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ORIGINAL ARTICLE

Highly active antiretroviral therapy-related hepatotoxicity in human immunodeficiency virus and hepatitis C virus co-infected patients with advanced liver fibrosis in Taiwan

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Liver fibrosis;
Protection

Background: The prevalence of patients co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is higher in Taiwan than in Western countries. This study aimed to analyze the frequency and risk factors for highly active antiretroviral therapy (HAART)-related liver toxicity in patients co-infected with HIV and HCV with advanced liver fibrosis in Taiwan.
Methods: This retrospective cohort study included 228 HAART-experienced and HAART-naïve patients who were co-infected with HIV and HCV from January 2013 to December 2013 in Taiwan. Transaminase elevation (TE) was defined by grades. Fibrosis 4 score and aspartate-to-platelet ratio index were used to evaluate liver fibrosis. Cox proportional hazard regression model was used to analyze the risk factors for time to TE events.
Results: A total of 228 patients were included. Only two episodes (1.28%) of high-grade TE were observed. The overall prevalence rate of TE was 16%, and the incidence was 1.38 cases/100 patient-months. Two predictive factors of TE were the initiation of HAART during the study period and CD4 cell count less than 350 cells/mm^3. Subgroup analysis showed that

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HAART improved liver fibrosis status in patients who had advanced liver fibrosis at baseline ($p = 0.033$).
Conclusion: The frequency of HAART-related TE in HIV and HCV co-infected patients in Taiwan was much lower than that observed in previous studies. Pre-existing advanced liver fibrosis had no influence on the frequency of TE. The use of HAART showed benefits on liver fibrosis progression in patients with underlying advanced liver fibrosis.

Introduction

Co-infection with hepatitis virus is a common condition in patients infected with human immunodeficiency virus (HIV). Hepatitis C virus (HCV), in particular, has become a major concern because of its high prevalence, especially in patients with intravenous drug use, and its association with higher morality and liver-related morbidities in HIV-infected patients.[1–3] With the introduction of highly active antiretroviral therapy (HAART), HIV-related mortality and the risk of opportunistic infections had greatly decreased. However, an increasing amount of research has been focused on the issue of HAART-related liver injury, especially in patients infected with both HIV and HCV.[4–7] Because they share the same route of infection, HCV co-infection with HIV is most commonly seen in patients with intravenous drug use. Compared to the prevalence of HCV in HIV-infected patients with intravenous drug use in Europe (75—82%), the prevalence in Taiwan (96.6%) and China (95.1—99.3%) is much higher,[1,8–11] which makes the management of HIV/HCV co-infection and the surveillance of HAART safety regarding liver injury more important in these regions. Several articles have discussed the impact of different HAART combinations on liver injury in those co-infected with HIV and HCV in Europe and the United States. HAART-related hepatotoxic events, such as high-grade (Grades III and IV) transaminase elevation (TE), acute liver failure, and death have been reported.[4–7,12] However, no relevant data reporting the incidence of HAART-related hepatotoxicity are available in Taiwan. In addition, co-infection with HIV and HCV also causes a more rapid progression of liver fibrosis,[13] and the status of liver fibrosis and the effect on HAART-related liver injury in this population in Taiwan are also unknown.

The aim of this study, therefore, was to evaluate the frequency of HAART-related liver injury and the effect of different HAART regimens in patients co-infected with HIV and HCV in Taiwan, a high-prevalence area. The status of advanced liver fibrosis was also assessed and the impact on HAART-induced liver injury was analyzed.

Patients and methods

Study design and patients

This study was a retrospective cohort study including HAART-experienced and HAART-naïve HIV-infected patients who were regularly followed up at a special outpatient clinic for intravenous drug users of a tertiary teaching hospital in southern Taiwan from January 1, 2013 to December 31, 2013. Patients with HIV and HCV co-infection were included. All of the patients were treated in accordance with the Taiwan Guidelines for Diagnosis and Treatment of HIV/AIDS at the time of prescription. The choice of HAART regimen was made by clinical physicians. All patients who experienced HAART during the study period received HAART for at least 1 week. Clinical and laboratory examinations were carried out at baseline, after the first 4 weeks, and every 4—6 months thereafter until the end of the study. No patients in this study received additional antiviral regimens other than HAART. The primary end point was the occurrence of TE. The study end date was December 31, 2013, if no TE was observed; otherwise, the date when TE level was found was used.

Definition of TE and other laboratory investigations

Baseline levels of plasma aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured. In the patients with normal baseline levels of AST and ALT, values of AST and ALT 1.25—2.5 times the upper level of normality (ULN) were considered to have Grade I TE, 2.6—5 times the ULN were considered to have Grade II TE, and more than five times the ULN were considered to have high-grade TE (Grades III and IV). In the patients who presented with abnormal baseline levels of AST and ALT, a 1.25—2-fold increase from baseline was considered Grade I TE, a 2.5—5-fold increase as Grade II TE, and a more than 5-fold increase as high-grade TE (Grades III and IV).

The diagnosis of hepatitis B virus (HBV) infection was based on the positive result of HBV surface antigen radioimmunoassay. HCV infection was diagnosed based on the presence of serum HCV antibody, determined by anti-HCV enzyme-linked immunosorbent assays kit (ARCHITECT i1000SR, Abbott Laboratories). Plasma HIV viral load was measured using COBAS AMPLICOR HIV-1 monitor test, version 1.5 (Roche Diagnostics Corporation, Indianapolis, IN, USA). Undetectable viral load was defined as plasma HIV viral load less than 50 copies/mL. CD4 lymphocyte subpopulations were quantified by FACSFlow (Becton Dickinson and Company, Franklin Lakes, NJ, USA).

Assessment of liver fibrosis

Two noninvasive models, namely, fibrosis 4 score (FIB-4) and aspartate-to-platelet ratio index (APRI), were used to evaluate the status of liver fibrosis. FIB-4 was calculated by age, AST level, ALT level, and platelet count, and a value