapy. Current statin therapy was suspended for 1 month ("washout period"), after which the patients were shifted to daily treatment with a combination of 10 mg ezetimibe and 10 mg simvastatin. Over the subsequent 12 months, the patients were again monitored for adverse events.

Patients were instructed to maintain a specified diet (30 – 35 kcal/kg daily; 7 g salt; 0.8 g/kg protein daily—diabetic or nondiabetic) throughout the study. Target home blood pressure (BP) was 130/80 mmHg or lower, and home BP measurements were encouraged. For CAPD therapy, patients used 1.5–2.5 L of dialysate per exchange for 3 – 5 exchanges daily. Exchanges using 2.5% dextrose were individually adapted: usually 1 – 2 bags daily of this concentration was used, until the desired dialysis goal was reached.

Patients were followed every month during the study period. At each clinic visit, serum creatinine, electrolyte concentrations, complete blood count, and other serum chemistries (uric acid, glucose, and liver enzymes) were measured. Residual glomerular filtration rate (GFR) was assessed at 0, 3, 6, and 12 months by 24-hour urine collection. Indices of dialysis adequacy, including weekly creatinine clearance (CCr), were calculated using the PD Adequest computer program (version 2.0: Baxter Healthcare, Tokyo, Japan) for Windows. Chest radiographs were obtained regularly, and cardiothoracic index was calculated according to established methods. Body mass index and levels of glycated hemoglobin, fasting plasma glucose, total cholesterol, LDL-C, triglycerides, alanine aminotransferase, aspartate aminotransferase, and creatinine phosphokinase were also assessed.

Statistical analysis

Continuous data are expressed as mean \pm standard error of the mean. Analyses of the effects of ezetimibe and low-dose simvastatin on longitudinal changes in serum total cholesterol, LDL-C, HDL-C, and triglycerides were performed by repeated-measures analysis of covariance, followed by a Neumann–Keuls test for evaluation of significance. In addition, BP, urine volume, serum creatinine, weekly CCr, electrolyte concentrations, complete blood count, and other serum chemistries (uric acid, glucose, and liver enzymes) were evaluated.

A *p* value less than 0.05 was considered significant.

Results

Effects of ezetimibe and low-dose simvastatin on laboratory values

No significant effects of ezetimibe and low-dose simvastatin were found during the study (Table I). Residual renal function gradually declined, but not at a significant rate. No significant change occurred in weekly CCr.

Effects of ezetimibe and low-dose simvastatin on cholesterol

Ezetimibe and low-dose simvastatin significantly reduced the levels of total cholesterol (by a mean of 27%), triglycerides (by 9%), and LDL-C (by 33%); levels of HDL-C increased (by 15%, Figure 1). During the first month, total cholesterol declined abruptly; it then gradually declined to the end of the study. Levels of LDL-C declined in a similar manner. These changes were significant ($p < 0.05$). Levels of triglycerides declined with the ezetimibe and low-dose simvastatin treatment, but the changes did not achieve significance. In addition, HDL-C gradually increased, but non-significantly, to the end of the study.

Adverse effects

Neither muscle pain nor weakness was observed in any patient, and no increase was found in creatinine kinase levels.

Discussion

The present study demonstrated that therapy with a combination of ezetimibe and a statin can safely reduce

LDL-C levels in patients on CAPD who experience adverse effects with statin monotherapy.

Currently, there is paucity of data to guide dyslipidemia treatment for CAPD patients. Goldfarb–Rumyantzev *et al.* (4) evaluated the effect of lipid-lowering therapy on clinical outcomes in CAPD patients using data for 1053 CAPD patients from the U.S. Renal Data System prospective Dialysis Morbidity and Mortality Wave 2 study. They reported that therapy with lipid-modifying medication may be associated with improved clinical outcomes in CAPD patients. In contrast, Habib *et al.* (5) evaluated the association of serum total cholesterol and triglycerides with clinical outcome in CAPD patients and reported that the data did not support aggressive lowering of plasma cholesterol in PD patients. In spite of these differences, two sets of current guidelines comment on lipid management in CAPD patients: the International Society for Peritoneal Dialysis (ISPD) guidelines (6) and the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines (7). Both guidelines recommend treatment for all chronic kidney disease patients with dyslipidemia.

In general, statin therapy is used to treat dyslipidemia because it has proven to be safe and effective (8), although several side effects, such as muscle pain and elevations of creatine kinase, can occur. Severe rhabdomyolysis is reported to be a serious complication. Recently, ezetimibe was proposed for use in combination with low-dose statin to reduce statin-induced side effects. Ezetimibe was licensed by the U.S. Food and Drug Administration in 2002 exclusively on the basis of its ability to reduce the level of LDL-C while having an acceptable short-term

