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ORIGINAL ARTICLE

Outcomes of switch to atazanavir-containing combination antiretroviral therapy in HIV-1-infected patients with hyperlipidemia

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Background: Prolonged exposure to combination antiretroviral therapy (CART) may result in hyperlipidemia and other metabolic complications. This study aimed to evaluate the clinical, virologic, and immunologic outcomes in HIV-infected patients with hyperlipidemia whose CART was switched to atazanavir-containing antiretroviral regimens.
Methods: In this 48-week prospective, observational study that was conducted at designated hospitals for HIV care in Taiwan, HIV-infected patients aged 18 years or older who had developed hyperlipidemia after receiving CART that did not contain atazanavir were enrolled. Antiretroviral regimens were switched to regimens containing two nucleoside reverse-transcriptase inhibitors plus atazanavir 400 mg once daily or atazanavir 300 mg boosted with ritonavir 100 mg once daily. The lipid profiles, including total triglycerides, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, CD4+ lymphocyte counts, and plasma HIV RNA load were determined every 3 months.

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Results: Sixty-six patients with hyperlipidemia were enrolled. At the end of the study, triglyceride levels declined by 49.0% ($p = 0.0002$) and total cholesterol levels by 18.1% from baseline ($p < 0.0001$), whereas there were no significant changes observed for low-density lipoprotein- and high-density lipoprotein-cholesterol levels. Mean CD4 lymphocyte count increased from 465 cells/μL at baseline to 498 cells/μL at the end of the study, whereas the proportion of patients with undetectable plasma HIV RNA load increased from 73.1% to 81.7%. The regimens were well tolerated.
Conclusions: Switch to atazanavir-containing regimens that were well tolerated resulted in significant improvement of hyperlipidemia and maintenance of clinical, immunologic, and virologic responses to CART.

Introduction

Since combination antiretroviral therapy (CART) was introduced in 1996, mortality and morbidity rate in HIV-infected patients have significantly declined.[1] However, prolonged exposure to antiretroviral therapy is associated with a multitude of metabolic complications, such as insulin resistance, diabetes mellitus, dyslipidemia, and abnormal fat distribution.[2–6] Among the three classes of antiretroviral therapy that were available in the first decade of CART, protease inhibitors (PIs) played a major role in the development of metabolic adverse events, notably hyperlipidemia.[7,8] The frequency of PI-associated hyperlipidemia ranged from 28% to 80%; hypertriglyceridemia was the most common presentation that ranged from 40% to 80%, followed by hypercholesterolemia that ranged from 10% to 50%, depending on the study populations and duration and types of antiretroviral regimens prescribed.[5,9–15] The incidence of hypertriglyceridemia is significantly higher in patients treated with antiretroviral regimens containing ritonavir compared with other regimens not containing ritonavir.[10] The mechanisms of PI-related dyslipidemia were not fully understood and several pathways were proposed, such as the homology of HIV-1 protease and cytoplasmic retinoic acid-binding protein type 1 and low-density lipoprotein (LDL) receptor-related protein, which are the proteins involved in lipid metabolism, suppression of adipogenesis and increased lipolysis, reduced triglyceride storage and increased circulating triglyceride levels, or suppression of proteasome-induced degradation of apolipoprotein B in hepatocytes.[11,16–18]

In association with impaired glucose tolerance and new-onset diabetes mellitus that may occur in 35% and 3% to 5%, respectively, in PI-treated HIV-infected patients,[3] hyperlipidemia may increase risk of myocardial infarction and morbidity and mortality.[7,19] Although adding lipid-lowering agents is an option to improve lipid profiles in HIV-infected patients with dyslipidemia, there were several concerns, such as drug-drug interactions between lipid-lowering agents and PI, rhabdomyolysis, and cost increment.[15]

Atazanavir is a novel azapeptide PI that is less frequently associated with insulin resistance and dyslipidemia.[20–23] In this study, we aimed to evaluate the effectiveness and safety of atazanavir-containing regimens in HIV-infected patients who had developed hyperlipidemia after exposure to other antiretroviral regimens.

