Original Article

Short-Term Efficacy and Safety of Adding Ezetimibe to Current Regimen of Lipid-Lowering Drugs in Human Immunodeficiency Virus-Infected Thai Patients Treated with Protease Inhibitors

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SUMMARY: Long-term complications of protease inhibitor (PI) treatment includes increased cardiovascular risks due to dyslipidemia in patients infected with human immunodeficiency virus (HIV). Ezetimibe reduces low-density lipoprotein cholesterol (LDL-C) without drug interactions with PIs and statins. Furthermore, the addition of ezetimibe to statins is an optional treatment in HIV-infected patients with uncontrolled dyslipidemia. The objective of this study was to determine the short-term efficacy and safety of adding ezetimibe to the currently administered statin regimen. Thirty-two patients received ezetimibe (10 mg daily) in addition to their ongoing lipid-lowering therapy for 18 weeks. Serum LDL-C, total cholesterol (TC), triglycerides (TGs), TC/high-density lipoprotein cholesterol (HDL-C) ratio, and HDL-C were measured at baseline, and weeks 6, 12, and 18. Safety parameters were assessed by adverse event reports and laboratory assessments throughout the study. The mean percent change from baseline to endpoint in LDL-C, TC, TGs, and TC/HDL-C ratio were −23.3% (p < 0.001), −15.0% (p = 0.001), −22.1% (p = 0.004), and −16.2% (p = 0.018), respectively. No adverse event or other abnormal laboratory results occurred. Addition of ezetimibe to currently administered lipid-lowering drugs in HIV-infected patients receiving PIs with uncontrolled dyslipidemia demonstrated significantly improved efficacy in reducing their LDL-C, TC, TGs, and TC/HDL-C ratio levels. Moreover, this therapy was safe and well-tolerated.

INTRODUCTION

Long-term use of highly active antiretroviral therapy (HAART) has significantly improved the quality of life, life expectancy, and the survival of patients infected with human immunodeficiency virus (HIV) (1–3). However, HIV-infected patients still have higher mortality rates than the general population, because of non-AIDS related diseases, such as an increased incidence of cardiovascular diseases (CVDs) (4–7). The results of the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) cohort showed that dyslipidemia was associated with an increasing incidence of myocardial infarction and occurred more frequently in patients receiving protease inhibitors (Pis) (4–13). Dyslipidemia is a major, primary risk of atherosclerosis for CVDs such as coronary heart disease, cerebrovascular disease, and peripheral arterial disease. In 2012, 31% of all global deaths could be attributed to CVDs (14).

Evidence-based treatment of hypercholesterolemia from many guidelines recommends statins as a first-choice medication (1,2,15–17). However, there are serious drug interactions between statins and PIs (2,16,18–21), which limit the recommendation of higher doses of statins when dyslipidemia control is not achieved. Ezetimibe, a cholesterol absorption inhibitor, is a new class of lipid-lowering drugs that exhibits fewer drug interactions between other lipid-lowering drugs and PIs (22–27). However, ezetimibe is not currently enlisted in the National List of Essential Medicines of Thailand; therefore, many patients cannot access this drug. Several studies have showed that adding ezetimibe to statins confers favorable efficacy and safety in patients with uncontrolled dyslipidemia (28–37). Furthermore, the addition of ezetimibe may be an alternative treatment to achieving the goal of lipid-lowering therapy in HIV-infected patients with uncontrolled dyslipidemia. Hence, this study reports the results of the first clinical trial in HIV-infected Thai patients to determine the short-term efficacy and safety of adding ezetimibe to the current regimen of lipid-lowering drugs in controlling dyslipidemia in these PI-treated patients.

MATERIALS AND METHODS

Patients and population: This study was a prospective, open-labeled, one-group, pre-test–post-test, short-term study with an 18 week follow-up.

