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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.