Retreatment of tuberculosis patients in the city of Porto Alegre, Brazil: outcomes*

Desfechos do retratamento de pacientes com tuberculose com o uso do esquema 3 em Porto Alegre, Brasil

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Abstract

Objective: To describe the outcomes of retreatment in tuberculosis patients receiving the regimen known, in Brazil, as regimen 3 (streptomycin, ethambutol, ethionamide, and pyrazinamide for 3 months + ethambutol and ethionamide for 9 months) after treatment failure with the basic regimen (rifampin, isoniazid, and pyrazinamide for 2 months + rifampin and isoniazid for 4 months). **Methods:** A descriptive, uncontrolled, historical cohort study involving adult tuberculosis patients treated with regimen 3. We evaluated adverse drug effects, recurrence, treatment outcomes, and associated factors. **Results:** The study included 229 patients. The overall cure rate was 62%. For the patients who used the medications regularly and those who did not, the cure rate was 88% and 31%, respectively. Adverse events occurred in 95 patients (41.5%), and most of those events were related to the gastrointestinal tract. In the five-year follow-up period, relapse occurred in 17 cases (12.0%). **Conclusions:** Overall, the outcomes of treatment with regimen 3 were unsatisfactory, in part because this regimen was administered to a selected population of patients at high risk for noncompliance with treatment, as well as because it presents high rates of adverse effects, especially those related to the gastrointestinal tract, which might be caused by ethionamide. However, for those who took the medications regularly, the cure rate was satisfactory. The recurrence rate was higher than that recommended in international consensus guidelines, which might be attributable to the short (12-month) treatment period. We believe that regimen 3, extended to 18 months, represents an option for patients with proven treatment compliance.

Keywords: Tuberculosis, pulmonary/therapy; Treatment outcome; Retreatment.

Resumo

Objetivo: Descrever os desfechos do retratamento de pacientes com tuberculose com o uso do esquema 3 (estreptomicina, etambutol, etionamida e pirazinamida por 3 meses + etambutol e etionamida por 9 meses) devido à falência do tratamento com o esquema básico (rifampicina, isoniazida e pirazinamida por 2 meses + rifampicina e isoniazida por 4 meses). **Métodos:** Estudo descritivo de coorte histórica, não controlada, com adultos que foram tratados com o esquema 3. Foram avaliados os desfechos desse tratamento, as reações adversas aos fármacos, as recidivas e os fatores associados. **Resultados:** Foram incluídos no estudo 229 pacientes. A taxa de cura geral foi de 62%. Entre os pacientes que usaram a medicação regularmente e aqueles que a usaram irregularmente, a taxa de cura foi de 88% e 31%, respectivamente. Observaram-se reações adversas em 95 pacientes (41,5%), principalmente digestivas. Ocorreram 17 recidivas (12,0%) nos cinco anos de seguimento. **Conclusões:** Os desfechos com o uso do esquema 3, em geral, não foram satisfatórios, pois esse esquema foi aplicado em uma população selecionada com alto risco de não adesão ao tratamento e apresenta altas taxas de reações adversas, especialmente as de tipo digestivo, possivelmente causadas pela etionamida. No entanto, para aqueles que conseguiram tomar a medicação regularmente, a taxa de cura foi satisfatória. A taxa de recidiva foi superior àquela preconizada por consensos internacionais, possivelmente devido ao tempo de tratamento curto (apenas 12 meses). Acreditamos que o esquema 3 estendido para 18 meses poderia ser uma alternativa para pacientes com comprovada adesão ao tratamento.

Descritores: Tuberculose pulmonar/terapia; Resultado de tratamento; Retratamento.