Patients and methods

Study design, populations, and evaluations

This was a 48-week, prospective, observational study. HIV-infected patients with hyperlipidemia who were followed at the designated hospitals for HIV care in Taiwan were eligible for enrollment from January 21, 2005 to November 18, 2005. Inclusion criteria were age ≥18 years, estimated therapeutic adherence ≥90% (evaluated by patients' self report and frequency of missing previous clinic appointments), and taking PI or non-nucleoside reverse transcriptase inhibitor (NNRTI)-based antiretroviral regimens with dyslipidemia. Dyslipidemia was defined as triglyceride >250 mg/dL or total cholesterol >240 mg/dL. Exclusion criteria were any changes to the nucleoside reverse-transcriptase inhibitors (NRTI) that were known to affect lipid levels or addition of other lipid-lowering agents. Data collected for each patient at baseline included demographic characteristics, medical history, family history, smoking history, antiretroviral therapy prescribed before the enrollment, other concomitant medications, physical findings, CD4+ lymphocyte counts, plasma HIV RNA load, and hematological and biochemistry tests.

The subjects were switched to regimens containing atazanavir 400 mg or atazanavir 300 mg boosted with ritonavir 100 mg once daily without changing backbone NRTI. After enrollment, medication adherence, CD4+ lymphocyte counts, HIV RNA load, and hematological and biochemistry tests were assessed every 3 months during the 48-week study period. All the blood samples were collected in the fasting state. The biochemistry examinations included renal function, liver function, glucose, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and LDL cholesterol. Plasma HIV RNA load and CD4 cell counts was quantified by the Cobas Amplicor HIV-1 Monitor™ Test, version 1.5, (Roche Diagnostics Corporation, Indianapolis, IN, USA) and FACSFlow (BD FACS Calibur, Becton Dickinson, CA, USA), respectively. Undetectable plasma HIV RNA viral load was defined as <400 copies/mL.

The primary endpoint was to evaluate the proportion of patients achieving normal lipid profiles after switch to an atazanavir-containing regimen, whereas the secondary endpoint was to evaluate the safety and immunologic and virologic responses after switch. The study was approved by the Research Ethics Committee of each participating hospital and all subjects gave written informed consent.

Management of adverse events or intolerance

Toxicities were graded according to the modified World Health Organization criteria: scale of 1 to 4. Subjects with more than Grade 2 adverse events or severe isolated hyperbilirubinemia (bilirubin levels was greater than five times of the upper limit of normal) would be withdrawn from the study.

Statistical analysis

Changes from baseline were calculated for lipid values, total bilirubin level, CD4 counts, and plasma HIV RNA loads. Qualitative baseline characteristics were compared using the Chi-square tests. Continuous variables were expressed as mean values with standard deviation. The statistical analysis was performed by SAS software (Version 6.2, SAS Institute, Cary, NC). All the tests were two-sided and a p value less than 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 66 HIV-infected patients with hyperlipidemia were enrolled. Table 1 summarizes the baseline characteristics of the patients. There were 63 (95.5%) males and 3 (4.5%) females, and their mean age was 42.1 years. Five patients (7.6%) were positive for hepatitis B surface antigen and 2 (3.0%) for anti-hepatitis C virus antibody. The baseline CD4 count before switch was 468 cells/μL; 41 patients (62.1%) had a CD4 count higher than 350 cells/μL. Forty-nine patients (74.2%) had undetectable plasma HIV RNA load before switch. Before switch, 38 patients (57.6%) were taking PI-containing regimens and 28 (42.4%) were taking NNRTI-containing regimens before enrollment. Regarding the backbone NRTI combinations, 27 patients (42.9%) were on zidovudine plus lamivudine (3TC); 12 (19.0%) were on stavudine plus 3TC; 5 (7.9%) were on didanosine plus 3TC; 5 (7.9%) were on abacavir plus 3TC; and 1 (1.6%) was on abacavir plus didanosine. In 16 (24.2%), NRTI prescribed were not described in the medical records before switch. Sixty-four patients (97.0%) were switched to regimens containing 400 mg of atazanavir, and 2 (3%) were switched to 300 mg of atazanavir boosted with 100 mg of ritonavir.