TABLE I Changes in baseline values during the study

| <i>Variable</i> | <i>Start</i> | <i>6 Months</i> | <i>12 Months</i> |
|---------------------|--------------|-----------------|------------------|
| Creatinine (mg/dL) | 10.34±3.43 | 11.25±3.66 | 11.31±1.33 |
| Systolic BP (mmHg) | 155.2±15.2 | 149.5±14.3 | 148.5±16.7 |
| Diastolic BP (mmHg) | 78.2±15.2 | 76.7±13.6 | 75.4±13.7 |
| Albumin (g/dL) | 3.8±0.6 | 3.5±0.9 | 3.9±0.7 |
| BUN (mg/dL) | 66.7±15.3 | 70.5±17.7 | 72.8±20.2 |
| Hemoglobin (g/dL) | 10.5±0.6 | 10.8±1.2 | 10.3±1.5 |
| Ca (mg/dL) | 8.5±0.6 | 8.8±0.7 | 9.0±1.4 |
| InsP (mg/dL) | 5.7±1.2 | 5.7±1.1 | 6.0±1.2 |
| Weekly CCr (L) | 55.6±5.2 | 59.5±4.3 | 58.5±6.7 |
| RRF (mL/min) | 3.0±2.4 | 2.5±2.3 | 1.9±3.7 |

BP = blood pressure; BUN = blood urea nitrogen; InsP = inositol phosphatase; CCr = creatinine clearance; RRF = residual renal function.

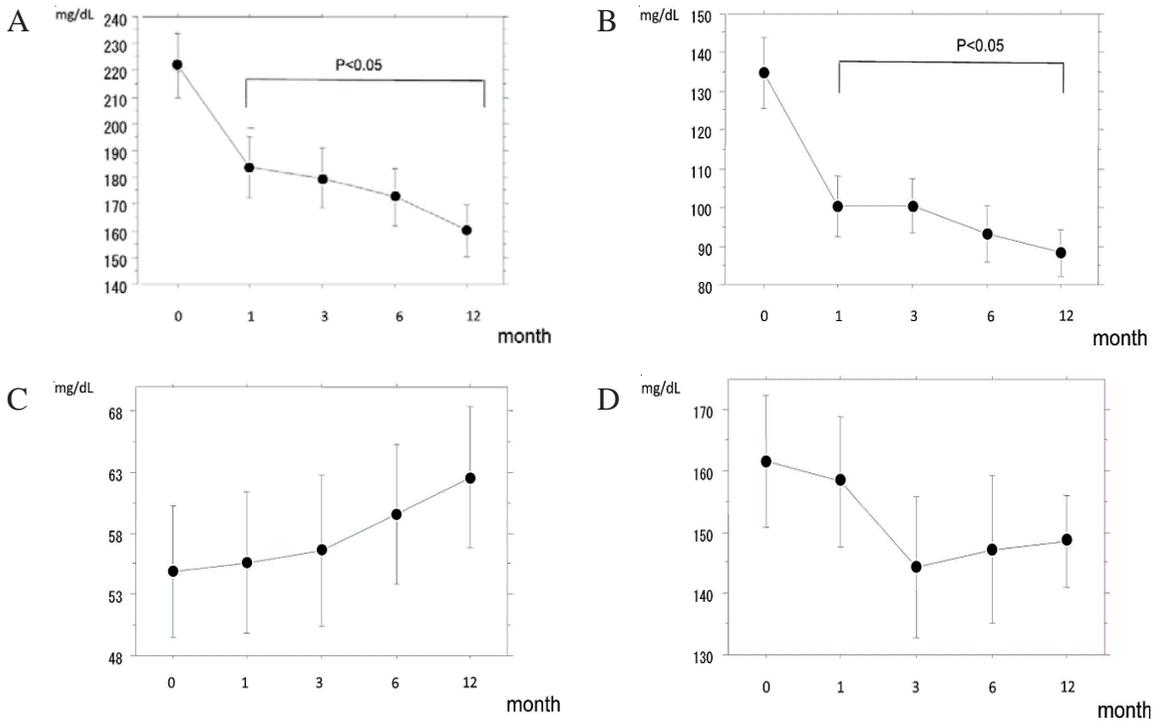


FIGURE 1 Mean changes in (A) serum cholesterol, (B) low-density lipoprotein, (C) high-density lipoprotein, and (D) triglycerides over the 12-month study period for the 12 patients treated with ezetimibe and simvastatin in combination.

side-effect profile. An understanding of the mechanism of action of ezetimibe has subsequently evolved. The mechanism appears to be more complex than the purported simple inhibition of cholesterol absorption at the enterocyte and than can be inferred from murine and other animal models (9).

The drug is systemically absorbed and entero-hepatically recirculated in a potent glucuronidated form (10). It inhibits multiple key cholesterol-transport proteins, including the primarily intracellular lipid cholesterol transport receptor, Niemann–Pick C1L1 (11). From this basic conceptual scheme of action, ezetimibe is considered less likely to have serious side effects when used in combination therapy. Indeed, patients who experienced adverse effects from high doses of statins alone experienced no side effects from combination therapy with ezetimibe and statin in the present study. However, before proceeding further, an examination of any ancillary actions of statins that may be relevant to nephrology is necessary (12).

In vitro and in vivo studies have both showed that statins may have important effects on the pathophysiology of progressive renal injury, including effects on inflammatory processes, cell proliferation, and intracellular signaling pathways (13,14). Therefore, future studies are warranted to investigate the potential role of lipid-lowering therapy in CAPD patients.

Conclusions

The present study suggests that treatment with a combination of ezetimibe and low-dose statin is a promising approach for safe and effective primary treatment of dyslipidemia in CAPD patients.

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