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Anti-Inflammatory Interventions in End-stage Kidney Disease: A Randomized, Double-Blinded, Controlled and Crossover Clinical Trial on the Use of Pravastatin in Continuous Ambulatory Peritoneal Dialysis

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Background and Aims. Inflammation is highly prevalent in patients on dialysis. Statins have anti-inflammatory actions but their use has been scarcely studied in continuous ambulatory peritoneal dialysis (CAPD). We undertook this study to compare the effect of pravastatin vs. placebo on the serum concentrations of C-reactive protein (CRP) in patients on CAPD.

Methods. In a double-blind, controlled and crossover clinical trial, 76 CAPD patients were randomized to either pravastatin or placebo for 2 months. After this first period of treatment, patients had a 1-month wash-out period and, finally, they were crossed-over to receive the other drug (or placebo) for 2 more months. Measurement of clinical and biochemical variables and CRP was performed at the beginning and at the end of each treatment period.

Results. Median CRP was only significantly decreased in the pravastatin group in both periods of treatment: first period (baseline vs. final, mg/L): pravastatin 7.4 (2–21) vs. 2.6 (1–6), $p < 0.05$; placebo 3.9 (2–10) vs. 6.8 (3–12), pNS; second period: pravastatin 4.3 (2–15) vs. 1.9 (1–7), $p < 0.05$; placebo 4.9 (2–17) vs. 6.8 (2–19), $p < 0.05$. Results were significantly different ($p < 0.05$) between groups only at the end of each treatment period. Additionally, total and LDL-cholesterol significantly decreased in the pravastatin group.

Conclusions. Pravastatin significantly reduced serum levels of CRP and total and LDL-cholesterol compared to placebo. This treatment may be of great help to decrease the inflammatory status and probably the cardiovascular disease of CAPD patients. © 2013 IMSS. Published by Elsevier Inc.

Key Words: Pravastatin, Crossover clinical trial, Continuous ambulatory peritoneal dialysis, C-reactive protein, Inflammation.

Introduction

Chronic inflammation is highly prevalent in patients with end-stage renal disease (ESRD) (1) and strongly linked to atherosclerosis, cardiovascular disease and malnutrition (2–4). Moreover, morbidity and mortality in these patients are remarkably higher than for the general population, largely due to atherosclerotic cardiovascular disease (3–5).

Benefits of statins have been reported on all-cause and cardiovascular mortality in chronic kidney disease (CKD) patients; however, some topics remain to be clarified (6). Such beneficial effect of statins were particularly observed in patients with non-dialysis CKD (7), but not in ESRD patients on dialysis (8,9). A more recent study, however, suggests that statins may be beneficial even in dialysis patients (10).

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In addition to their well-known hypolipidemic actions, statins have anti-inflammatory effects, which have been extensively demonstrated in patients without kidney disease (11). In patients with ESRD on hemodialysis, statins have been shown to decrease C-reactive protein (CRP) (9,12,13); however, data in patients on peritoneal dialysis are sparse and limited.

Therefore, the aim of this study was to compare the effect of pravastatin vs. placebo on the serum concentrations of CRP in patients on continuous ambulatory peritoneal dialysis (CAPD).

Patients and Methods

Study Design

The present study was a randomized, double-blind, controlled and crossover clinical trial. Patients from the Regional General Hospital No. 110, Mexican Institute of Social Security (IMSS), Guadalajara, Mexico were invited to participate if they were 18–70 years old and had at least 1 month on CAPD. Subjects were excluded if they had any of the following: inflammatory cause of ESRD, hepatic or malignant disease, any infectious disease within the last 3 months, drug intake with anti-inflammatory effect (including statins, steroids or NSAIDs), or uncontrolled cholesterol levels ≥400 mg/dL.

Protocol

After inclusion, patients were randomized to receive either pravastatin or placebo orally during 2 months. After this first period of treatment, patients had a 1-month wash-out period and, finally, they were crossed-over to receive the other drug (or placebo) for an additional 2 months (Figure 1).

From baseline to the end of the study, patients had monthly visits with detailed clinical examinations. Measurement of biochemical variables was performed at the beginning and at the end of each treatment period and included blood cell count, blood chemistry, and lipid profile, determined by usual methods. At these same time points,

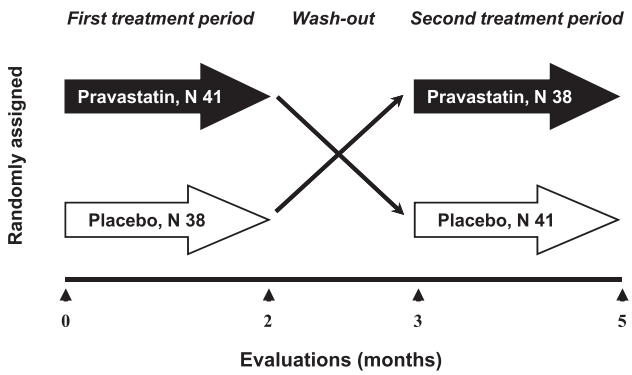

Figure 1. Flow diagram describing recruitment, assignment to groups and follow-up of patients.

CRP measurement was performed by nephelometry using high-sensitivity kits (Dade Behring, Marburg, Germany) in a Nephelometry Analyzer II (Dade Behring). All laboratory determinations were performed by the same personnel blinded to patients' details in the Central Laboratory of the Hospital de Especialidades, CMNO. Inter- and intra-assay variations for CRP are 3.4 and 3.4%, respectively (14).

All patients used a double bag system with four standard glucose-based 2-L exchanges per day (Laboratorios Pisa, SA de CV, Guadalajara, Mexico), the concentration being prescribed accordingly to individual patient's requirements. Individuals of both groups were treated by their primary nephrologist according to standard CAPD practice in our setting.

Pravastatin (20 mg tablets) and placebo, as starch identical-looking tablets, were administered orally in the morning (once a day).

Assignment and masking. Patients were assigned to the treatment sequence by using a simple randomization code with a block size of 6. Investigators allocated patients consecutively by time of inclusion at the study site. Both investigators and patients were blinded. One investigator (JRAZ) enrolled all patients and allocated them to treatment. Randomization data were maintained blinded until analysis was completed.

Statistical Analysis

Data are shown as mean ± SD or median (percentiles 25–75%) in case of dimensional variables and as number or percentages in case of nominal variables. Wilcoxon or paired *t* tests were employed to evaluate the difference *before-after* every period of treatment, whereas inter-group comparisons were performed by Mann-Whitney U or unpaired *t* tests as appropriate; $p < 0.05$ was accepted as significant, but the exact value is preferentially shown.

Results

Seventy-six patients were included, 43 (57%) males and 33 (43%) females. In the whole sample, mean age was 54.4 ± 12.4 years, median dialysis vintage 15.0 (10–24) months, and previous peritonitis rate 1.0 (0–1) episode/patient/year. Main cause of ESRD was diabetes mellitus in 49 (65%) patients. No significant demographic differences were found between the two treatment sequences at the beginning of the study (Table 1).

Regarding clinical and biochemical variables (Table 2), the only significant differences between groups were the lower total and LDL cholesterol levels with the use of pravastatin compared to placebo.

Median CRP levels of patients randomly allocated to receive active medication or placebo (Figure 2) in the first period were not significantly different between groups;