Changes of lipid profiles

Before switch, baseline mean triglyceride level was 792 mg/dL (range: 83—5,933) and total cholesterol was 240.7 mg/dL (range: 134—690). Twenty-five patients

Table 1 Baseline characteristics of 66 patients receiving atazanavir-containing combination antiretroviral therapy

Variables	Value
Age (mean, yr)	42.1
Male sex, *n* (%)	63 (95.5)
Positive HBsAg, *n* (%)	5 (7.6)
Positive anti-HCV antibody, *n* (%)	2 (3.0)
CD4 count before switch, mean (SD), cells/μL	468 (271)
CD4 count>350 cells/μL, *n* (%)	41 (62.1)
Log HIV RNA viral load before switch, mean (SD), $\log_{10}$ copies/mL	3.1 (1.2)
HIV RNA viral load <400 copies/mL, *n* (%)	49 (74.2)
Baseline triglycerides, mean (SD), mg/dL	792.0 (838.0)
Baseline total cholesterol, mean (SD), mg/dL	240.7 (96.1)
Baseline total bilirubin, mean (SD), mg/dL	0.7 (0.4)
Receiving lipid-lowering agents, *n* (%)	25 (37.9)
NRTI before switch, *n* (%)	58 (87.9)
AZT + 3TC	27 (40.9)
D4T + 3TC	12 (18.1)
Other combinations	8 (12.1)
ddI + 3TC	5 (7.6)
ABC + 3TC	5 (7.6)
ABC + ddI	1 (1.5)
NNRTI before switch, *n* (%)	28 (42.4)
Efavirenz	25 (37.9)
Nevirapine	3 (4.5)
PI before switch, *n* (%)	38 (57.6)
Lopinavir/ritonavir	19 (28.8)
Indinavir/ritonavir	9 (13.6)
Nelfinavir	5 (7.6)
Indinavir	3 (4.5)
Saquinavir/ritonavir	1 (1.5)
Other combinations	1 (1.5)

3TC = lamivudine; ABC = abacavir; AZT = zidovudine; D4T = stavudine; ddI = didanosine; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; PI = protease inhibitor; SD = standard deviation.

(37.9%) were taking lipid-lowering agents at baseline. Twelve months after switch to atazanavir-containing regimens, mean triglyceride level declined by 49.0%, from 792.0 to 399.4 mg/dL ($p = 0.0002$) (Fig. 1A), and total cholesterol level by 18.1%, from 240.7 to 196.2 mg/dL ($p < 0.0001$) (Fig. 1B). Twenty-four patients (36.4%) achieved triglyceride levels less than 250 mg/dL and 48 patients (72.7%) achieved total cholesterol levels less than 240 mg/dL after switch. The most significant decreases were observed between 3 and 6 months after switch. Although there was an increase of total mean cholesterol level 9 to 12 months after switch, this level was still significantly lower than that at baseline. Contrary to the findings of significant improvement of triglyceride and total cholesterol level after switch, there was no significant changes in LDL ($p = 0.43$) and high-density lipoprotein cholesterol ($p = 0.61$) levels.

