Prevalence of drug-resistant *Mycobacterium tuberculosis* in patients under intermittent or daily treatment*

Prevalência de *Mycobacterium tuberculosis* resistente em pacientes sob tratamento parcialmente intermitente ou sob tratamento diário

Tomás Aiza Alvarez, Marcelo Palmeira Rodrigues, Carlos Alberto de Assis Viegas

Abstract

Objective: To compare the prevalence rates of drug-resistant *Mycobacterium tuberculosis* in patients under intermittent treatment with those observed in patients under daily treatment. **Methods:** We used World Health Organization data regarding 5,138 patients with active pulmonary TB in Brazil, separated into two groups: patients in the Federal District of Brasília, treated with a one-month daily regimen followed by an intermittent thrice-weekly regimen; and patients in other parts of Brazil, treated with a daily regimen only. The resistance pattern was categorized as primary or acquired, based on the history of previous treatment. Multidrug resistance was defined as resistance to at least isoniazid and rifampin, whereas monoresistance was defined as resistance to only one drug. **Results:** The prevalence of primary resistance in the Federal District of Brasília and in the other parts of Brazil, respectively, was as follows: overall, 9.2% and 9.3% (p = 0.94); monoresistance, 6.6% and 6.9% (p = 0.89); and multidrug resistance, 1.0% and 1.2% (p = 0.85). The prevalence of acquired resistance in the Federal District of Brasília and in the other parts of Brazil, respectively, was as follows: overall, 15.8% and 26.8% (p = 0.39); monoresistance, 5.3% and 13.7% (p = 0.33); and multidrug resistance, 0.0% and 10.2% (p = 0.16). **Conclusions:** No significant differences were found between patients treated with an intermittent regimen and those treated with a daily regimen in term of resistance rates.

Keywords: Tuberculosis, pulmonary; Drug resistance; Drug administration schedule; Tuberculosis, multidrug-resistant.

Resumo

Objetivo: Comparar as taxas de prevalência de *Mycobacterium tuberculosis* resistentes entre pacientes sob tratamento parcialmente intermitente e daqueles sob tratamento diário. **Métodos:** Foram utilizados dados da Organização Mundial de Saúde de 5.138 pacientes com TB pulmonar bacilífera no Brasil, que foram separados em dois grupos: um grupo de pacientes do Distrito Federal submetidos a um regime intermitente de três tomadas semanais após o primeiro mês de regime diário, e um grupo de pacientes dos estados brasileiras, submetidos somente a um regime diário. O padrão de resistência foi categorizado em resistência primária ou adquirida, conforme a existência de tratamento anterior. Além disso, multirresistência foi definida como a resistência simultânea à isoniazida e à rifampicina, enquanto monorresistência como a resistência a uma única droga. **Resultados:** A prevalência da resistência primária como um todo no Distrito Federal e no restante do Brasil foi de 9,2% e 9,3% (p = 0,94), respectivamente. A prevalência de monorresistência foi de 6,6% e 6,9% (p = 0,89), respectivamente, e a de multirresistência, 1,0% e 1,2% (p = 0,85), respectivamente. A prevalência de resistência adquirida como um todo no Distrito Federal e no restante do Brasil foi de 15,8% e 26,8% (p = 0,39), respectivamente. A prevalência de monorresistência adquirida foi de 5,3% e 13,7% (p = 0,33), respectivamente, e a de multirresistência, 0,0% e 10,2% (p = 0,16), respectivamente. **Conclusões:** Não houve diferença significativa entre os índices de resistência observados na comunidade usuária do esquema parcialmente intermitente e do diário.

Descritores: Tuberculose pulmonar; Resistência a medicamentos; Esquema de medicação; Tuberculose resistente a múltiplos medicamentos.

* Study carried out at the *Universidade de Brasília* – UnB, University of Brasília – School of Medicine, Brasília, Brazil.
Correspondence to: Marcelo Palmeira Rodrigues. Hospital Universitário de Brasília, SGAN 604-605, Anexo II, Térreo, Sala de Pneumologia, CEP 70840-050, Brasília, DF, Brasil.
Tel 55 61 3307-3224 or 55 61 3327-8525. E-mail: pmarcelo@unb.br
Financial Support: None.
Submitted: 5 November 2008. Accepted, after review: 20 December 2008.

