Original Article

Risk factors for recurrence of tuberculosis*

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Abstract

Objective: To identify risk factors for recurrence of tuberculosis. **Methods:** We studied a cohort of 610 patients with active pulmonary tuberculosis who were enrolled for treatment between 1989 and 1994 and cured using a three-drug treatment regimen of rifampin, isoniazid and pyrazinamide (RHZ). The risk factors studied were age, gender, race, duration of symptoms, lesion cavitation, extent of disease, diabetes mellitus, alcoholism, HIV infection, delayed negative sputum conversion, treatment compliance, and medication doses. In order to detect recurrence, the patients were monitored through the Rio Grande do Sul State Health Department Information System for 7.7 ± 2.0 years after cure. Data were analyzed using the Student's t-test, the chi-square test or Fisher's exact test, and Cox regression models. **Results:** There were 26 cases of recurrence (4.3%), which corresponds to 0.55/100 patient-years. The recurrence rate was 5.95 and 0.48/100 patient-years in HIV-positive and HIV-negative patients, respectively ($p < 0.0001$). In the multivariate analysis, HIV infection [RR = 8.04 (95% CI: 2.35-27.50); $p = 0.001$] and noncompliance [RR = 6.43 (95% CI: 2.02-20.44); $p = 0.002$] proved to be independently associated with recurrence of tuberculosis. **Conclusions:** Recurrence of tuberculosis was more common in HIV-positive patients and in patients who did not comply with the self-administered treatment (RHZ regimen). Patients presenting at least one of these risk factors can benefit from the implementation of a post-treatment surveillance system for early detection of recurrence. An alternative to prevent noncompliance with tuberculosis treatment would be the use of supervised treatment.

Keywords: Tuberculosis; Recurrence; Risk factors.

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Introduction

A treatment regimen for tuberculosis (TB) is appropriate when it provides high cure rates, few adverse effects, and low disease recurrence rates. With the combined use of rifampin (RIF), isoniazid (INH), and pyrazinamide (PZA), these parameters are reached as long as the medications are administered in the right doses and for the appropriate amount of time in patients without a history of treatment, that is, treatment-naïve patients. Therefore, cure rates near 100%, as well as rates of regimen change due to toxicity and rates of recurrence lower than 5%, can be obtained. Various factors, such as duration of treatment, bactericidal/bacteriostatic activity of the medications, mode of administration (daily or intermittent), and noncompliance, have been identified as being associated with recurrence of TB. With the outbreak of the HIV infection epidemic, some studies have shown higher recurrence rates in infected (HIV-positive) patients,[2-8] whereas others show similarvalues.[9-11]

The knowledge of the risk factors for recurrence of TB makes it possible to take measures to ensure treatment success. The present study aimed to identify factors associated with recurrence in patients treated with the short-course regimen used in Brazil (RIF+INH+PZA regimen).

Methods

The present study was designed as a historical cohort study. This was a controlled, observational study comparing the incidence of recurrence in a group of individuals who had TB and were exposed to a series of potential risk factors with the incidence of recurrence in another group of individuals who also had TB but were not exposed to such factors. Initially, exposure was measured and, at a later time, it was determined whether or not recurrence had occurred. Therefore, we attempted to identify patient characteristics or attributes that could be associated with a greater likelihood of recurrence of TB.

The risk factors studied were age, gender, race, duration of symptoms, extent of disease, cavitation on chest X-ray, noncompliance, delayed negative sputum conversion (after the 4th month of treatment), diabetes mellitus (DM), alcoholism, medication doses, and HIV infection. The information was collected in an electronic database, with 152 variables, containing information about patients who were enrolled for TB treatment in the outpatient clinic of the *Programa de Controle da Tuberculose do Rio Grande do Sul* (PCT/RS, Rio Grande do Sul State Tuberculosis Control Program) in the city of Porto Alegre. This database was created in 1989 for study and research purposes. The quality of the information was guaranteed by the fact that the information was digitized in real time, in a standardized way, and with proper quality control by one of the researchers, who was responsible for 66% of the medical care activities of the outpatient clinic. This outpatient clinic treated approximately 25% of the TB cases in the city of Porto Alegre.