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Introduction

From the early 1980s until the end of 2009 in Brazil, it was recommended that cases of tuberculosis (TB) in which the use of the basic regimen, consisting of rifampin, isoniazid, and pyrazinamide—known in Brazil as regimen 1, or the RHZ regimen—resulted in treatment failure be treated with the combination of streptomycin, ethambutol, ethionamide, and pyrazinamide—known in Brazil as regimen 3, or the SEEtZ regimen.[1] The latter regimen was, therefore, a retreatment regimen administered to patients who had experienced treatment failure (as identified by clinical, bacterioscopic, and radiological criteria, without the use of susceptibility testing) while receiving rifampin and isoniazid. It is assumed that the bacilli have become resistant to these two drugs; such bacilli would meet the World Health Organization criteria for multidrug-resistant TB (MDR-TB).[2]

For the treatment of MDR-TB, various authors have recommended the use of at least four drugs, including a quinolone and an injectable agent (streptomycin, kanamycin, amikacin, or capreomycin), preferably in patients who are naïve to treatment with those drugs. In addition, the treatment with those drugs should continue for at least 18 months.[2]

The SEEtZ regimen does not include a quinolone and is administered for only 12 months. In the 3-month intensive phase, the SEEtZ regimen includes streptomycin, ethionamide, and ethambutol, none of which are included in the RHZ regimen, plus pyrazinamide, which is included in the first 2 months of treatment with the RHZ regimen. It is relatively common for patients to have been exposed to pyrazinamide more than once prior to experiencing treatment failure, raising the question of whether and to what extent the bacillus is susceptible to this drug. During the 9-month continuation phase, ethionamide and ethambutol are maintained, although gastrointestinal tolerance of the latter is poor.[3] In 2010, the SEEtZ regimen was replaced with a new regimen for MDR-TB, known as the MR regimen, consisting of five drugs (streptomycin, levofloxacin, terizidone, ethambutol, and pyrazinamide) administered for 18 months.[4]

There have been few studies evaluating the effectiveness and efficiency of the SEEtZ regimen in Brazil.[5-7] The objective of the present study was to describe adverse effects, recurrence, outcomes, and associated factors in TB patients undergoing retreatment with the SEEtZ regimen. Although the data were collected more than 10 years prior, the findings of this study can contribute to increasing the body of knowledge about the SEEtZ regimen and, occasionally, be useful as points of comparison with the outcomes that will be obtained with the use of the new MR regimen in similar populations in the future.

Methods

This was a descriptive, uncontrolled, historical cohort study. The data are secondary in nature and were collected for the purpose of patient follow-up and for academic purposes. These data were collected and recorded in a rigorous manner, because, at the time, the researchers were planning to use them in future publications.

The diagnostic and therapeutic procedures were standardized, and the data were recorded on clinical forms by the authors themselves, who were attending physicians. The information on the clinical forms was entered into a database by two of the authors, using dBASE III software (Ashton-Tate, 1985). For each patient, 75 variables were recorded, including demographic data, anthropometric data, data on alcohol abuse, diagnostic test results, TB treatment history, and information about current treatment (bacteriological follow-up, adverse effects, and outcomes).

For the detection of recurrence, we reviewed outpatient records up to post-discharge (i.e., post-cure) year 5, as well as data in the former Rio Grande do Sul State Tuberculosis Control Program database, an electronic system for compulsory registration of all TB cases. The broad coverage of this system ensured that virtually 100% of the TB cases diagnosed at the time were registered.

The study population comprised TB patients who were undergoing retreatment and resided in the greater metropolitan area of Porto Alegre, Brazil, between 1983 and 1993. The inclusion criteria were being at least 18 years of age and having experienced RHZ regimen treatment failure. Pregnant women were excluded. All of the eligible patients had been treated with the RHZ regimen at one of three outpatient clinics

in Porto Alegre. The researchers had access to patient data from two of those outpatient clinics, so that the present study included data on approximately 65% of the cases in the city of Porto Alegre and 100% of the cases in the other cities comprising the greater metropolitan area. All of those patients had sought medical attention spontaneously and were consecutively admitted to the outpatient clinics.

The patients were treated with the SEEtZ regimen for the first 3 months and subsequently with a regimen of ethambutol and ethionamide for another 9 months, for a total of 12 months. The treatment was self-administered, the drugs being dispensed at the TB outpatient clinics once every 30 days.

We evaluated adverse drug effects, recurrence, treatment outcomes, and associated factors.

The outcomes were defined as cure (satisfactory follow-up with definitive sputum smear conversion by the end of the regular treatment period), treatment abandonment (failing to report to the health care facility for more than 30 days after the last visit), treatment failure (unsatisfactory follow-up with smear-positive results for 2 or more consecutive months after month 4 or 5 of treatment), death (from any cause during the treatment period), and any change in the regimen due to toxicity (change of one or more drugs due to adverse effects).