Introduction

Resistance of *Mycobacterium tuberculosis* to the medication typically used constitutes a relevant obstacle to the success of the treatment, regardless of whether a daily or intermittent regimen is used. Many times, resistance is established by previous contact between *M. tuberculosis* and the drug; therefore, the previous treatment is the greatest clinical indicator of the development of multidrug-resistant TB forms.[1]

The efficiency of the intermittent TB treatment has long been observed.[2-4] In a systemic review, the cure and recurrence rates have proven to be very similar between the daily and intermittent treatment.[5] The efficiency of the intermittent regimen has also been shown in patients in retreatment,[6] in pediatric patients,[7] in HIV patients[8] and in patients with clinical indicators of low adherence to treatment.[9]

Normally, when the treatment regimen is self-administered, daily use of medication is preferred, probably due to the fact that omission of a day of treatment would be less ominous. In contrast, the intermittent regimen is preferentially used in the supervised forms of treatment. Therefore, even in countries such as Brazil, in which the self-administered form is adopted, the use of the intermittent supervised form is particularly interesting in situations in which a low adherence rate is presumed, such as in alcoholic, chemically-dependent and homeless patients.

The appearance of drug resistance associated with the intermittent regimen is unclear. One group of authors observed elevated resistance rates in Burundi,[10] above the mean of other African countries, suggesting that the intermittent treatment form practiced for 11 years in this country might be implicated. In accordance with this point of view, other authors highlight a relationship between acquired resistance to rifampin (RMP) and its intermittent use during the initial phase of the treatment in HIV-infected patients.[11] Conversely, another group of authors[12] did not detect the appearance of RMP-resistant mycobacteria in the course of the fully intermittent treatment in a series of 467 cases (2 months with 3 weekly administrations of isoniazid [INH], RMP, pyrazinamide [PZA] and ethambutol [EMB]; followed by 6 months with a weekly administration of INH and EMB).

Therefore, knowing and monitoring mycobacterial resistance to the treatment regimen used is of utmost importance. Our study aims at comparing the mycobacterial resistance rates between TB patients in two communities: one which has received intermittent treatment since 1974 and another which receives daily treatment.

Methods

We used data from a worldwide survey produced by the World Health Organization together with the International Union Against Tuberculosis and Pulmonary Diseases. Between 1994 and 1997, those two organizations make efforts to establish a worldwide plan of surveillance of bacterial resistance to anti-tuberculous drugs. This project involved the measurement of the prevalence rates of this resistance in many countries worldwide and, or particular importance, using standardized measurement methods.

Brazil participated in that project under the coordination of the National Ministry of Health Professor Hélio Fraga Referral Center, and included patients assisted in all its macroregions, namely: North (Amazonas and Pará); Northeast (Ceará, Pernambuco and Bahia); Southeast (Espírito Santo, Minas Gerais, Rio de Janeiro and São Paulo); South (Santa Catarina and Rio Grande do Sul); and Central-West (Goiás and the Federal District of Brasília).

Differently from the other Brazilian regions, in which the treatment form with daily administrations and self-administrations of medication, in the Federal District of Brasília the self-administered intermittent treatment regimen is used, that is, the first month with daily use and the following months with a frequency of three times a week, with adjusted doses. The doses in the intermittent phase are the following: 20 mg/kg up to 600 mg per day for INH; 40 mg/kg to 2.000 mg per day for EMB; 20 mg/kg to 600 mg per day for RMP; 50 mg/kg to 2,000 mg per day for PZA; and 35 mg/kg to 1,000 mg per day for streptomycin (SM). The choice of medication, however, follows the same pattern in the Federal District of Brasília and in the other regions.

As a rule, in all Brazilian regions, the treatment is conducted in the public health care system, and the medications are provided free of charge. The National Ministry of Health has standardized four treatment regimens. Regimen 1 (use of RMP+INH+PZA for 2 months, followed by the use of RMP+INH for 4 months) is indi-

Table 1 - Frequency of studied patients susceptible to the tested drugs or with any resistance, according to history of previous treatment.

Treatment	Brazil			Federal District of Brasília		
	Susceptible	Resistance	Total	Susceptible	Resistance	Total
Treatment-naive	3,680	344	4,024	196	18	214
History of previous treatment	665	178	843	19	3	22
Total	4,345	522	4,867	215	21	236

cated for new cases. Reinforced regimen I (use ofRMP+INH+PZA+EMB for 2 months, followed by the use of RMP+INH+EMB for 4 months) is indicated for the retreatment of abandonment and recurrent cases. Regimen II (use ofRMP+INH+PZA for 2 months, followed by the use of RMP+INH for additional 7 months) is indicated for the treatment of tuberculous meningitis. Regimen III (use of SM+ ethionamide (ETH)+PZA+EMB for 3 months, followed by the use of ETH+EMB for 9 months) is used in the failure of the aforementioned regimens.