Every the treatment, an additional chest X-ray was performed as a control. The treatment was self-administered, delivered to the patient every 30 days, and consisted of RIF+INH+PZA for 2 months and RIF+INH for another 4 months. In the second phase, 12 HIV-positive patients and 9 patients with DM received RIF+INH for 7 months. A group of 43 patients with delayed negative sputum conversion received RIF+INH until they had 3 consecutive negative sputum samples. The medication doses were adjusted to the patient weight in accordance with the norms established by the PCT/RS (weight < 45 kg, R: 300 mg, H: 200 mg, and Z: 1000 mg; weight from 45 to 55 kg, R: 450 mg, H: 300 mg, and Z: 1500 mg; weight > 55 kg, R: 600 mg, H: 400 mg, and Z: 2000 mg).

The duration of symptoms was defined as the interval between the onset of the respiratory symptoms and the diagnosis of TB. Pulmonary lesions on chest X-rays were classified as 'cavitary' or 'noncavitary' and as 'extensive' (affecting an area greater than that of one lung) or 'non-extensive'. Treatment compliance was evaluated by pill counts, regularity in attending medical appointments, and information obtained from the patient or family members. All patients with a history of excessive alcohol consumption to the point of causing harm to their personal or professional relationships were considered alcoholics.

The results are presented as means and standard deviations or as the percentage of patients with a given characteristic. The variable duration of symptoms, without normal distribution, was logarithmically transformed prior to the analyses and is expressed as medians (with minimum and maximum values). Data regarding the comparison between the patients who were tested and those who were not tested for HIV,

and between treatment compliance and the presence of alcoholism and DM were analyzed using the Student's t-test, the chi-square test, or Fisher's exact test. The potential risk factors for recurrence were analyzed using the Cox proportional hazards model. The relative risks and the (95%) confidence intervals for each variable were estimated by univariate analysis. The variables presenting values of $p < 0.20$ were included in the multivariate analysis. These analyses were performed considering all 610 patients and were repeated for the 279 patients tested for HIV. The relationship between length of observation and recurrence was analyzed graphically using a cumulative incidence plot. The analyses were carried out using the Statistical Package for the Social Sciences, version 12.0. Values of $p < 0.05$ were considered significant.

The review of data was performed prior to the official existence of ethics in research committees. There was no interference with the routine treatment of patients. The permission to consult the PCT database was granted by the Rio Grande do Sul State Department of Health Tuberculosis Team based on the safeguards ensuring patient privacy.

Results

The study population comprised 610 patients with a mean age of 36 ± 14 years and symptom duration of 90 (14-540) days. Of those, 376 (61.6%) were male; 476 (78.0%) were Caucasian; 134 (22.0%) were alcoholics; and 54 (8.9%) had DM. In 76 patients (12.5%), the pulmonary disease was extensive, and it was cavitated in 527 (86.4%). There were 75 patients (12.3%) who did not comply with the treatment. The rate of noncompliance was higher in alcoholics than in nonalcoholics (20.9% *vs.* 9.9%; p = 0.01), and was lower in patients with than in those without DM (3.7 *vs.* 13.1%; p = 0.044). A total of 279 patients (45.7%) were tested for HIV, and 13 (4.6%) tested positive. The demographic and clinical characteristics of the patients who were tested for HIV were similar to those of the patients who were not tested.

After a follow-up period of 7.7 ± 2.0 years, 26 cases of recurrence of TB (4.3%) were identified (0.55/100 patient-years). Recurrence occurred within 2 to 96 months after TB case in which the patient developed active pulmonary TB 30 or more days following discharge after cure was considered a case of recurrence. The PCT/RS electronic database was reviewed for cases of recurrence up to the year 2000. The wide coverage of the PCT/RS guaranteed that practically 100% of the cases being treated in the state appeared in this system.

We included all patients who were sequentially enrolled for treatment in the 1989-1994 period, through spontaneous demand, and who met the following inclusion criterion: being a treatment-naïve adult with pulmonary TB confirmed by positive sputum smear microscopy and cured using the RIF+INH+PZA regimen. Of the 1559 new patients who were enrolled during the period evaluated, 610 met the inclusion criterion.

In the routine assessment, patients were evaluated in terms of TB symptoms, alcoholism, and DM, as well as being submitted to sputum smear microscopy and chest X-ray. Throughout the treatment period, the patients were monitored monthly using the clinical evolution and sputum tests. A total of 279 patients were tested for HIV using the ELISA method, and positive results were confirmed by Western blot. Since HIV testing was not part of the routine treatment at the time, only 46% of the patients were tested. At the end of cure (Figure 1). Of the 6 patients (19.2%) who had recurrence within the first 6 months, 4 (66.7%) did not comply with the treatment, and 2 (33.3%) had delayed n egative sputum conversion. Of those 6 patients, 4 underwent serologic testing for HIV, and all 4 tested negative.