The adverse effects observed were classified as gastrointestinal (symptoms such as nausea, vomiting, and epigastric pain), dermatologic (rashes), articular (joint pain or arthritis), auditory/vestibular (hearing loss, tinnitus, or dizziness), hepatic (signs or symptoms of liver damage or abnormal liver function test results), and visual (difficulty in distinguishing colors).

Cases of recurrence were defined as those in which patients who had been cured with the SEEtZ regimen again developed active pulmonary TB 3 or more months after cure and within 5 years after discharge.

The occurrence of adverse events, as well as patient age, gender, race (White and non-White), alcohol abuse, the regularity of anti-TB drug use, and drug dose (mg/kg of body weight) were evaluated as prognostic factors (in relation to treatment outcomes) and risk factors (in relation to recurrence). The last six variables were also evaluated as potential risk factors for the occurrence of adverse events.

The regularity of anti-TB drug use was evaluated on the basis of scheduled visit attendance and on the basis of information provided by the patient or family members, as documented in the patient charts. Irregular use was defined as failing to take ≥ 10% of the doses recommended.

The daily dose of drugs was calculated on the basis of the initial dose prescribed and patient weight at baseline (mg/kg per day).

The outcomes are expressed as mean and standard deviation or as absolute and relative frequency. The patients who were exposed to the risk or prognostic factors and those who were not were compared in terms of outcomes. Student's t-test was used for continuous variables, and the chi-square test or Fisher's exact test was used for categorical variables. For the analysis of the whether associated factors correlated with retreatment outcomes, adverse effects, and recurrence, we used multiple logistic regression. Values of $p < 0.05$ were considered significant.

The study was approved by the Research Ethics Committee of the School of Public Health of the Rio Grande do Sul State Health Department (Protocol no. 626/11).

Results

The study included 229 patients, of whom 167 (72.9%) were male, 175 (76.4%) were White, and 101 (44.1%) were alcohol abusers. The mean age was 38.3 ± 12.1 years (range: 17-73 years).

The mean drug doses used were as follows: streptomycin, 17.1 ± 2.8 mg/kg per day; ethambutol, 20.6 ± 3.6 mg/kg per day; ethionamide, 12.8 ± 2.1 mg/kg per day; and pyrazinamide, 31.9 ± 5.0 mg/kg per day. In 9.6% of the patients, the prescribed ethambutol dose was higher than maximum recommended daily dose (25 mg/kg per day), as was the pyrazinamide dose (higher than 30 mg/kg per day) in 60.3%.

A total of 104 patients (45.4%) used the medications irregularly. The rate of irregular anti-TB drug use was significantly higher among the patients who abused alcohol than among those who did not (58.4% vs. 36.7%; $p = 0.003$), as well as being higher among the patients who

Table 1 - Outcomes of tuberculosis treatment with the use of the regimen known in Brazil as regimen 3, or the SEEtZ regimen.[a] Porto Alegre, Brazil.

Outcome	Total	
	n	%
Cure	142	62.0
Treatment abandonment	33	14.4
Failure	38	16.6
Death	9	3.9
Change in the regimen (toxicity)	7	3.1
Total	229	100.0

[a]Streptomycin, ethambutol, ethionamide, and pyrazinamide for 3 months + ethambutol and ethionamide for 9 months.

experienced adverse gastrointestinal effects than among those who did not (59.7% vs. 21.7%; p = 0.002). There were no significant differences between patients who used the medications regularly and those who did not in terms of age, gender, race, drug dose, or other types of adverse effects.

Table 1 shows the treatment outcomes for the 229 patients evaluated. Of the 7 patients in whom the regimen was changed because of toxicity, 3 were subsequently cured, 1 after having received treatment with an alternative regimen and 2 after undergoing lung resection. The overall cure rate was 62%.

