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Hepatotoxicity due to rifampicin, isoniazid and pyrazinamide in patients with tuberculosis: Is anti-HCV a risk factor?

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ABSTRACT

Background and Rationale. Among the adverse events related to tuberculosis treatment, hepatotoxicity is the most serious, and recognition of risk factors for it is essential to achieve successful therapy. The aim of the study is to evaluate the role of anti-HCV as a risk factor for hepatotoxicity in hospitalized patients under tuberculosis treatment with rifampicin, isoniazid and pyrazinamide (RHZ). **Methods.** Historical cohort study carried out at Hospital Sanatório Partenon, from 1998 to 2006. Patients aged 18 years or older, tested for anti-HCV, who presented normal pre-treatment aminotransferases (AST, ALT) and bilirrubin and who used RHZ during hospitalization were included in the study. Individuals who used anti-tuberculosis drugs six months prior to hospitalization, had clinical evidence of chronic liver disease or showed previous history of hepatotoxicity to RHZ were excluded. **Results.** A sample of 534 patients was studied. The incidence of hepatotoxicity was 8.8% (n = 47). After univariate analysis, the following variables were associated to hepatotoxicity: anti-HIV positive, anti-HCV positive, use of antiretroviral therapy and high doses of rifampicin and isoniazid per kg of body weight ($p < 0.05$). When Cox regression was performed, anti-HIV positive [RR = 2.3 ($IC_{95\%}$ 1.2-4.1); $p = 0.008$] and high doses of isoniazid per kg of body weight [RR = 1.3 ($IC_{95\%}$ 1.1-1.7); $p = 0.016$] remained independently associated to development of hepatotoxicity. **Conclusions.** In conclusion, the anti-HIV positive and high doses of isoniazid were considered independent risk factors for hepatotoxicity due to RHZ esqueme in the present study. Though univariate analysis showed that anti-HCV was associated to the outcome, it was not identified as an independent risk factor for hepatotoxicity related to the use of RHZ when the analysis was controlled to HIV.

Key words. HIV. Hepatitis C. Anti-tuberculosis medications.

INTRODUCTION

Tuberculosis (TB) has always represented a serious public health problem in developing countries. In developed nations, it reached importance again after the emergence of the infection by human immunodeficiency virus (HIV). The growth in the number cases of TB became progressive, with an annual incidence of active pulmonary TB in the world approaching eight million, and with approximately two million deaths per year.[1-3]

With regard to the treatment, the scheme for recently diagnosed TB cases in Brazil since 1980 is combining rifampicin, isoniazid and pyrazinamide (RHZ) for two months, followed by rifampicin and isoniazid (RH) for another 4-7 months (first-line therapy).[4] This scheme is almost 100% effective and presents good tolerance. The need to change schemes due to toxicity occurs at a rate of less than 5%. Hepatotoxicity is among the most serious adverse effects.[5]

Some authors suggest that HIV and hepatitis C virus (HCV) are independent risk factors for developing hepatotoxicity induced by anti-tuberculosis medications.[6]

Ungo, *et al.*[6] describe the risk of developing hepatotoxicity from anti-tuberculosis drugs in patients with hepatitis C or HIV as being four and five times greater respectively. In patients co-infected by HCV and HIV, this risk increased 14.4 times.

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Kwon, *et al*.[7] also revealed a greater incidence of hepatotoxicity during treatment of tuberculosis in patients infected with hepatitis C virus.

This study intends to assess the role of anti-HCV as a risk factor for hepatotoxicity in hospitalized patients treated for tuberculosis.

PATIENTS AND METHODS

A historical cohort study was carried out with a sample comprised of patients who were hospitalized at Hospital Sanatório Partenon, Porto Alegre, Brazil, for treatment of tuberculosis, during the period from 1998 to 2006. The criteria for inclusion were: being 18 years of age or older; having an anti-HCV test; having serum aminotransferases (AST, ALT) and bilirubin levels within the normal range prior to tuberculosis treatment; being under RHZ during hospitalization. The criteria for exclusion were: having made use of anti-tuberculosis drugs during the six months that preceded hospitalization; presenting with clinical evidences of chronic liver disease; having a prior history of hepatotoxicity induced by RHZ. Patients were consecutively included in the study.

Hepatotoxicity was considered whenever a patient, using RHZ, presented with altered liver tests, that is: increase in ALT more than three times the upper limit of normality and/or levels of total bilirubin greater than two times the upper limit of normality.[8]

Before beginning treatment, routine blood tests were run on the patients in order to analyze liver function, as well as to determine anti-HCV (3rd generation ELISA method) and anti-HIV (ELISA method and, if positive, confirmation by Western-Blot).