This study was approved by the Institutional Review Board of the Bamrasnaradura Infectious Diseases Institute (Protocol No.S003h/57). The study participants were adult HIV-infected patients who visited the Bamrasnaradura Infectious Diseases Institute, Ministry of Public Health between September 2014 and December 2015. HIV-infected patients who were receiving stable PIs and with dyslipidemia that was being treated by statins (with or without fibrates) for at least 6 months prior to the study were recruited. Patients who were pregnant or lactating, or exhibited gastrointestinal tract malabsorption, abnormal
Ezetimibe Added to Lipid-Lowering Drugs in HIV-Infected Patients

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RESULTS

A total of 105 patients were screened and met the inclusion criteria, but only 38 patients consented to participate in this study. Thirty-two patients completed the study, while 6 patients withdrew due to inconvenience with the follow-up schedule of the study. Baseline characteristics, including sex, age, body mass index (BMI), duration of exposure to PIs, absolute CD4 cell count, HIV-1 viral load, lipid-lowering drugs, and PI regimens are shown in Tables 1–3.

Efficacy outcome: After 18 weeks, mean (SD) of LDL-C, TC, TGs, and TC/HDL-C ratio were 126.8 (32.7) mg/dL, 202.4 (38.7) mg/dL, 212.7 (81.3) mg/dL, and 3.7 (1.1), respectively. Comparing of the lipid profiles between baseline and week 18 revealed that statistically significant decreases in the mean serum LDL-C, TC, TGs, and TC/HDL-C ratio (all p < 0.05). Eighteen (56.2%) patients presented LDL-C levels of < 130 mg/dL. The percent changes of mean serum lipid profiles compared to the baseline value is shown in Fig. 1.

Safety outcome: No patient experienced adverse events (including muscle-related adverse events) or abnormal laboratory parameters during the study period. The safety monitoring parameters are shown in Table 4.

DISCUSSION

As the results of the IMPROVE-IT study, Vytorin Efficacy International Trial (IMPROVE-IT) study have shown, the combination of ezetimibe and statins have significant benefits in non-HIV-infected patients with acute coronary syndrome (ACS), in the absence of any serious adverse events (31). The IMPROVE-IT study only included patients with ACS and compared the therapeutic

| Lipid-lowering drug | n (%) |
|---------------------|-------|
| Statin alone (mg/day) | 18 (56.2) |
| atorvastatin 10 | 2 (6.2) |
| atorvastatin 20 | 10 (31.2) |
| atorvastatin 40 | 6 (18.8) |

Table 2. Regimens of lipid-lowering drugs among HIV-infected patients

| HAART regimen (PIs-based) | n (%) |
|---------------------------|-------|
| LPV/RTV | 30 (93.8) |
| 2 NRTIs + LPV/RTV | 13 (40.6) |
| NRTI (s) + NRTI (s) + LPV/RTV | 3 (9.4) |
| NRTI (s) + LPV/RTV | 6 (18.8) |
| NRTI (s) + LPV/RTV | 5 (15.6) |
| LPV/RTV (mono-therapy) | 3 (9.4) |
| ATV + RTV | 2 (6.2) |
| 2 NRTIs + ATV + RTV | 1 (3.1) |
| NRTI (s) + ATV + RTV | 1 (3.1) |

Table 3. PIs-based HAART regimens among HIV-infected patients

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus.

Table 1. Baseline characteristics of patients

| Characteristics | Value |
|----------------|-------|
| women; n (%) | 19 (59.4) |
| age; yr, mean (SD) | 48.2 (6.7) |
| BMI; kg/m², mean (SD) | 22.0 (2.9) |
| LDL-C; mg/dL, mean (SD) | 165.4 (26.8) |
| duration of exposure to PIs; yr, mean (SD) | 8.7 (2.1) |
| absolute CD4 cell count; cells/μL, mean (SD) | 666 (246) |
| plasma HIV viral load; undetected (< 20 copies/mL), n (%) | 30 (93.8) |

BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus.

hepatic functions (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] elevation of > 3 times the upper normal limit), and renal impairment (chronic kidney disease stage 3–5; estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²) were excluded. All patients provided written informed consent prior to their enrollment. All eligible patients were administered ezetimibe (10 mg/day) on day 1 in addition to their current lipid-lowering drugs with HAART and were instructed to continue with the ezetimibe treatment until day 126 (week 18). They were also instructed to continue their routine dietary, exercise, and activities. All patients were scheduled to meet the study’s researchers at each visit for medication adherence counseling and drug interaction screening.

Data collection: Study visits were scheduled at screening, baseline (week 0), and weeks 6, 12, and 18. Fasting lipid profiles, and biochemistry and hematology data were collected during each visit. CD4 cell counts and plasma HIV-1 viral loads were assessed from their routine treatment workup. Adverse events, including signs and symptoms, were evaluated as safety parameters at every follow-up visit.

