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Co-administration of rifampin and nevirapine in HIV-infected patients with tuberculosis

[CORRESPONDENCE]

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Before the advent of highly active antiretroviral therapy, there was no contraindication for the concomitant administration of antituberculous agents and the few available antiretroviral drugs. The response rate to standard antituberculosis therapy in HIV-infected patients was similar to that observed in uninfected patients with tuberculosis [1]. Paradoxically, the introduction of protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) compounded the adequate treatment of tuberculosis and HIV infection if the two infections were to be treated together. The interactions between rifampin and PI or NNRTI led to initial recommendations contraindicating the concomitant use of the two classes of drugs [2]. Later, it was shown that rifampin can be concomitantly administered with some PI [3,4]. Although it has been suggested that rifampin could be administered with the two NNRTI, efavirenz and nevirapine, clinical data are still scarce [5-7].

We present the results of an observational study performed in seven Spanish hospitals. We have reviewed the records of all HIV-infected patients who had culture-confirmed tuberculosis and who were treated for tuberculosis and HIV infection after January 1998. For the purposes of this study, we have collected data from the patients who received an antituberculosis regimen that included rifampin 600 mg a day for 9 months (in all cases in combination with isoniazid and pyrazinamide during the first 2 months) and an antiretroviral regimen that included nevirapine 400 mg a day (in all cases in combination with two nucleoside reverse transcriptase inhibitors). The objectives of the study were to evaluate the clinical, virological and immunological outcomes of HIV infection, as well as the response to antituberculosis therapy and the potential toxicity of the co-administration of the two drugs.

A total of 36 patients were included in the study. Of these, four were lost to follow-up soon after the initiation of the treatment and could not be evaluated. The characteristics of the remaining 32 patients are shown in [Table 1](#). All patients were clinically and microbiologically cured of their tuberculosis at the end of therapy. No relapses have been observed after a median follow-up of 6 months. HIV-RNA levels decreased a median of 4.1 log copies/ml (from 4.4 to < 2.3 log), with 74% of patients reaching undetectable viral loads. The CD4 cell count increased from 121 to 284 cells/mm³, with a median increase of 116 cells/mm³. With regard to the clinical outcome of HIV infection, three patients developed an AIDS-defining illness during the study (*Pneumocystis carinii* pneumonia, one case; non-Hodgkin's lymphoma, two cases) and six additional patients had oral candidiasis. There were three deaths, one before the completion of antituberculosis treatment (non-Hodgkin's lymphoma) and two after the end of therapy (lung cancer and non-Hodgkin's lymphoma).

Table 1. Baseline characteristics of 32 HIV-infected patients with tuberculosis treated concomitantly with nevirapine and rifampin. IQR, Interquartile range.

Significant toxicity developed in eight patients (25%), leading to the discontinuation of one or more drugs in five patients (16%). Four patients developed hepatitis that was attributed to rifampin, and led to withdrawal of the drug in two patients. Four patients presented with adverse events that were deemed secondary to nevirapine (gastrointestinal disturbances, two patients; hepatitis plus rash, one patient; rash, one patient). Nevirapine was discontinued in all four patients.

According to different pharmacokinetic studies and reports, the administration of rifampin results in a decrease in the plasma levels of nevirapine ranging from 37 to 58% [8]. However, nevirapine is characterized by a high therapeutic index. With the usual dose of 400 mg a day, the C_{min} in the steady state was 4.5 ± 1.9 µg/ml, which is much higher than the usual IC₅₀ for the drug (0.0025–0.025 µg/ml) [9]. Sufficient drug levels to inhibit the virus are thus present in the plasma even after the most significant interaction found with rifampin. Moreover, two clinical studies [6,7] have shown that the interaction between rifampin and nevirapine was in the range of a 20% reduction of the nevirapine plasma levels, with no significant impact on the virological effect of the drug.

The good virological and immunological response observed in our patients are consistent with the pharmacokinetic data. A response rate of 74% of patients achieving undetectable plasma viral loads is within the range found in clinical studies with combinations that included nevirapine. We were especially concerned about potentially increased toxicity, but the development of liver toxicity or skin rash was no higher for the combination than when the drugs were given separately.

Although a prospective clinical trial may be warranted, the conclusions of the study are helpful for physicians caring for patients with tuberculosis and HIV infection. Nevirapine can be included in an antiretroviral regimen to treat HIV-infected patients newly diagnosed with tuberculosis who receive rifampin. This possibility may facilitate the still difficult task of treating the two diseases concomitantly.

Table 1. Baseline characteristics of 32 HIV-infected patients with tuberculosis treated concomitantly with nevirapine and rifampin.

Characteristic	
Age, years (median IQR)	35 (25–51)
Male sex (%)	85
Intravenous drug use (%)	59
Previous antiretroviral therapy (%)	40
Previous AIDS (%)	53
CD4 cell count, cells/mm ³ (median IQR)	121 (11–975)
HIV RNA, log copies/ml (median IQR)	4.4 (< 2.3–5.7)
Localization of tuberculosis	
Pulmonary (%)	52
Extrapulmonary (%)	48
Length of treatment, months (median IQR)	9 (7–21)
Follow-up, months (median IQR)	15 (7–24)

IQR, Interquartile range.

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