The multivariate analysis revealed that the patients presenting recurrence did not differ from those not presenting recurrence in terms of age (33 ± 12 *vs.* 36 ± 14 years; p = 0.243), duration

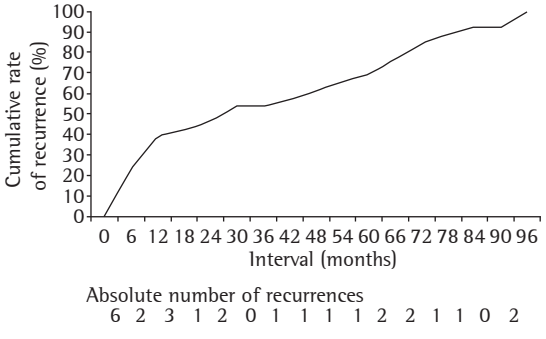

Figura 1 - Rate of recurrence according to the number of months elapsed between the cure and the new TB diagnosis.

of symptoms [90 (15-180) *vs.* 90 (14-540) days; p = 0.323), gender, race, extent of disease, cavitation on chest X-ray, delayed negative sputum conversion, alcoholism, and DM (Table 1). There was also no difference in terms of the doses of RIF, INH, or PZA (Table 2). The rates of treatment compliance or noncompliance (regular or irregular use of the medication), as well as of HIV-positivity and HIV-negativity, were different between the two groups (Table 1). There were 4 recurrences in the HIV-positive patients and 8 in the HIV-positive patients (30.8 *vs.* 3.0%) (Table 1). In the HIV-positive patients, recurrence occurred within 15 to 46 months (mean of 27 months) after cure, whereas in the HIV-negative patients, recurrence occurred within 2 to 65 months (mean of 19 months; p = 0.548). The recurrence rate was 5.95/100 patient-years in the HIV-positive patients and 0.48/100 patient-years in the HIV-negative patients.

In the multivariate analysis with all patients, without including the HIV testing results, only noncompliance proved to be associated with recurrence of TB. In the multivariate analysis of the 279 patients who were tested for HIV, HIV infection also proved to be independently associated with the recurrence of TB (Table 3). Since the two groups are similar, the results obtained in the patients who were tested could eventually be applied to the entire population studied.

Discussion

Recurrence of TB is defined as a new episode of the disease after the cure of a previous episode. It can occur due to endogenous reactivation or to exogenous re-infection,[12] which are conditions that are clinically indistinguishable[13] but can be differentiated by molecular techniques.[12-14] In the state of Rio Grande do Sul, these techniques are not available in the public health care network for the treatment of TB. However, the failure to use these techniques does not cause greater harm to patients since, at recurrence, patients again receive the RIF+INH+PZA regimen, which is indicated in cases of endogenous reactivation as well as in cases of re-infection.

In areas of low TB incidence, recurrence is usually due to endogenous reactivation.[15] In areas of high incidence, the incidence of cases of recurrence attributed to re-infection can reach 75%.[12] Recurrence due to re-infection is a constant risk over time,[13] whereas recurrence due to reactivation seems to occur closer to the time of cure.[16] In the present study, approximately 40% of the cases of recurrence occurred in the first 12 months, and were more likely to be due to endogenous reactivation. The remaining cases occurred during the observation period (an average of 2 cases per year), and it was not possible to infer whether they were due to reactivation or to re-infection (Figure 1).

Incomplete bacteriological cure, which is usually caused by irregular medication intake, is the most common cause of endogenous reactivation. Endogenous reactivation can also result from the use of regimens with low bactericidal potency, from inadequate treatment duration, from underdosing of the medications, or, from the inappropriate

Table 1 - Univariate analysis of demographic, clinical, and laboratory characteristics of patients with and without recurrence of tuberculosis.