In the bivariate analysis, the cure rate was significantly lower in the patients who used the medications irregularly, in those who experienced adverse effects, and in those who were alcohol abusers (Table 2). Of the adverse effects, only those were related to the gastrointestinal tract were shown to be related to lower cure rates, the values being 51.5% and 66.9%, respectively, in the patients who experienced these adverse effects and those who did not (p = 0.025). Failure to achieve a cure was only weakly associated with alcohol abuse and with the occurrence of adverse events. In both situations, the relative risk (RR) was 1.4. Conversely, there was a strong association between the lack of a cure and irregular use of anti-TB drugs (RR = 5.8). This was corroborated by the results of the multivariate analysis with multiple logistic regression: only irregular use of anti-TB drugs was found to be independently associated with the lack of a cure (OR = 16.5; 95% CI: 8.3-33.6; p < 0.0001). The cure rate was not found to be significantly associated with gender or race (Table 2). The mean age of the patients who were cured was 39.2 years, whereas the mean age of those who were not cured was 37.1 years, a difference that was not significant (p = 0.208). There were also no significant differences between those who were cured and those who were not in terms of drug doses.

Adverse events occurred in 95 patients (41.5%), some of whom experienced more than one type of event. Gastrointestinal events occurred in 72 (31.4%) of the patients, auditory/vestibular events occurred in 21 (9.2%), articular events occurred in 4 (1.7%), dermatologic events occurred in 4 (1.7%), visual events occurred in 3 (1.3%), and other types of adverse events occurred in 5 (2.2%). The regimen had to be

Table 2 - Distribution of the potential prognostic factors in patients treated with the regimen known in Brazil as regimen 3, or the SEEtZ regimen,[a] by outcome (cure/no cure). Porto Alegre, Brazil.

Prognostic factor	Cure		No cure		Total	p
	n	%	n	%	n	
Male	109	65.3	58	34.7	167	0.095
Female	33	53.2	29	46.8	62	
White	106	60.6	69	39.4	175	0.420
Non-White	36	66.7	18	33.3	54	
Use of alcohol	55	54.5	46	45.5	101	0.036
No use of alcohol	87	68.0	41	32.0	128	
With adverse effects	51	53.7	44	46.3	95	0.029
With no adverse effects	91	67.9	43	32.1	134	
Irregular use	32	30.8	71	69.2	104	< 0.0001
Regular use	110	88.0	15	12.0	125	
Total	142	62.0	87	38.0	229	

[a]Streptomycin, ethambutol, ethionamide, and pyrazinamide for 3 months + ethambutol and ethionamide for 9 months.

changed because of toxicity in only 3.1% of the patients.

The proportion of patients experiencing adverse effects was higher among female patients than among male patients, as well as being higher among patients who did not abuse alcohol than among those who did. The occurrence of such events was not found to be associated with race or with the irregular use of anti-TB drugs (Table 3). There was also no association between adverse events and patient age or between these events and drug doses. In the multivariate analysis, alcohol abuse was found to be a protective factor (OR = 0.46; 95% CI: 0.27-0.80; p = 0.006).

The higher incidence of adverse effects in women than in men resulted from a higher frequency of adverse gastrointestinal effects (50.0% vs. 24.6%; p = 0.0002). The same was true for the patients who did not abuse alcohol in relation to those who did (39.1% vs. 21.8%; p = 0.005).

Among the 142 patients who were cured, recurrence was reported in 17 (12.0%), 14 (9.9%) experiencing recurrence within the first 2 years of the 5-year follow-up period. Because of the small sample size, no significant associations could be found between recurrence and the potential risk factors examined in this study.

Discussion

The SEEtZ regimen was established for use in cases of failure of the RHZ regimen. In general, these failures are observed in patients who do not comply with the RHZ regimen treatment. It is recognized that irregular treatment translates to higher rates of treatment abandonment, treatment failure, and death, thus lowering the cure rate.[8] In another study conducted in Porto Alegre, the authors evaluated 399 adults with active TB and treated with the RHZ regimen between 1983 and 1987. The authors reported that 18.3% used the medications irregularly, the rate of treatment failure being 7.5 times higher in the group of patients who used the medications irregularly than in the group of those who used them regularly.[5]

A high proportion of the patients for whom the SEEtZ regimen was indicated had a history of using the medications irregularly, and, therefore, were, *ab initio*, at significant risk of using the retreatment drugs irregularly. This risk was potentiated by the fact that the SEEtZ regimen includes a greater number of drugs to be used for a longer period, as well as by the fact that one of the drugs is administered parenterally. The rate of irregular use of the SEEtZ regimen was 45.4%, 2.5 times higher than that reported in the aforementioned study involving the RHZ regimen.[5] However, the rate of irregular use might be even higher, because the data on the way in which the drugs were used were based, in part, on information provided by the patients, who might have failed to report their irregular use, which would constitute an information bias.

