Clinical treatment outcomes of tuberculosis treated with the basic regimen recommended by the Brazilian National Ministry of Health using fixed-dose combination tablets in the greater metropolitan area of Goiânia, Brazil*

Desfechos clínicos do tratamento de tuberculose utilizando o esquema básico recomendado pelo Ministério da Saúde do Brasil com comprimidos em dose fixa combinada na região metropolitana de Goiânia

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Abstract

Objective: To describe the rates of cure, treatment failure, and treatment abandonment obtained with the basic regimen recommended by the Brazilian National Ministry of Health—rifampin, isoniazid, pyrazinamide, and ethambutol for two months, followed by isoniazid and rifampin for four months—using the use of fixed-dose combination tablets (self-administered treatment), as well as to describe adverse events and their potential impact on treatment outcomes. Methods: This was a descriptive study based on prospective data obtained from the medical records of tuberculosis patients (≥18 years of age) treated with the basic regimen at either of two primary health care facilities in the greater metropolitan area of Goiânia, Brazil. Results: The study sample comprised 40 tuberculosis patients. The rate of cure was 67.5%, the rate of treatment abandonment was 17.5%, and there were no cases of treatment failure. Of the 40 patients in the sample, 19 (47%) reported adverse reactions, which were mild and moderate, respectively, in 87% and 13% of the cases. It was not necessary to alter the regimen or discontinue the treatment in any of the cases evaluated. Conclusions: The rate of cure obtained with the self-administered, fixed-dose combination tablet form of the new basic regimen was similar to the historical rates of cure obtained with the previous basic regimen. The rate of treatment abandonment in our sample was much higher than that considered appropriate (up to 5%).

Keywords: Tuberculosis; Treatment outcome; Drug combinations.

Resumo

Objetivo: Descrever as taxas de cura, falência e abandono do tratamento da tuberculose com o esquema básico preconizado pelo Ministério da Saúde — tratamento com rifampicina, isoniazida, pirazinamida e etambutol por dois meses seguido de isoniazida e rifampicina por quatro meses — utilizando comprimidos em dose fixa combinada em regime autoadministrado e descrever os eventos adversos e seus possíveis impactos nos desfechos do tratamento. Métodos: Estudo descritivo utilizando dados coletados prospectivamente dos prontuários médicos de pacientes com tuberculose (idade ≥ 18 anos) tratados com o esquema básico em duas unidades básicas de saúde da região metropolitana de Goiânia, GO. Resultados: A amostra foi composta por 40 pacientes com tuberculose. A taxa de cura foi de 67,5%, a taxa de abandono foi de 17,5%, e não ocorreram casos de falência. Nessa amostra, 19 pacientes (47%) relataram reações adversas aos medicamentos. Essas foram leves e moderadas, respectivamente, em 87% e 13% dos casos. Em nenhum caso houve necessidade de mudança do esquema ou suspensão do tratamento. Conclusões: A taxa de cura do esquema básico com o uso de comprimidos em dose fixa combinada sob regime autoadministrado foi semelhante às taxas históricas do esquema anterior. A taxa de abandono, na amostra estudada, foi muito acima da taxa preconizada como adequada (até 5%).

Descritores: Tuberculose; Resultado de tratamento; Combinación de medicamentos.

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Introduction

The efficacy of tuberculosis treatment is approximately 95%, and tuberculosis treatment rapidly reduces disease transmission, breaking the disease cycle. Although antituberculosis drugs are provided free of charge in Brazil, the effectiveness of tuberculosis treatment varies greatly from place to place within the country. Problems at various levels of adherence to treatment, such as incorrect or irregular drug use and treatment abandonment, can be regarded as important factors affecting treatment effectiveness and, consequently, tuberculosis control in Brazil.

Despite the Brazilian National Tuberculosis Control Program technical norms, factors such as social inequalities, the fragility of the Brazilian public health system, and poor management prevent the goals set together with the World Health Organization (WHO) from being fully achieved in Brazil.