In our study, all patients included in the original project were considered, except for those diagnosed and treated in the Federal District of Brasília, although resident in other regions.

Patients with infectious pulmonary TB admitted for treatment in the health care clinics of the Brazilian Tuberculosis Control Program in the period between 1995 and 1997 were included in the original project, totalizing 5,138 patients. Patients were separated into two groups: with or without history of previous specific treatment. Resistance was then categorized into primary or acquired, according to absence or presence of previous treatment in the collected data.

Resistance patterns were classified in monoresistance (a single drug), multi-resistance (INH and RMP necessarily, with or without another drug) or other patterns (more than one drug, except for INH and RMP simultaneously).

Isolation, culture and susceptibility testing were described in another publication.[13] The summarized description follows. Sputum smear microscopy was carried out by the Ziehl-Neelsen technique. Positive sputum samples were maintained packed in ice until arrival at the referral laboratory, when they were decontaminated by the Petroff technique and cultivated in the Löwenstein-Jensen medium for up to 60 days. Positive cultures were submitted to first-line antituberculous drug susceptibility testing and to *M. tuberculosis* identification and differential testing (niacin testing, nitrite reduction testing and catalase testing).

In data analysis, the chi-square test was used for comparison of the proportions. The level of significance of α was 5%. Due to the importance of estimating the type II error, in which no significant difference is shown when in fact it exists, the power was calculated to each comparison. To that end, calculation was carried out *a posteriori*. The w effect size was necessary and was estimated based on the real difference observed among the two groups, admitting that the proportions among these two groups should be equal. The w effect size is typically considered small, medium or large, as a reference, when equal to 0.1, 0.3 and 0.5, respectively. We used Excel 2002, and, for the calculation of power and w effect size, we used G*Power version 3.0.3.

Table 2 - Prevalence of primary resistance in the Federal District of Brasília and in the other parts of Brazil.

Type of resistance	Primary resistance				
	FDB, %	Brazil, %	p	W effect size	Power, %
Isoniazid	4.6	6.8	0.24	0.1972	100
Rifampicin	2.0	1.5	0.52	0.1634	99
Streptomycin	6.6	4.3	0.15	0.2080	100
Any resistance	9.2	9.3	0.94	0.0088	9
Monoresistance	6.6	6.9	0.89	0.0200	25
Multidrug	1.0	1.2	0.85	0.0676	99
Other patterns	1.5	1.3	0.76	0.0902	99

FDB: Federal District of Brasília.

Table 3 - Prevalence of acquired resistance in the Federal District of Brasília and in the other parts of Brazil.

Type of resistance	Acquired resistance				
	FDB, %	Brazil, %	p	W effect size	Power, %
Isoniazid	15.8	21.9	0.59	0.1634	99
Rifampicin	0.0	11.7	0.13	1.0000	100
Streptomycin	15.7	9.1	0.38	0.2650	100
Any resistance	15.8	26.8	0.39	0.2580	100
Monoresistance	5.3	13.7	0.33	0.4444	100
Multidrug	0.0	10.2	0.16	1.0000	100
Other patterns	10.5	2.9	0.07	0.5730	100

FDB: Federal District of Brasília.

Results

In the studied period, 271 patients were diagnosed with TB in the Federal District of Brasília; of those, 35 patients were excluded for not residing in the Federal District of Brasília. Of the 236 patients included, 161 (68.2%) were male and 75 (31.8%) were female. Age ranged from 15 to 86 years, and mean according to gender was 41.5 and 36.7 years, respectively. The results observed in those 236 patients were compared to those obtained from a total of 4,867 patients studied in the other parts of Brazil.

In the Federal District of Brasília, 214 patients (90.7%) were treatment-naïve, whereas 22 (9.3%) reported a history of previous treatment. In the other parts of Brazil, these values were 4,024 (82.7%) and 843 (17.3%), respectively. The frequency of cases with or without resistance to any drugs is shown in Table 1.