Characteristic	Recurrence		Relative risk[a] (95% CI)	p
	Present (n = 26)	Absent (n = 584)		
Gender (male/female)	20/6	356/228	2.10 (0.84-5.22)	0.111
Race (non-Caucasian/Caucasian)	6/20	128/456	1.09 (0.44-2.72)	0.850
Alcoholism (yes/no)	9/17	125/459	1.90 (0.85-4.25)	0.121
Diabetes mellitus (yes/no)	0/26	54/530	0.04 (0.00-16.68)	0.301
Cavitation on chest X-ray (yes/no)	24/2	503/66	1.55 (0.37-6.56)	0.551
Advanced tuberculosis (yes/no)	6/20	70/511	2.06 (0.83-5.12)	0.122
Negative sputum conversion after month 4 (yes/no)	3/23	40/544	1.68 (0.55-5.61)	0.396
Treatment compliance (yes/no)	9/17	66/518	4.02 (1.79-9.01)	0.001
HIV testing (positive/negative)	4/8	9/258	11.25 (3.38-37.43)	<0.0001

[a]Relative risk estimated by multivariate analysis using Cox proportional hazard ratio.

Table 2 - Medication doses (rifampin, isoniazid, and pyrazinamide) at the beginning of the treatment by the presence or absence of recurrence of tuberculosis.

	Recurrence		p
	Present (n = 26)	Absent (n = 584)	
Rifampin (mg/kg)	10.6 ± 1.3	10.4 ± 1.3	0.461
Isoniazid (mg/kg)	6.9 ± 1.0	6.8 ± 1.0	0.698
Pyrazinamide (mg/kg)	29.2 ± 3.3	29.2 ± 3.1	0.971

Data presented as means and standard deviation.

choice of medications, ignoring the presence of pre-existing resistance.[4,6,7,13,17,18] In the present study, the regimen used was appropriate in terms of its composition, duration, indication (treatment-naïve patients living in an area of low prevalence of primary resistance), and doses prescribed. Doses of INH higher than the 5 mg/kg of body weight recommended for adults were used due to the formulation of the capsule (300 mg of RIF and 200 mg of INH), which does not allow the prescription of the ideal INH dose without lowering the RIF dose.[19]

In the present study, only noncompliance and HIV infection proved to be related to higher rates of recurrence. Unlike previous studies, which have demonstrated that recurrence is more frequent in patients with DM, in those with extensive disease, and in those with pulmonary cavitation at the beginning of the treatment, the present study did not confirm that these conditions are risk factors for recurrence. Regarding DM, it is possible that the results of the present study are mainly due to the greater treatment compliance. It was not possible to determine whether the prolonged treatment of patients with DM played any role in preventing recurrence, due to the small number of cases that were treated for 9 months.

Treatment noncompliance is deemed responsible for poor results in TB treatment. Alcoholism has been identified as a major predictor of noncompliance from the initiation of TB chemotherapy, being a common cause of abandonment, death, and recurrence of TB.[20] In recent studies, poor treatment compliance has been a significant risk factor for recurrence of TB in HIV-positive patients.[6,21] In the present study, alcoholism was more common in patients who did not comply with the treatment than in those who did. However, alcohol abuse, in its relationship with recurrence, is no longer important when noncompliance is considered, since it is not alcoholism that leads to recurrence of TB, but rather treatment noncompliance.

The recurrence rates of 5.95/100 patient-years in HIV-positive patients and of 0.48/100 patient-years in HIV-negative patients [RR = 8.04 (95% CI: 2.35-27.50); p = 0.001] are similar to those obtained in a study conducted in Haiti, which found 4.8 *vs.* 0.4/100 patient-years [RR = 10.7 (95% CI: 1.4-81.6; p = 0.004)].[5] A study conducted in Kenya found an RR of recurrence of 33.8 (95% CI: 4.3-264; p = 0.001),[3] possibly due to the use of a standard thiacetazone+INH regimen, which has less sterilizing power than does the RIF+INH+PZA regimen. The finding that recurrence rates are higher in HIV-positive than in HIV-negative patients has been confirmed in other studies: 8.2 *vs.* 2.2/100 patient-years (p < 0.001)[4] and 2.0 *vs.* 0.4/100 patient-years (p < 0.001).[6] Studies involving only HIV-positive patients have reported high recurrence rates: 7.9/100 patient-years[21] and 9.7/100 patient-years.[22]

A limitation of many of those studies is the lack of information about the degree of immunosuppression of HIV-positive patients, since severity of immunosuppression is a predictor of TB recurrence.[21,23] In one of those studies, recurrence in HIV-positive patients only occurred in individuals with HIV-related symptoms, which are indicative of a more advanced stage of immunosuppression.[5] In other studies, low CD4 counts proved to be associated with a greater likelihood of recurrence.[21,24] In addition to the limitation imposed by the small number of HIV-positive patients in the present study, this topic was also not investigated. Since AIDS treatment was little effective at the time the patients were recruited, it is to be presumed that the immunity of many patients was compromised.