From 2005 to 2010 in the state of Goiás, the cure rate for new cases of tuberculosis decreased from 74.2% to 70.8%; the treatment failure rate remained constant (0.1%), and the treatment abandonment rate decreased from 9.8% to 7.1%. It should be taken into account that Goiás has one of the lowest tuberculosis incidence rates in Brazil, with 13 cases per 100,000 population (data from internal documents issued by the Goiás State Department of Health), whereas the mean incidence rate in the country is 38 cases per 100,000 population.

In 2010, because of the data obtained in the Second Brazilian National Survey on Antituberculosis Drug Resistance (2007-2008), which showed that primary isoniazid and rifampin resistance increased, respectively, from 3.5% to 6.0% and from 0.2% to 1.5% between 1997 and 2007, the Brazilian National Tuberculosis Control Program decided to change the regimen used—rifampin, isoniazid, and pyrazinamide for two months, followed by rifampin and isoniazid for four months (2RHZ/4RH)—by adding a fourth drug (ethambutol) to the intensive phase of tuberculosis treatment, the new regimen being designated 2RHZE/4RH. Simultaneously, capsules containing rifampin and isoniazid, associated with pyrazinamide tablets, were replaced by fixed-dose combination (FDC) tablets containing rifampin, isoniazid, pyrazinamide, and ethambutol.

The use of drugs combined in a single tablet is recommended by the WHO as an additional measure to increase adherence to tuberculosis treatment. This pharmaceutical formulation facilitates drug management, reduces prescription errors, and reduces the risk of monotherapy, as well as reducing the number of tablets to be taken. However, the use of combination tablets has no impact on treatment abandonment or irregular drug use.

The primary objective of the present study was to describe the clinical outcomes of tuberculosis patients treated with the self-administered, FDC tablet form of the 2RHZE/4RH regimen at either of two primary health care (PHC) clinics in the greater metropolitan area of Goiânia, Brazil. Our secondary objective was to describe adverse events and their potential impact on treatment outcomes.

Methods

This was a descriptive study based on secondary data from patients treated either at the Referral Center for Diagnosis and Treatment or at the Cais Nova Era clinic, which are PHC clinics located in the greater metropolitan area of Goiânia, Brazil. We included in the study patients who were treated at either of the abovementioned PHC clinics between November of 2010 and October of 2011 and who met the following inclusion criteria: being 18 years of age or older; and being at the beginning of tuberculosis treatment with the basic regimen. We excluded patients who were transferred to PHC clinics other than the two mentioned above or whose medical records did not contain the necessary information.

A data collection instrument was developed and pretested for the present study. The ability of the data collection instrument to produce information related to the variables of interest was confirmed by instrument completion tests using medical records of patients who had previously been treated for tuberculosis and in whom the clinical outcomes of the treatment. After participants gave written informed consent, the instrument was completed once a month, always by the same person, on the basis of data obtained from the medical records of the participants.

The following information was collected: personal data; type of diagnosis (sputum smear microscopy for AFB, sputum culture for Mycobacterium tuberculosis, histopathological examination, or clinical probability); type of tuberculosis case (new case, case of retreatment,
and severity criteria described by the National Institutes of Health.\(^{(13)}\)

All of the drugs used by the patients included in the present study were provided by the Brazilian National Ministry of Health following the 2RHZE/4RH regimen, meaning that the intensive phase (the first two months of treatment) consisted of oral administration of FDC tablets containing 150 mg of rifampin, 75 mg of isoniazid, 400 mg of pyrazinamide, and 275 mg of ethambutol per tablet, the maximum daily doses of isoniazid and pyrazinamide being 300 mg and 1,600 mg, respectively, whereas the maintenance phase (the last four months of treatment) consisted of oral administration of capsules containing the rifampin-isoniazid combination. The capsules used contained 300 mg of rifampin and 200 mg of isoniazid or 150 mg of the former and 100 mg of the latter. The maximum daily dose of isoniazid was 400 mg.