As observed in Tables 2 and 3, there was no statistically significant difference between the prevalences, regardless of the patterns, between primary and acquired resistance in the Federal District of Brasília and in the other parts of Brazil. In two analyzed situations, the "any resistance" or "monoresistance" patterns for the primary type, the prevalences showed virtually identical, translating into a minimal size difference and implying a reduced power. In the Federal District of Brasília, no resistance to EMB was observed, nor was there resistance to PZA and ETH, in accordance with reports for the other parts of Brazil.

Discussion

The development of higher rates of bacterial anti-tuberculous drug resistance, especially regarding multiple-drug resistance, is related to the contact between the microorganism and these drugs.[1] Resistance is classified as acquired, when the very individual was previously submitted to treatment, or primary, when the infected individual acquired the bacillus from another individual.

Therefore, higher resistance rates can be expected due to the degree of inefficiency of the treatment. Inefficiency is to be understood as factors related not only to drug efficacy, but to the system of administration and to various factors related to the use of these drugs in the community.

The data in the present study evidence a similarity between the resistance rates in the Federal District of Brasília and in the other parts of Brazil. First, the presence of possible biases must be questioned. Factors related to the profile of the studied patients, such as the prevalence of AIDS, alcoholism, use of illicit drugs and other morbidities in the sample, can interfere with the adherence to treatment.[14] Regardless of any possible difference between the Federal District of Brasília and the other parts of Brazil concerning any of those factors, some authors[15] reported a virtually identical abandonment rate: 25.7% for the Federal District of Brasília and 25.9% for the other parts of Brazil.

Other factors related to a more efficient health care system, although unmeasured, seem to be inexistent, due to the fact that the same guidelines instruct the activities in the TB control clinics. Other factors related to the form of drug administration, which is self-administered throughout Brazil, also seem to be inexistent.

The question of the group of drugs available for the treatment can have direct importance in relation to the appearance of resistant bacilli. The non-addition of PZA to the treatment regimen, for example, evaluated in a study in which four

intermittent regimens were compared to a daily one, was capable of resulting in a recurrence rate four times higher in a year, compared to that in which PZA was present.[3] Again, in the Federal District of Brasília the same recommendations regarding the drugs used are followed, differing only in the intermittent form starting on the second month of treatment.

Indeed, in a recent systematic review, the intermittent regimen consisting of three administrations per week following a continuous initial phase, such as it is conducted in the Federal District of Brasília, seems to reach the lowest recurrence rates together with the daily administration regimen. The odds ratio in these two regimens was significantly lower than in those fully intermittent or with lower weekly frequency.[16]

Although the intermittent treatment used for more than 20 years in the Federal District of Brasília has not resulted in different bacterial resistance rates from the other Brazilian regions, caution is necessary in its extrapolation. Some authors[17] have observed a relation between the acquisition of RMP resistance and the low count of CD4 cells in HIV-infected patients. In the same study, these authors pointed out a tendency to the association between the RMP resistance and the intermittent treatment with two weekly administrations in the initial phase ($p = 0.15$) and also with the non-use of antiretroviral treatment in the 2 first months of TB treatment ($p = 0.05$).

Considering the level of plasma concentration of the drugs in the treatment with two weekly administrations,[18] these authors have postulated that in a context of immunosuppression, low concentrations of RMP at the end of long intervals can allow the selective replication of resistant mycobacteria.[17]

In this sense, some authors[11] have also studied TB and HIV infected patients, and observed a relative risk of 6.4 for RMP-acquired resistance, when it was administered intermittently since the treatment was initiated.

Given the multiplicity of factors involved, it is difficult to impute, through observational studies, the intermittent form of treatment as exclusively responsible for the failure, recurrence or the appearance of resistance. In Burundi,[10] a sample of 496 new cases evidenced 16.1% resistance to any drug (2% to RMP). The study was carried out 11 years after the implementation of the directly observed treatment, short-course program, using an intermittent regimen. These are levels above the African means. A possible bias regards the prevalence of HIV-infected patients. Conversely, in India,[12] in a fully intermittent controlled clinical assay, there was no appearance of primary RMP resistance.

In our study, a similarity in the population group, in the abandonment rate, health care system and group of drugs used in the treatment gathers a unique opportunity to observe the effect of the intermittent form, used since 1974 in the Federal District of Brasília, on the mycobacterial resistance, compared to the daily treatment. Our data allow the conclusion that the resistance rates are similar between the two groups.