Treatment was carried out using the RHZ scheme, with daily doses of drugs adjusted to body weight, as per Norms of the State Program for the Control of Tuberculosis (weight 20 to 40 kg, R: 300 mg, H: 200 mg and Z: 1000 mg; from 40 to 60 kg, R: 450 mg, H: 300 mg and Z: 1500 mg; over 60 kg, R: 600 mg, H: 400 mg and Z: 2000 mg).[9]

Patients were followed up during treatment, with special attention to the development or not of adverse effects to the drugs used to treat tuberculosis, especially hepatotoxicity, which was screened for using liver function tests. Patients who developed hepatotoxicity had drug discontinuation.

The project was approved by the Ethics Committees of Universidade Federal de Ciências da Saúde de Porto Alegre and of Escola de Saúde Pública do Rio Grande do Sul.

The results are shown as averages and standard deviation or frequency of patients with a given characteristic. The statistical tests used in this analysis are: Chi-Square test, Fisher's Exact test, Student's t test, and Cox Regression technique, which was used for the variables with $p \leq 0.20$ in the univariate analysis. The study's calculated power was of 80% and its level of statistical significance was 5%. *Statistical Package for the Social Sciences* (*SPSS*), version 13.0, was used in the analysis.

RESULTS

The sample was comprised of 534 patients, with a mean age of 39.08 years (± 12.2), and a maximum age of 80 years. From the studied population, 75.1% (n=401) were men and 57.7% (n = 308) where white. With the purpose of analysis we divided patients in two groups according to skin color: white and non-white. The majority of the non-white were black skin (n = 135).

With regard to behavioral factors, alcoholism was present in 65.7% (n = 351) of the sample, and drug addiction, in 37.1% (n = 198).

Only 6.2% presented miliar tuberculosis (n = 33). Besides that, 39.1% (n = 209) of the patients were anti-HIV positive and 33.3% (n = 178), anti-HCV positive. The co-infection rate (HIV/HCV) in the study was 23.9%. Of the total sample, 12.2% (n = 65) of the patients used antiretrovirals.

The incidence of hepatotoxicity was 8.8% (n = 47), and of those with antibodies for the hepatitis C virus (178), 14% developed hepatotoxicity (the same occurred in only 6.2% of those who were anti-HCV negative). Likewise, anti-HIV positive patients presented more frequently with hepatotoxicity (13.9%) than anti-HIV negative patients (6.0%).

The associations between the presence of hepatotoxicity and the following variables were tested using univariate analysis: age, gender, skin color,

Table 1. Mean age and doses of RHZ (mg/kg)-Rifampicin, Isoniazid and Pyrazinamide - and hepatotoxicity.

Variable	With hepatotoxicity Mean (±SD)	Without hepatotoxicity Mean (±SD)	p Value
Age	39.3 (±11.3)	39.1 (±12.3)	0.91*
Rifampicin	10.68 (±1.91)	9.97 (±1.54)	0.02*
Isoniazid	7.12 (±1.27)	6.64 (±1.03)	0.02*
Pyrazinamide	27.55 (±4.22)	26.83 (±4.04)	0.25*

* Student's t test.

alcoholism, drug addiction, use of anti-retroviral drugs, miliar tuberculosis, presence of anti-HIV and anti-HCV. A statistically significant association was observed between the presence of hepatotoxicity and the presence of anti-HIV ($p = 0.003$) and anti-HCV ($p = 0.002$), as well as the use of antiretroviral drugs ($p = 0.046$).

Table 1 shows the age and dosage in milligrams per kilogram of weight for the anti-tuberculosis drugs (RHZ) used by patients with and without hepatotoxicity.

No statistical association was observed between the mean age and the mean dose of pyrazinamide and development of hepatotoxicity. There was a statistically significant association between the use of high doses of rifampicin and isoniazid (> 12 and 6mg/kg of weight, respectively) and the incidence of liver toxicity.

In the Cox regression model, when variables with $p \leq 0.20$ (use of antiretroviral drugs, anti-HIV, anti-HCV and dose of rifampicin and isoniazid) were analyzed, only the following variables remained independently associated to the development of hepatotoxicity: presence of anti-HIV [RR=2.3 ($CI_{95\%}$ 1.2-4.1); $p = 0.008$] and high dose of isoniazid per kilogram of weight [RR = 1.3 ($CI_{95\%}$ 1.1-1.7); $p = 0.016$].

Anti-HCV did not remain associated in an independent manner to the development of hepatotoxicity caused by the use of RHZ, when controlled for the anti-HIV variable.

Of the total number of patients who developed hepatotoxicity (n = 47), 89.4% did so during the first 30 days of RHZ.