In order to test the hypothesis that the 2RHZE/4RH and 2RHZ/4RH regimens were similar in terms of treatment success rates, we calculated the sample size. Considering the average treatment success rate in Brazil, i.e., 70%, which coincides with those in the state of Goiás and in the greater metropolitan area of Goiânia, as well as a level of significance of 5% and a power of 90%, we estimated that a sample size of 38 individuals was required in order to detect a percentage difference of up to 25% in either direction.\(^{(14)}\)

The results were analyzed with the STATA program, version 11.0 (StataCorp LP, College Station, TX, USA). Data are expressed as mean, median, interquartile range, and standard deviation. The t-test was used for comparisons of continuous variable means. Univariate logistic regression was used in order to calculate unadjusted relative risks and their respective confidence intervals. When necessary, multivariate logistic regression was performed to adjust the association between the outcome and each independent variable. The Kruskal-Wallis test was used for comparisons of medians. For all tests, values of \(p < 0.05\) were considered statistically significant.

The study was presented to the boards of technical directors of the PHC clinics involved and was approved by the Human and Animal Research Ethics Committee of the Federal University of Goiás (Protocol no. 157/2010).
Results

We studied 40 individuals who underwent tuberculosis treatment with the 2RHZE/4RH regimen (self-administered treatment). Most were male (72.5%) and were in the 18–44 year age bracket. The most common clinical presentation was pulmonary tuberculosis (in 92.5%), and recurrence occurred in only 2 cases (5%). Extrapulmonary tuberculosis occurred in 3 patients (7.5%), and all had pleural tuberculosis (Table 1). In 23 patients (57.5%), the diagnosis was made on the basis of a positive sputum smear, whereas in 5, 4, 1, and 8 patients, respectively, the diagnosis was made on the basis of AFB-positive bronchoalveolar lavage fluid smears, pulmonary or pleural histopathology, a positive sputum culture for *M. tuberculosis*, and clinical probability. Of the 23 individuals with positive sputum smears, 20 (87%) had AFB-negative sputum smears by the end of two months of treatment, whereas 2 (8.7%) still had positive sputum smears by the end of two months and 1 (4.3%) had no sputum smear result reported by the end of two months. The median attendance at follow-up medical visits was 5.4 ± 1.3 per individual and 1.1 ± 0.4 per month.

In our study sample, 14 patients (35%) had one or more comorbidities, the most common of which was diabetes mellitus (in 12.5%; Table 2). Although it had been recommended for all of the individuals included in the present study, HIV serology was requested for only 32 (80.0%), HIV serology results being available for only 21 (65.6%).

The treatment success rate (cure and treatment completion) was 67.5%, and the treatment abandonment rate was 17.5% (Table 3). There were no cases of treatment failure. In 4 cases (10%), there was a change in diagnosis. In 3 of those 4 cases, the diagnosis was changed to atypical mycobacteriosis, whereas, in 1, the new diagnosis was missing from the medical record. Although 2 patients (5%) died, the deaths were unrelated to tuberculosis or tuberculosis treatment. The treatment success rate was found to be unaffected by the presence of comorbidities (OR = 1.09; 95% CI: 0.65–1.84; p = 0.74), the occurrence of adverse reactions (OR = 2.8; 95% CI: 0.69–11.4; p = 0.15), or patient gender (OR = 0.3; 95% CI: 0.05–1.70; p = 0.17). The median ages did not differ statistically among the “treatment success” outcome, the “treatment abandonment” outcome, and the combined “death and change in diagnosis” outcomes.