References

1. Mitchison DA. Antimicrobial therapy of tuberculosis: justification for currently recommended treatment regimens. Semin Respir Crit Care Med. 2004;25(3):307-15.
2. Controlled trial of intermittent regimens of rifampicin plus isoniazid for pulmonary tuberculosis in Singapore. Lancet. 1975;2(7945):1105-9.
3. Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Lancet. 1981;1(8213):171-4.
4. Castelo A, Jardim JR, Goihman S, Kalckman AS, Dalboni MA, da Silva EA, et al. Comparison of daily and twice-weekly regimens to treat pulmonary tuberculosis. Lancet. 1989;2(8673):1173-6.
5. Mwandumba HC, Squire SB. Fully intermittent dosing with drugs for treating tuberculosis in adults. Cochrane Database Syst Rev. 2001;(4):CD000970.
6. Hong YP, Kim SC, Chang SC, Kim SJ, Jin BW, Park CD. Comparison of a daily and three intermittent retreatment regimens for pulmonary tuberculosis administered under programme conditions. Tubercle. 1988;69(4):241-53.
7. Te Water Naude JM, Donald PR, Hussey GD, Kibel MA, Louw A, Perkins DR, et al. Twice weekly vs. daily chemotherapy for childhood tuberculosis. Pediatr Infect Dis J. 2000;19(5):405-10.
8. Chaisson RE, Clermont HC, Holt EA, Cantave M, Johnson MP, Atkinson J, et al. Six-month supervised intermittent tuberculosis therapy in Haitian patients with and without HIV infection. Am J Respir Crit Care Med. 1996;154(4 Pt 1):1034-8.
9. Caminero JA, Pavón JM, Rodríguez de Castro F, Díaz F, Julià G, Caylá JA, et al. Evaluation of a directly observed six months fully intermittent treatment regimen for tuberculosis in patients suspected of poor compliance. Thorax. 1996;51(11):1130-3.
10. Sanders M, Van Deun A, Ntakirutimana D, Masabo JP, Rukundo J, Rigouts L, et al. Rifampicin mono-resistant Mycobacterium tuberculosis in Bujumbura, Burundi: results of a drug resistance survey. Int J Tuberc Lung Dis. 2006;10(2):178-83.

11. Li J, Munsiff SS, Driver CR, Sackoff J. Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin- or rifabutin-based regimens in New York City, 1997-2000. Clin Infect Dis. 2005;41(1):83-91.
12. Evaluation of a non-rifampicin continuation phase (6HE) following thrice-weekly intensive phase for the treatment of new sputum positive pulmonary tuberculosis. Indian J Tuberc. 2007;54(2):84-90.
13. World Health Organization. Anti-tuberculosis drug resistance in the world. The WHO/IUATLD Global Project on Antituberculosis drug resistance surveillance 1994-1997. Geneva: WHO; 1998.
14. Ribeiro SA, Amado VM, Camelier AA, Fernandes MM, Schenkman S. Estudo caso-controle de indicadores de abandono em doentes com tuberculose. J Pneumol. 2000;26(6):291-6.
15. Diniz LS, Gerhardt G, Miranda JA, Manceau JN. Efetividade do tratamento da tuberculose em 22 municípios de capitais brasileiras e Distrito Federal. Bol Pneumol Sanit. 2003;11(1):5-14.
16. Chang KC, Leung CC, Yew WW, Chan SL, Tam CM. Dosing schedules of 6-month regimens and relapse for pulmonary tuberculosis. Am J Respir Crit Care Med. 2006;174(10):1153-8.
17. Burman W, Benator D, Vernon A, Khan A, Jones B, Silva C, et al. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. Am J Respir Crit Care Med. 2006;173(3):350-6.
18. Weiner M, Benator D, Burman W, Peloquin CA, Khan A, Vernon A, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. Clin Infect Dis. 2005;40(10):1481-91.

About the authors

Tomás Aiza Alvarez
Associate Professor. *Universidade de Brasília* – UnB, University of Brasília – School of Medicine, Brasília, Brazil.

Marcelo Palmeira Rodrigues
Adjunct Professor. *Universidade de Brasília* – UnB, University of Brasília – School of Medicine, Brasília, Brazil.

Carlos Alberto de Assis Viegas
Associate Professor. *Universidade de Brasília* – UnB, University of Brasília – School of Medicine, Brasília, Brazil.