Statistical analysis: For statistical assessment, it was estimated that 38 patients would have 95% power to detect a mean difference of low density lipoprotein cholesterol (LDL-C), which would be decreased to 17.3 mg/dL at week 18 from baseline at α-value equal to 0.05 (one-sided). Demographic data were analyzed by descriptive statistics. Repeated-measure analysis of variance (ANOVA) was used to compare the mean difference of LDL-C and other parameters between pre- and post-treatment of each visit to baseline parameters. Data were analyzed using SPSS ver. 18.0 for Windows (SPSS, Chicago, IL, USA).

P-values (p) < 0.05 were considered as statistically significant.

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efficacy in patients administered either 40 mg simvastatin alone or a combination of 40 mg simvastatin plus 10 mg ezetimibe. The difference in the current study was that our study population comprised HIV-infected patients who were receiving PIs and lipid-lowering drugs for uncontrolled dyslipidemia. The prevalence of hypercholesterolemia in Thai HIV-infected patients was high (38). This study showed that the addition of ezetimibe to currently administered therapy significantly decreased LDL-C, TC, TGs, and TC/HDL-C ratio and slightly increased the HDL-C levels in week 18, albeit not significantly. These results are consistent with the results of previous studies (35–37). In the present study, the mean LDL-C reduction observed (38.6 mg/dL, 23.3%) was even lower than that previously reported (17.3–32.0 mg/dL, 7–18%), because our patients had a higher mean baseline LDL-C than that of the previous studies. Despite many patients being treated with atorvastatin (a higher potency statin), the reduction effects on LDL-C might be from a combination with fibrates in our patients. The changes of TGs in this study were statistically significant, which could have been due to 14 patients (43.8%) being treated with a combination with fibrates.

We found no difference between the lopinavir (LPV)/ritonavir (RTV) and atazanavir (ATV) + RTV groups in the outcome of dyslipidemia. However, only 2 patients (6.2%) were administered ATV (boosted with RTV) when compared to the LPV/RTV group (n = 30, 93.8%); thus, the former had too small of a sample size to enable a definite conclusion regarding this issue. In contrast, the addition of ezetimibe was beneficial and decreased the LDL-C in both groups. This study found that more than half of the patients (18 patients, 56.2%) achieved the LDL-C goal. There were 11 patients (34.4%) who received statin alone and 7 patients (21.9%) who received combination of statins and fibrate. These results could suggest that most patients had problems with hypercholesterolemia and dyslipidemia because they received moderate to high doses of statins in both groups (statin alone and combination groups).

Additionally, we found that the remaining of 10 patients (31.2%) could possibly achieve the LDL-C goal if they

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**Table 4. Laboratory parameters as part of safety monitoring**

| Parameter (unit, reference range) | Mean (SD) | Week 0 | Week 6 | p-value | Week 12 | p-value | Week 18 | p-value |
|----------------------------------|-----------|--------|--------|---------|---------|---------|---------|---------|
| **Hematology**                   |           |        |        |         |         |         |         |         |
| WBC (× 10^3/μL, 4.5–8)           | 7.3 (1.7) | 7.5 (1.9) | 1.000 | 7.2 (1.4) | 1.000 | 7.2 (1.7) | 1.000 |
| Hb (g/dL, 11–14)                 | 12.9 (1.6) | 12.6 (2.6) | 1.000 | 12.7 (1.6) | 1.000 | 12.6 (1.6) | 1.000 |
| Hct (%) (35–41)                  | 39.3 (4.2) | 39.6 (4.0) | 1.000 | 38.9 (4.5) | 1.000 | 38.4 (4.5) | 1.000 |
| Plt (× 10^3/μL, 140–400)         | 267.6 (64.6) | 270.3 (54.8) | 1.000 | 259.2 (61.3) | 1.000 | 265.1 (58.0) | 1.000 |
| **Renal related parameters**     |           |        |        |         |         |         |         |         |
| BUN (mg/dL, 7–20)                | 12.7 (3.9) | 12.4 (3.8) | 1.000 | 12.9 (3.7) | 1.000 | 13.5 (3.5) | 1.000 |
| S-Cre (mg/dL, 0.5–0.9)           | 0.9 (0.7) | 0.8 (0.2) | 1.000 | 0.8 (0.2) | 1.000 | 0.8 (0.2) | 1.000 |
| **Liver function tests**         |           |        |        |         |         |         |         |         |
| AST (IU/L, 0–31)                 | 23.1 (5.3) | 24.8 (9.5) | 1.000 | 24.5 (6.0) | 1.000 | 23.7 (6.6) | 1.000 |
| ALT (IU/L, 0–31)                 | 23.0 (9.9) | 24.3 (12.4) | 1.000 | 23.6 (10.1) | 1.000 | 22.3 (8.6) | 1.000 |
| ALP (IU/L, 35–104)               | 76.1 (22.0) | 72.4 (22.7) | 0.480 | 75.6 (22.3) | 1.000 | 73.3 (19.8) | 1.000 |