Of the sample as a whole, 19 patients (47.5%) had one or more adverse reactions to the drugs contained in the FDC tablets in the intensive phase, a total of 31 adverse drug reactions having occurred. The most common adverse reactions were those related to the digestive system (in 63.2%) and the skin (42.1%), and there was no need to change the treatment regimen (Table 4). Being female was associated with the presence of adverse reactions, even after adjustment for age and for the presence of comorbidities (OR = 10.8; 95% CI: 1.67–70.2; p = 0.01). There were no statistically significant differences between individuals with adverse drug reactions and those without in terms of the mean age (p = 0.18), and the presence of comorbidities had no influence on the onset of adverse drug reactions (OR = 1.08; 95% CI: 0.65–1.78; p = 0.76).

Table 1 - Characteristics of the 40 tuberculosis patients treated with fixed-dose combination tablets in the intensive phase of treatment between November of 2010 and October of 2011 in the greater metropolitan area of Goiânia, Brazil.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n (%)</th>
<th>Mean ± SD</th>
<th>Median (IQR)</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender</td>
<td>29 (72.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Age, years</td>
<td>-</td>
<td>49.0 ± 18.6</td>
<td>47.5 (35.5)</td>
<td>18-85</td>
</tr>
<tr>
<td>18-44</td>
<td>16 (40.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>45-59</td>
<td>11 (27.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥ 60</td>
<td>13 (32.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary tuberculosis</td>
<td>37 (92.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Positive pulmonary tuberculosis*</td>
<td>30 (75.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>New case</td>
<td>38 (95.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

IQR: interquartile range. *Positive sputum smear; positive sputum culture; positive bronchoalveolar lavage fluid smear; positive bronchoalveolar lavage fluid culture; positive pulmonary or pleural histopathology; or any combination thereof.
Discussion

The treatment success rate for the FDC tablet form of the 2RHZE/4RH regimen in the present study (67.5%) was found to be similar to those reported in other studies conducted in Brazil and using the 2RHZ/4RH regimen involving the use of rifampin-isoniazid capsules plus pyrazinamide tablets (61.2% and 68.6%).\(^{15,16}\) Controlled studies conducted outside Brazil and designed to compare the FDC tablet form of the 2RHZE/4RH regimen with the single-drug tablet form of the same regimen in patients in the intensive phase of treatment have found cure rates ranging from 80.4% to 95.0% and similar cure rates between the two groups of patients.\(^{17-19}\)

In our study sample, the high treatment abandonment rate (17.5%) was the factor that was most strongly associated with the low treatment success rate, given that the “transfer” outcome did not occur. The national rates of treatment abandonment\(^{20}\) and the municipal rates of treatment abandonment (data from internal documents issued by the Goiânia Municipal Department of Health) are lower than those found in the present study, being close to 12% and 10%, respectively, in the last 5 years. In order to analyze this difference, we should take into consideration the influence of the “transfer” outcome on the indicators from the Sistema de Informação de Agravos de Notificação (SINAN, Brazilian Case Registry Database), with lower cure rates and lower rates of treatment abandonment.

Although the treatment abandonment rate was high in the present study, it was lower than were those reported in two studies conducted in Brazil (22% and 27.3%, respectively).\(^{15,21}\) In addition to reporting a high incidence of treatment abandonment, Rabahi et al.\(^{15}\) reported that treatment abandonment was related to retreatment, hospitalization, use of a treatment regimen other than that recommended by the Brazilian National Ministry of Health, and no participation in a treatment monitoring program. In the present study, treatment abandonment was not related to other variables because the sample size was insufficient for this type of analysis.