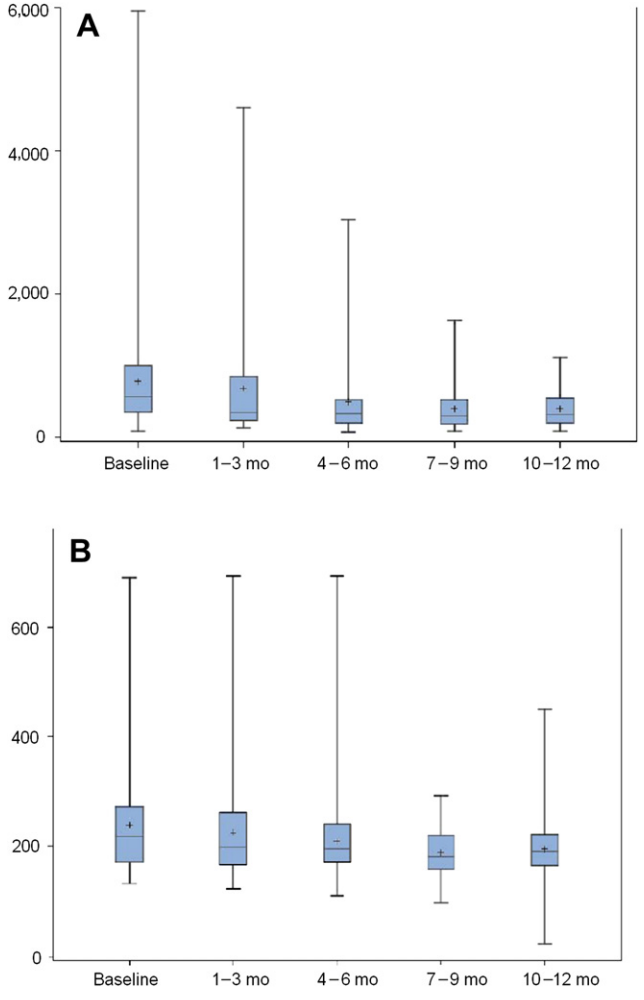

Figure 1. (A) Evolution of triglyceride levels (mg/dL) after switch to atazanavir-containing combination antiretroviral therapy during the study period. Top and bottom lines represent minimum and maximum values of triglyceride levels of the patients at different time points. The upper and lower end of the box represent first quartile and third quartile, respectively, whereas the bar and cross in the box indicates median and mean value, respectively. (B) Evolution of total cholesterol levels (mg/dL) during the study period.

Safety

Nine patients were withdrawn from the study during the study period, eight because of adverse effects of atazanavir, including five (7.6%) patients who developed hyperbilirubinemia greater than 5 mg/dL, one (1.5%) patient who had elevation of aminotransferases from 73 to 500 U/L after 41 days of CART containing atazanavir 400 mg daily, and two (3.0%) had skin rashes. Compared with baseline bilirubin levels, there was a significant increase in total bilirubin levels from 0.75 to 1.79 mg/dL after switch to atazanavir-containing regimens ($p < 0.001$) and this increase could be observed during the first 3 months of switch. The evolution of total bilirubin level is shown in Fig. 2.

Clinical, virologic, and immunologic responses after switch

Serial changes of CD4 counts are shown in Fig. 3. At baseline, 60 patients (90.9%) had a CD4 count greater than 200 cells/μL and 41 patients (62.1%) had a CD4 count greater than 350 cells/μL. There were no significant changes of CD4 counts after switch to atazanavir-containing regimens during the 48-week study period, whereas a significant reduction of plasma HIV RNA load was observed in the first 6 months after switch. The percentage of patients who had undetectable plasma HIV RNA load increased from 73.1% to 81.7%. After switch, no patients who had achieved undetectable plasma HIV RNA load experienced virologic rebound. None of the patients developed opportunistic infections or malignancies during the study period.

Discussion

Atazanavir is a PI known for a lower incidence of dyslipidemia compared with other PI and efavirenz.[24–26] The reasons why atazanavir had less dyslipidemia were not clearly understood. Switching to atazanavir-containing regimen has been proposed as a measure to improve lipid profiles in patients who develop dyslipidemia caused by

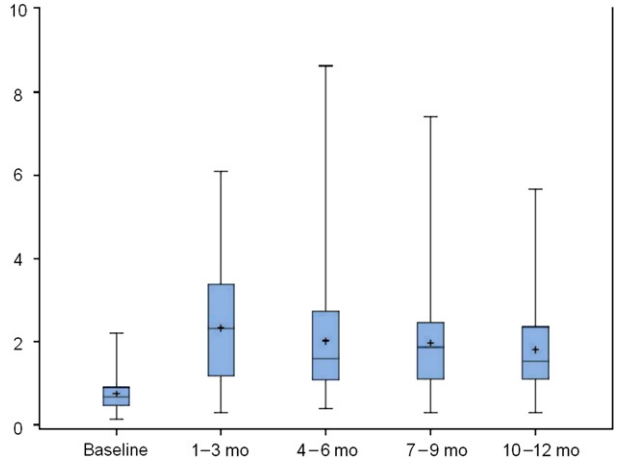

Figure 2. Evolution of total bilirubin levels (mg/dL) during the study period.

