Comparison of the Efficacy and Safety Profile of Morning Administration of Controlled-release Simvastatin Versus Evening Administration of Immediate-release Simvastatin in Chronic Kidney Disease Patients With Dyslipidemia

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ABSTRACT

Purpose: Evening administration of the conventional immediate-release (IR) formulation of simvastatin is recommended because of its short half-life (1.9 hours). In a healthy population, morning administration of a controlled-release (CR) formulation of simvastatin was shown to have equivalent lipid-lowering efficacy and a safety profile similar to that of evening doses of IR simvastatin. The present study aimed to verify noninferiority and to compare the safety of morning administration of CR simvastatin with that of evening administration of IR simvastatin in patients with chronic kidney disease (CKD) who have dyslipidemia.

Methods: The present study was a prospective, multicenter, double-blind, Phase IV trial with an active comparator. We randomly assigned 122 patients with CKD and dyslipidemia to 1 of 2 drug administration groups: morning administration of CR simvastatin 20 mg (test group) and evening administration of IR simvastatin 20 mg (control group). After 8 weeks, the treatment outcomes and adverse effects of the 2 treatments were compared.

Findings: The mean (SD) percentage of change in serum LDL-C at the end of treatment was –35.1% (15.7%) for the test group and –35.6% (14.6%) for the control group. The difference between the 2 groups was not significant ($P = 0.858$). The 95% CI of the difference in the percentage of change of LDL-C between the test and control groups was –6.0 to 5.0. There was no difference in the percentage of change of total cholesterol (–24.3% [12.5%] vs –26.5% [12.0%], $P = 0.317$), triglyceride (–10.6% [35.1%] vs –12.4% [33.2%], $P = 0.575$) and HDL-C (10.2% [20.7%] vs 4.5% [11.4%], $P = 0.064$). Treatment-related adverse events were similar in both groups (10 events in the test group vs 8 events in the control group, $P = 0.691$).

Implications: The efficacy of morning administration of CR simvastatin was noninferior to evening administration of IR simvastatin in patients with CKD. Furthermore, the safety profile analysis showed no significant difference between the 2 treatments. Morning administration of CR simvastatin is expected to increase patient compliance and therefore better control of dyslipidemia in CKD patients. (*Clin Ther.* 2014;36:1182–1190) © 2014 The Authors. Published by Elsevier HS Journals, Inc.

Accepted for publication June 2, 2014.
http://dx.doi.org/10.1016/j.clinthera.2014.06.005
0149-2918/$ - see front matter

Key words: chronic kidney disease, controlled-release preparations, drug administration schedule, dyslipidemia, simvastatin.

INTRODUCTION

3-Hydroxy 3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, also known as statins, are a highly potent group of agents that reduce serum LDL-C levels. Previous clinical trials have reported that statin therapy is beneficial for the primary[1] and secondary[2–4] prevention of cardiovascular disease, such as coronary atherosclerosis. Statin therapy is of particular benefit to dyslipidemia patients with chronic kidney disease (CKD), which is associated with a high incidence and increased severity of cardiovascular disease.[5] The Kidney Disease Outcome Quality Initiative guidelines for dyslipidemia[6] recommend that lipid-lowering therapy, along with therapeutic lifestyle modification, should be initiated for CKD patients with LDL-C levels above 100 mg/dL. According to the latest meta-analysis of statin therapy in CKD, all-cause and cardiovascular mortality was significantly decreased without increasing treatment-related adverse effects.[7,8]

Despite the beneficial effects of statin therapy, patients with chronic diseases who are taking medications in multiple doses are frequently noncompliant in taking their medication.[9–11] There is a diurnal variation of plasma LDL-C levels, with the lowest levels detected in the morning and the highest levels peaked in the evening.[12] Simvastatin is an established HMG-CoA reductase inhibitor that has been clinically evaluated in thousands of cases.[2,13] In some trials comparing the efficacy of morning and evening administration of simvastatin, there was significantly lower reduction in LDL-C levels when simvastatin was given in the morning.[14] However, taking simvastatin in the evening may increase the complexity of the dosing regimen, in turn, reducing patient compliance.[9]

Recently, a controlled-release (CR) simvastatin formulation was released (Simvast CR tablet*); it has a longer half-life (11.4 hours) than that of the conventional immediate-release (IR) formulation (1.9 hours). In a Phase III trial of CR simvastatin, the formulation was reported to have equivalent efficacy and a similar safety profile within the study population as those of IR simvastatin.[15] We designed a Phase IV, postmarketing trial of CR simvastatin in CKD patients. The purposes of the present study were twofold: (1) to verify in CKD patients whether the efficacy of CR simvastatin administered in the morning was noninferior to that of IR simvastatin administered in the evening and (2) to assess whether a regular dose regimen of CR simvastatin was safe compared with that of IR simvastatin in CKD patients.

METHODS

The present study was a prospective, randomized, double-dummy, double-blind,, multicenter Phase IV trial that evaluated the efficacy and safety profile of morning administration of CR simvastatin tablets compared with evening administration of IR simvastatin tablets (Zocor tablet†) in CKD patients. The participants were recruited from the following hospitals in South Korea: Seoul National University Hospital, Gachon University Gil Medical Center, Seoul Eulji General Hospital, Hallym University Sacred Heart Hospital, Inje University Ilsan Paik Hospital, Hanyang University Seoul Hospital, and Korea University Anam Hospital. Before entering the study, all patients provided written informed consent. The institutional review boards of each hospital approved the study design, and the study was performed in accordance with the Declaration of Helsinki and its amendments.

Patients

The study was conducted from December 2010 to May 2012. Patients, 20 to 75 years of age, with CKD stage 3, 4, or 5 (predialysis) were enrolled if their serum LDL-C levels were between 100 and 220 mg/dL and their serum triglyceride (TG) levels were <400 mg/dL. The reasons for exclusion of patients were as follows: previous hypersensitivity to components of any HMG-CoA reductase inhibitor, drug abuse and alcohol consumption of least 14 standard units per week,[16,17] impaired liver function (serum aspartate aminotransferase or alanine aminotransferase level of >2 times the upper limit of normal), uncontrolled diabetes (HgA_{1c} level of $>9.0\%$), uncontrolled

*Trademark: Simvast CR tablet®, Hanmi Pharmaceutical Co, Ltd, Seoul, Republic of Korea.

†Trademark: Zocor® tablet, Merck & Co, Inc, Whitehouse Station, New Jersey.