1: Bamrasnaradura Infectious Diseases Institute (BIDI) reference range.

WBC, white blood cell; Hb, hemoglobin; Hct, hematocrit; Plt, platelet; BUN, blood urea nitrogen; S-Cre, serum creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.
Ezetimibe Added to Lipid-Lowering Drugs in HIV-Infected Patients

were treated with the recommended maximum daily dose of statins with or without fibrates. Therefore, the addition of ezetimibe tended to decrease LDL-C and help achieve this goal. On evaluating the safety of this treatment, none of the patients in this study presented with any ezetimibe-related adverse events or laboratory abnormalities. This results little varied when compared to that of previous studies. A prospective, open-label study by Berg-Wolf et al. showed that only 1 patient who experienced asymptomatic elevation of creatine phosphokinase level, which subsequently returned to normal after ezetimibe discontinuation (36). Another randomized, placebo-controlled, crossover study by Chow et al. showed that 5 of 44 patients experienced grade 3 toxicities, including fever (n = 1), decreased absolute neutrophil count (n = 1), increased total bilirubin (n = 2), and nausea/vomiting (n = 1). The most common toxicities were ache/pain/discomfort and gastrointestinal symptoms such as nausea, diarrhea, and distention. However, none of the patients experienced a serious ezetimibe-related adverse event and required to discontinue treatment due to drug toxicities from adding ezetimibe to ongoing statin therapy when compared with placebos (37). Thus, the addition of ezetimibe to statins in HIV-infected patients receiving PIs appeared to be safe and well-tolerated (35–37).

There were some limitations to this study. First, this study was a single-center, pre–post study with a small sample size and short-term therapy. Second, patients received only general counseling about lifestyle modification that was not an intensive program for diet control or exercise. Third, patients were treated with a variation on the backbone of HAART and lipid-lowering drugs. In conclusion, the addition of ezetimibe to the current regimen of lipid-lowering drugs in HIV-infected patients with controlled dyslipidemia receiving PIs, significantly improved short-term efficacy by reducing their LDL-C, TC, TGs, and TC/HDL-C ratio, and was safe and well-tolerated.

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Conflict of interest None to declare.