DISCUSSION

Tuberculosis is one of the major causes of death among infectious diseases in the world[2] and its presence is reported as being higher in patients with anti-HCV, when compared to individuals without this antibody.[10,11]

Measuring the incidence of hepatotoxicity from drugs used in the treatment of tuberculosis is difficult, since the studied populations are different, the methodologies employed are distinct and the criteria for defining hepatotoxicity are diverse.[8,12,13] Thus, there is great variability in the incidence recorded in several countries. For example, Spain[14] reports an incidence of 5.8% in a study involving 446 patients. Huang YS, *et al.*[15] in Taiwan, reported an incidence of 14.7% in a population of 224 patients.

In this study, when assessing the whole sample, the incidence of hepatotoxicity associated to RHZ was 8.8%. Shakya R, *et al.*[16] reported an incidence of 8% for hepatotoxicity after assessing 50 patients who underwent treatment for active tuberculosis in Nepal. In Turkey, the incidence of liver toxicity was 8.1% in a population of 705 patients.[17] In India, after assessing 200 patients with tuberculosis, Agal S, *et al.*[18] reported an incidence of 10.5%. Shaberg T, *et al.*[19] reported an incidence of 11% when retrospectively analyzing 519 patients hospitalized with tuberculosis in Germany.

It is still undefined whether anti-HCV reagent patients are subject to a greater incidence of hepatotoxicity during treatment for tuberculosis, since some authors only reported it when using univariate analysis[20] and others were unable to observe this association.[21]

When assessing the cohort in question, it was observed that the presence of anti-HCV was high among patients hospitalized with tuberculosis, with a prevalence of 33.3%. In a multicentric study that assessed 272 hospitalized patients, the prevalence of hepatitis C virus was 22%.[10] The high rate of anti-HCV/tuberculosis co-infection verified may suggest incorporation of anti-HCV test as a routine for patients with tuberculosis.

In the 178 patients with anti-HCV, the increase in aminotransferases during treatment for tuberculosis with RHZ was more frequent (14%) than in anti-HCV non-reagent patients (6.2%). In the univariate analysis, the presence of this antibody was associated in a statistically significant manner to the development of hepatotoxicity. However, this association was not present when Cox regression model was applied. Both viruses share practically the same transmission routes and frequently coexist, with anti-HIV being a confounding variable for hepatotoxicity in HCV-infected patients.

When analyzing this result, among the possible factors of error, it is necessary to consider that the presence of anti-HCV in the blood does not necessarily mean viremia. In a prospective study, Fernandez-Villar, *et al.*[14] assessed viremia by PCR HCV-RNA in HIV-negative patients who took isoniazid for treatment of latent tuberculosis and they found an association between the presence of hepatitis C virus and hepatotoxicity from the use of isoniazid. Another consideration to be made is the fact that patients with high pretreatment aminotransferases were not included in the study, which may have underestimated the actual influence of HCV as a risk factor for hepatotoxicity due to the exclusion of higher risk individuals.

Current therapy for tuberculosis/HIV co-infection requires the concomitant use of anti-tuberculosis drugs and at least three anti-retroviral drugs, which increases the chance for complications, hepatotoxicity and medication interactions.[22] The incidence of liver toxicity during anti-retroviral therapy varies between 2% and 18%.[23] When assessing the data from this study in the univariate analysis, the use of anti-retroviral drugs was observed to be associated to the development of hepatotoxicity, but after Cox regression, this association was not shown.

Of the 534 patients included in this study, 209 were infected with HIV. The incidence of hepatotoxicity was higher in this group, when compared to not infected patients. Using the Cox regression model, a significant association was verified between hepatotoxicity and the presence of anti-HIV. This result agrees with other published studies[24,25] and it ratifies the importance of tracking this infection in this population.

Although in the study by Yee, *et al*.[26] there was no difference between patients with and without hepatotoxicity and doses of anti-tuberculosis drugs, the study in question found an association between high doses of isoniazid and development of liver toxicity, which is why appropriate treatment is deemed to be of utmost importance, respecting internationally recommended rules, which suggest 5 mg/kg of isoniazid and doses of pyrazinamide no greater than 30 mg/kg of weight.

We had a very small population infected by HBV in this study and so we did not analyse this variable.

With regard to the time involved for developing hepatotoxicity, the majority of patients (89.4%) developed it within the first 30 days of RHZ use, which is in agreement with other authors.[16]

In conclusion, the results of this study indicate that patients with tuberculosis should be treated respecting recommended doses in terms of body weight. TB/HIV co-infection increases the risk of developing hepatotoxicity, thus screening for HIV is indispensable. Although univariate analysis showed that anti-HCV was associated to the outcome, it was not identified as an independent risk factor for hepatotoxicity related to the use of RHZ when the analysis was controlled to HIV. Prospective studies, preferably with the use of HCV-RNA by PCR, will certainly contribute to a more precise assessment and handling of these patients.

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