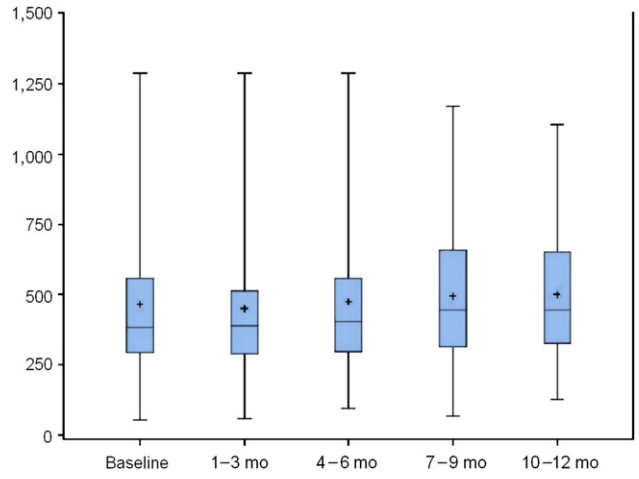

Figure 3. Evolution of CD4 counts (cells/μL) during the study period.

non-atazanavir-containing regimens other than switching to NNRTI or addition of lipid lowering agents.[27–31]

Our study demonstrated that HIV-infected patients who had developed hyperlipidemia after CART had improvement of lipid profiles after switch to atazanavir-containing regimens throughout the 48-week study period, and the reduction could be seen as early as the first 3 months after switch in our study. Furthermore, virologic response also improved after switch without encountering significant adverse events. All the studies showed more significant decrease in triglyceride levels compared with the change in total cholesterol levels. The findings of *in vitro* studies that atazanavir does not induce triglyceride synthesis in HepG2 cells as other PI may explain the reason why significant improvement of triglyceride levels occurs.[32,33] Although sustained favorable effect on lipid profiles has been reported in a study conducted for greater than 72 weeks,[34] we observed a rebound in total cholesterol levels in the later study period, which suggests that other factors, such as diet and life style, should also be taken into account to maintain the favorable effect of atazanavir on the lipid levels.

Soriano et al.[27] demonstrated that unboosted atazanavir-containing regimens had more favorable lipid profiles than atazanavir boosted with ritonavir. In our study, we were not able to compare the extent to which lipid levels may decline between boosted and unboosted atazanavir-containing regimens because only two were switched to boosted atazanavir-containing regimens.

In our study, 60% of the patients had a triglyceride level greater than 250 mg/dL after switch for 48 weeks. Other than diet and life style, genetic factors may also play a role. There were several studies suggesting that single-nucleotide polymorphism on *APOA5* is associated with variations of plasma lipid levels, especially hypertriglyceridemia.[35,36] In Chinese populations, c.553G>T polymorphism in *APOA5* may present as a prognostic indicators of hypertriglyceridemia.[37] Decreased triglyceride metabolism because of this genetic background causes extremely high triglyceride even after switch to atazanavir-containing regimens.

Most of the patients in this study had achieved good viral suppression before switch. After switch, we did not observe any immunologic and virologic failures. Our study results are comparable with those of The Switch to Another Protease Inhibitor study, which demonstrated that patients who switched to atazanavir-containing regimens had a lower rate of virologic rebound than those who continued other comparator PIs.[31] Other studies that compared the efficacy of atazanavir with that of other PI also showed same results.[27–29,38] Therefore, switching to atazanavir-containing regimen can be considered safe for patients who had good virologic suppression under non-atazanavir-containing regimens.

Atazanavir is a competitive inhibitor of the uridine diphosphate-glucuronosyl transferase 1A1 enzyme, which may result in unconjugated hyperbilirubinemia, the most common side effect in our study.[34,39] This mechanism is similar to the pathogenesis of Gilbert syndrome, which is of little clinical significance because this effect is neither hepatotoxic nor irreversible.[40,41] Several studies have demonstrated that the frequency of atazanavir-containing regimens had a low frequency of hepatotoxicity even in patients with hepatitis B and/or C coinfection.[41,42] Besides, the short-term effectiveness of antiretroviral agents in HIV-infected patients with hepatitis B and/or C coinfection was similar to patients without coinfection.[41] Therefore, atazanavir-containing regimens seem to be safe in patients with hepatitis B or C coinfection.

In conclusion, atazanavir-containing antiretroviral therapy had favorable effects on plasma triglyceride and cholesterol levels without increasing immunologic or virologic failure. Switch to atazanavir-containing regimen could be considered in patients who develop severe dyslipidemia because of other PI- or NNRTI-based regimens.

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