REFERENCES
1. Monassithi W, Ongwandee S, Bhakecooep S, et al. Guidelines for antiretroviral therapy in HIV-1 infected adults and adolescents 2014, Thailand. AIDS Res Ther. 2015;12(12).
2. Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. Available at https://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Accessed April 27, 2017.
3. Erb P, Battagay M, Zinneri W, et al. Effect of antiretroviral therapy on viral load, CD4 cell count, and progression to acquired immunodeficiency syndrome in a community human immunodeficiency virus-infected cohort. Swiss HIV Cohort Study. Arch Intern Med. 2000;160:1134-40.
4. Fellay J, Boubaker K, Ledergerber B, et al. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. Lancet. 2001;358:1322-7.
5. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet. 2002;360:1747-8.
6. Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. JAMA. 2003;289:2978-82.
7. Frix-Moller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients–association with antiretroviral therapy. Results from the DAD study. AIDS. 2003;17:1179-93.
8. Frix-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med. 2003;349:1993-2003.
9. Grover SA, Coupal L, Gilmore N, et al. Impact of dyslipidemia associated with highly active antiretroviral therapy (HAART) on cardiovascular risk and life expectancy. Am J Cardiol. 2005;95:586-91.
10. Sackoff JE, Hanna DB, Pfeiffer MR, et al. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. Ann Intern Med. 2006;145:397-406.
11. DAD Study Group, Frix-Moller N, Reiss P, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med. 2007;356:1723-35.
12. Haubrick RH, Riddler SA, DiRienzo AG, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. AIDS. 2009;23:1109-18.
13. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (DAD) study. J Infect Dis. 2010;201:318-30.
14. WHO. Cardiovascular diseases (CVDs), fact sheet N 317. Available at http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed April 27, 2017.
15. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). JAMA. 2001;285:2486-97.
16. Dubé MP, Stein JH, Aberg JA, et al. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. Clin Infect Dis. 2003;37:613-27.
17. Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004;110:227-39.
18. Fichtenbaum C, Gerber JG, Rosenkranz SL, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS. 2002;16:569-77.
19. Hare CB, Vu MP, Grunfeld C, et al. Simvastatin–nelfinavir interaction implicated in rhabdomyolysis and death. Clin Infect Dis. 2002; 35:e11-2.
20. Hsuu P-H, Schultz-Smith MD, Lillibridge JH, et al. Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutaryl co-enzyme A reductase inhibitors lovastatin and simvastatin. Antiim- crob Agents Chemother. 2001;45:3445-50.
21. Chuck SK, Penzak SR. Risk-benefit of HMG-CoA reductase inhibi- tors in the treatment of HIV protease inhibitor-related hyperlipidemia. Expert Opin Drug Saf. 2002;1:5-17.
22. Davis HR, Veltri EP, Zetia: inhibition of Niemann-Pick C1 like 1 (NPC1L1) to reduce intestinal cholesterol absorption and treat hyperlipidemia. J Atheroscler Thromb. 2007;14:99-108.
23. Suthip T, Lüttjohann D, Kodal A, et al. Inhibition of intestinal chole- stoler absorption by ezetimibe in humans. Circulation. 2002;106:1943-8.
24. Knopp RH, Gitter H, Truitt T, et al. Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J. 2003;24:729-41.
25. Jeu L, Cheng JWM. Pharmacology and therapeutics of ezetimibe (SCH 58235), a cholesterol-absorption inhibitor. Clin Ther. 2003;25:35:e11-2.
26. Ros J, Grau AC, Bright RA, et al. Ezetimibe: a new cholesterol absorption inhibitor. Expert Opin Investig Drugs. 2003;12:845-57.
27. Kosoglou T, Statkevich P, Johnson-Levonas AO, et al. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. Clin Pharmacokinet. 2005;44:467-94.
28. Gagné C, Bays HE, Weiss SR, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol. 2002;90:1084-91.
29. Ballantyne CM, Houri J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation. 2003;107:2409-15.
30. Melani L, Mills R, Hassman D, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J. 2003;24:717-28.
31. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372:2387-97.
32. Stein E, Stender S, Mata P, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J. 2004;148:447-55.
33. Coll B, Aragonés G, Parra S, et al. Ezetimibe effectively decreases LDL-cholesterol in HIV-infected patients. AIDS. 2006;20:1675-7.
34. Wohl DA, Waters D, Simpson RJ Jr, et al. Ezetimibe alone reduces low-density lipoprotein cholesterol in HIV-Infected patients receiving combination antiretroviral therapy. Clin Infect Dis. 2008;47:1105-8.
35. Negredo E, Moltó J, Puig J, et al. Ezetimibe, a promising lipid-lowering agent for the treatment of dyslipidaemia in HIV-infected patients with poor response to statins. AIDS. 2006;20:2159-64.
36. Van den Berg-Wolf M, Klibanov OM, Gaughan JP, et al. Ezetimibe combined with low-dose statin effectively lowers LDL in protease inhibitor treated patients. AIDS Patient Care STDS. 2008;22:483-8.
37. Chow D, Chen H, Glesby MJ, et al. Short-term ezetimibe is well tolerated and effective in combination with statin therapy to treat elevated LDL cholesterol in HIV-infected patients. AIDS. 2009;23:2133-41.
38. Hiransuthikul N, Hiransuthikul P, Kanasook Y. Lipid profiles of Thai adult HIV-infected patients receiving protease inhibitors. Southeast Asian J Trop Med Public Health. 2007;38:69-77.