If the high rate of recurrence of TB in HIV-positive patients is due to the deterioration of immunity, recurrence due to re-infection would be more frequent in areas of high TB prevalence. In such areas, individuals cured of TB are four times more likely to develop the disease when they are re-infected than are treatment-naïve patients.[14] In patients treated with highly active antiretroviral therapy (HAART), it has been observed that cured patients are more likely to become sick than are treatment-naïve patients (11.3 *vs.* 3.0/100 patient-years; p = 0.02).[25] The role of re-infection as a cause of

Table 3 - Significant risk factors for recurrence in patients tested for HIV in a multivariate analysis using Cox proportional hazards model.

Risk factor	Coefficient	Standard error	Relative risk	95% CI	p
HIV-positivity	2.08	0.63	8.04	2.35-27.50	0.001
Treatment noncompliance	1.82	0.59	6.43	2.02-20.44	0.002

recurrence in HIV-positive patients living in areas of high prevalence is well established.[12]

The cases of recurrence of the present study might have been due to re-infection since, in the city of Porto Alegre, where TB and HIV infection are highly prevalent, the opportunities of being exposed to the diseases are multiple and increase insofar as HIV-positive patients cured of TB, and who often are immunosuppressed, routinely go to places where there is a greater risk of exposure, such as health care facility waiting rooms. Immunodeficiency and the consequent re-infections basically occur in patients who do not comply with or do not respond to HAART, as well as in those who are not treated or who are treated with an ineffective antiretroviral regimen. This could be an explanation for the high incidence of recurrence in the HIV-positive patients of this study, which was conducted prior to the advent of HAART, despite the fact that TB treatment was prolonged to 9 months in 92% of the individuals infected with the virus. The use of HAART reduces the incidence of TB in HIV-positive patients.[24,26,27] In one of those studies, the incidence of TB was lower in patients who received HAART than in those who did not (2.4 *vs.* 9.7/100 patient-years; p = 0.0001), being 3.4 and 17.5/100 patient-years, respectively, in patients with CD4 counts < 200 cells/mm^3.[24] The rate of TB in patients with CD4 counts > 350 cells/mm^3 was 2.0 and 3.6/100 patient-years, respectively, in the group that received HAART and in the group that did not,[24] these values being higher than those found in HIV-negative patients.[28] In another study, duration of TB treatment for less than 9 months and inadequate response to HAART were independently associated with the occurrence of recurrence in HIV-positive patients.[29]

These facts underscore the importance of protecting HIV-positive patients, both treatment-naïve patients and patients cured of TB. An appropriate measure would be the regular use of HAART in patients who present more severe immunosuppression,[24,29] whereas, in patients for whom HAART is not indicated and who have higher CD4 counts, the alternative would be the use of INH.[24] One study showed the protective effect of INH in HIV-positive patients, in which the risk of TB was reduced by 38%, with a greater reduction (46%) in treatment-naïve patients.[30] In the study conducted in Haiti,[5] the HIV-positive patients who used INH for 12 months after cure presented lower rates of recurrence. In the study conducted in Zaire,[8] the recurrence rate was lower when the use of RIF+INH was maintained for another 6 months than when these medications were discontinued at the end of the 6th month (respectively, 1.9 and 9.0%; p < 0.01). In a study conducted in New York,[6] recurrence was higher in patients treated for 9 months than in those treated for a longer period (respectively, 7.9% *vs.* 1.4%; p < 0.001). In a studied conducted in Madrid,[21] the rates were 1.7 and 10.9/100 patient-years (p < 0.001), respectively, in patients treated for 9 months and in those treated for a shorter period. Those studies show that prolonged treatment reduces the recurrence rate in HIV-positive patients.

The results of the present study indicate that noncompliance and HIV infection are independent risk factors for recurrence of TB after cure using the self-administered RIF+INH+PZA regimen. Therefore, patients cured of TB who present at least one of these risk factors can benefit from the implementation of a post-treatment surveillance system for early detection of possible cases of recurrence. In order to prevent noncompliance with TB treatment, especially in areas of high prevalence of TB and HIV infection, it becomes more important that supervised treatment be used. For HIV-positive patients, the use of INH after TB is cured can be contemplated. However, clinical and epidemiological studies are needed in order to calculate the cost-benefit ratio of this chemoprophylaxis, as well as to determine the appropriate duration of treatment.

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