| Table 2 - Comorbidities in the 40 tuberculosis patients treated with fixed-dose combination tablets in the intensive phase of treatment between November of 2010 and October of 2011 in the greater metropolitan area of Goiânia, Brazil. |
|----------------------------------|------------------|-----------------|-----------------|
| Comorbidities                   | Patients         | n (%)           |
| No comorbidities                | 26 (65.0)        |
| HIV positivity                  | 2 (5.0)          |
| Diabetes mellitus               | 5 (12.5)         |
| Cardiovascular disease          | 2 (5.0)          |
| Pulmonary disease               | 2 (5.0)          |
| Alcoholism                      | 3 (7.5)          |

| Table 3 - Clinical outcomes in the 40 tuberculosis patients treated with fixed-dose combination tablets in the intensive phase of treatment between November of 2010 and October of 2011 in the greater metropolitan area of Goiânia, Brazil. |
|----------------------------------|------------------|-----------------|-----------------|
| Clinical outcomes                | Patients         | n (%)           |
| Cure                             | 15 (37.5)        |
| Treatment completion             | 12 (30.0)        |
| Treatment abandonment            | 7 (17.5)         |
| Death*                           | 2 (5.0)          |
| Change in diagnosis              | 4 (10.0)         |
| Treatment failure                | 0 (0.0)          |
| Transfer                         | 0 (0.0)          |

*Deaths unrelated to tuberculosis or adverse drug effects.

| Table 4 - Types of adverse reactions in the 40 tuberculosis patients treated with fixed-dose combination tablets in the intensive phase of treatment between November of 2010 and October of 2011 in the greater metropolitan area of Goiânia, Brazil.* |
|----------------------------------|------------------|-----------------|-----------------|
| Type of adverse reaction         | Total            | Mild            | Moderate        | Severe          |
| Digestive                        | 12 (63.2)        | 11 (91.7)       | 1 (8.3)         | -               |
| Cutaneous                        | 8 (42.1)         | 6 (75.0)        | 2 (25.0)        | -               |
| General                          | 6 (31.6)         | 6 (100.0)       | -               | -               |
| Hepatic                          | 2 (10.5)         | 1 (50.0)        | 1 (50.0)        | -               |
| Musculoskeletal                  | 2 (10.5)         | 2 (100.0)       | -               | -               |
| Neurological                     | 1 (5.3)          | 1 (100.0)       | -               | -               |

*Values expressed as n (%).
The WHO recommends the use of four FDC tablets per day in the intensive phase and in the maintenance phase of treatment. Considering that the 2RHZ/4RH regimen consisted of four tablets and two capsules (a total of six pills) in the initial phase of tuberculosis treatment, there was a reduction in the number of pills to be taken in this phase of treatment. Given that in Brazil rifampin and isoniazid are available in the form of capsules containing a combination of the two drugs and that two rifampin-isoniazid capsules are taken per day in the maintenance phase of the 2RHZ/4RH regimen, the use of FDC tablets increases the number of pills to be taken during this phase of treatment. Therefore, in Brazil, the use of FDC tablets has not reduced the total number of pills.

In the present study, we evaluated the FDC tablet form of the 2RHZE/4RH regimen. However, this pharmaceutical formulation was used only in the first phase of treatment. In the second phase, capsules containing the rifampin-isoniazid combination were used because FDC tablets were not available for use in that phase of treatment via the public health care system. Therefore, specifically in our study, there was a reduction in the total number of pills taken. However, the rates of treatment success and treatment abandonment were 67.5% and 17.5%, respectively, i.e., rates that were similar to those obtained with the previous regimen. These data strongly suggest that the use of FDC tablets does not have a significant impact on adherence to treatment. Therefore, measures to improve adherence, such as supervised treatment, should not be neglected.

In Brazil, it has been demonstrated that being male, having dropped out of treatment before, and being on unsupervised treatment are predictors of treatment abandonment. The WHO recommends supervised treatment as one of the strategies to reduce treatment abandonment. In a clinical trial in which this strategy was used in order to ensure adherence to the treatments under study, the adherence rate was 95%, regardless of the pharmaceutical formulation used. In addition, studies conducted in Brazil have demonstrated the association between lower rates of treatment abandonment and supervised treatment.

One group of authors reported a reduction in treatment abandonment even for patients on semi-supervised treatment, an important finding in view of the high financial burden that directly observed treatment can represent to patients, especially those in the lowest income group. The high cost of directly observed treatment is likely to contribute to the low rates of success of supervised treatment in Brazil, which are below the 85% recommended by the WHO.

