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Risk factors for hepatotoxicity in patients treated with highly active antiretroviral therapy: a cohort study

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BACKGROUND: Recent studies have evaluated the risk factors of hepatic toxicity in HIV patients treated with highly active antiretroviral therapy (HAART). Some authors identified as risk factors treatment with ritonavir and co-infection with hepatitis C virus (HCV) and/or hepatitis B virus (HBV); others, treatment with stavudine and chronic HBV hepatitis.

OBJECTIVE: To identify the different risk factors in the development of hepatotoxicity in patients treated with protease inhibitors (PI).

METHODS: To assess the incidence of adverse events related to PI treatment, we are conducting a prospective cohort, multicentre study on HIV-positive patients starting treatment with at least one PI. The study began in September 1997 and was carried out in 10 Infectious Diseases Departments in Northern Italy. Severity of reaction was evaluated using the ACTG (AIDS Clinical Trial Group) adverse experience grading scales, but AST, ALT and γ GT increases were analysed with reference to baseline levels. The variables considered for the analysis of risk factors were the following: sex, age, epidemiology, CDC stage, CD4 cell count at enrolment, antiretroviral drugs used, history of cytolysis, HCV and/or HBV co-infections. Rates ratios (RR) of hepatotoxicity were calculated, and logistic regression was used to adjust simultaneously for the potentially confounding effects of selected variables (Cox model). The RR of adverse events during PI treatment was calculated as users versus non-users for each drug.

RESULTS: The results presented here concern 1480 patients, 1066 male. Average age was 37.1 years (SD \pm 8.1), and CD4 lymphocyte count at enrolment was 265 cell/mm³ (SD \pm 201). Average follow-up time is equal to 22 months. The incidence rate (IR) for hepatotoxicity per 100 person-years was 5.8 (95% CI 5.7-5.9) for reactions of any grade; the IR for grades 3 and 4 was 2.7 (2.6-2.8). The risk of developing hepatotoxicity was significantly increased with the presence of cytolysis at enrolment (RR 2.2; P <0.002) and of HCV-Ab positivity (RR 2.2; P <0.01). Neither HBsAg positivity nor co-infection with HCV/HBV were not statistically significant. Furthermore, our study showed a significant correlation with ritonavir treatment (RR 2.1; P <0.001).

CONCLUSIONS: Our study confirms that hepatotoxicity is a frequent adverse event in HAART therapy. Risk factors are the presence of hepatitis at baseline, while treatment with ritonavir involves a risk, which is at least twice as high as with other protease inhibitors.

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