The frequency of adverse reactions in the intensive phase of tuberculosis treatment was 47.5% in our study. The most common adverse reactions were those related to the digestive system and the skin. There were no severe adverse reactions, and there were no changes in the treatment regimen as a result of adverse reactions. Specifically, no ophthalmic adverse reactions, which could have been attributed to the new drug in the regimen, i.e., ethambutol, were reported. In fact, the main adverse reaction to ethambutol (retrobulbar optic neuritis) is rare at the doses and schedule typically used in tuberculosis treatment. However, it should be highlighted that, in addition to an information bias, which is a limitation of the present study, the power of the sample size was not enough to identify uncommon reactions.

Adverse reactions contribute to changes in the treatment regimen, as well as contributing to treatment abandonment, increased costs, treatment failure, and even death in cases that are more severe. Historically in Brazil, the incidence of minor adverse events in patients treated with the regimen of rifampin, isoniazid, and pyrazinamide ranges from 5% to 20%, whereas the incidence of major adverse events ranges from 2% to 8%. The frequency or severity of adverse reactions to the FDC tablet form of the new tuberculosis treatment regimen in the Brazilian population is unknown.

Controlled studies have shown that the incidence of adverse reactions to the FDC tablet form of the new regimen was similar to or lower than that of adverse reactions to the single-drug tablet form of the same regimen. In addition, in two of those studies, the groups treated with FDC tablets had no severe adverse reactions or need for any changes in the treatment regimen because of adverse reactions.

A prospective, descriptive study conducted in the city of Vitória, Brazil, and investigating 79 tuberculosis patients showed the occurrence of adverse reactions in 83% of the patients treated with the 2RHZE/4RH regimen of rifampin–isoniazid capsules and single-drug tablets of ethambutol and...
pyrazinamide. Musculoskeletal adverse reactions were the most common (in 24.94%), followed by cutaneous adverse reactions (in 22.09%).

There was no relationship between a higher incidence of adverse reactions and age or between a higher incidence of adverse reactions and the presence of comorbidities in our study sample. However, being female correlated with the presence of adverse reactions, even after adjustment for age and for the presence of comorbidities. Such a relationship has also been reported for major adverse reactions. Nevertheless, it is well established that the doses, the time of day at which the drugs are administered, age, nutritional status, and HIV seropositivity are factors related to adverse reactions to antituberculosis drugs.

The individuals in our study sample were selected from among those treated at either of two PHC clinics where, although there was no shortage of drugs, there was a lack of skilled human resources for the treatment and diagnosis of tuberculosis, as well as structural and laboratory deficiencies, together with a lack of treatment supervision. In this context, the absence of treatment failure is questionable. However, this is probably due to the fact that the treatment failure rate is low in the greater metropolitan area of Goiânia, Brazil.

One limitation of the present study was that the study sample included tuberculosis patients who differed in terms of how the diagnosis of tuberculosis was established and in terms of disease stage and clinical presentation. This heterogeneity of the study sample, together with the deficiencies of the PHC clinics, might explain the high rate obtained for the “change in diagnosis” outcome.

Another limitation of the present study is the fact that the study sample included only patients treated at either of two PHC clinics in the greater metropolitan area of Goiânia, Brazil. Therefore, it is possible that our conclusions do not apply to advanced-care facilities or to PHC clinics in other regions. However, a study conducted in a tertiary care hospital that is a referral center for infectious diseases in central-western Brazil showed comparable results for treatment abandonment and cure.

In conclusion, the cure rates obtained with the self-administered, FDC tablet form of the 2RHZE/4RH regimen were similar to those obtained with the 2RHZ/4RH regimen of single-drug tablets and capsules. The latter rates were obtained from the SINAN and from studies conducted in Brazil. The treatment abandonment rate in our sample was much higher than that considered appropriate (up to 5%).

References

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