The irregular use of anti-TB drugs is usually due to psychosocial problems, such as alcohol abuse, which is recognized as a risk factor for noncompliance with treatment,[8,9] but it can also be due to medication toxicity, which results in frequent interruptions in medication use. In

Table 3 - Distribution of potential risk factors for the occurrence of adverse events with the use of the regimen known in Brazil as regimen 3, or the SEEtZ regimen.[a] Porto Alegre, Brazil.

Risk factor	Adverse events		No adverse events		Total	p
	n	%	n	%	n	
Male	61	36.5	106	63.5	167	0.012
Female	34	54.8	28	45.2	62	
White	76	43.4	99	56.6	175	0.282
Non-White	19	35.2	35	64.8	54	
Use of alcohol	31	30.7	70	69.3	101	0.003
No use of alcohol	64	50.0	64	50.0	128	
Regular use	47	37.6	78	62.4	125	0.191
Irregular use	48	46.2	56	53.8	104	
Total	95	41.5	134	58.5	229	

[a]Streptomycin, ethambutol, ethionamide, and pyrazinamide for 3 months + ethambutol and ethionamide for 9 months

this study, the prevalence of alcohol abuse was 44.1% and the incidence of adverse effects was 41.5%, the latter rate being far superior to that observed with the use of the RHZ regimen.[4] We found that the proportion of patients who used the medications irregularly was significantly higher among those who abused alcohol and among those who experienced adverse effects than it was among the other patients.

In the particular case of adverse gastrointestinal effects, we cannot rule out the possibility that these effects affected the outcomes, especially among the women, in whom their incidence was significantly higher than it was among the men ($p = 0.0002$).

Adverse effects were less common among the patients who abused alcohol than among those who did not. In the statistical analysis, the use of alcohol was found to be a protective factor for the occurrence of adverse events. Because of the retrospective nature of this study, explanations for this finding could not be tested. However, one possible explanation for this protection is the fact that the patients who abused alcohol used a smaller quantity of the pills prescribed.

The overall cure rate with the use of the SEEtZ regimen was 62%. This low rate is mainly due to irregular use of anti-TB drugs; of the patients who used the medications irregularly, only 31% were cured. Among the patients who used the medications regularly, the cure rate was 88%, almost three times higher. Despite the limitations of the drugs comprising the regimen, this a quite satisfactory result, surpassing even the 85% recommended by the World Health Organization as the target cure rate for active cases.[10] Streptomycin and ethionamide are not first-line drugs for the treatment of TB,[2] because of their poor bactericidal and sterilizing activities.[6] In addition, ethionamide has a greater potential for causing adverse gastrointestinal effects that do the other drugs in the regimen.[2,3] However, in some cases, the possibility that treatment failure was due to primary drug resistance cannot be ruled out, because no susceptibility tests were performed prior to the initiation of treatment. This made it impossible for the authors to evaluate, separately, the cases of primary resistance and the cases of acquired resistance, the latter being generally secondary to the irregular use of anti-TB drugs.

There is an international consensus guideline stating that a good regimen should not produce a recurrence rate higher than 5%.[11] In the present study, the patients who were cured with the use of the SEEtZ regimen had a recurrence rate of 12% over the 5-year follow-up period. This rate was almost three times higher than the rate found in another study of RHZ regimen use in Porto Alegre.[12] Assuming that those were cases of endogenous reactivation, because of incomplete bacteriological cure, recurrence might have resulted from the poor bactericidal activity of the regimen, from the short (12-month) treatment period, from undermedication (in cases of irregular use of the drugs), or even from the choice of medications having been made without taking preexisting resistance into consideration.[12]

Therefore, the SEEtZ regimen was found to be inappropriate for treating 38% of the cases of RHZ regimen failure, as well as for treating 12% of those that had been cured with the regimen and in which there was recurrence. This can be attributed to three major problems: the SEEtZ regimen is indicated for a selected population of patients at high risk for noncompliance with treatment; ethionamide is not very potent and is associated with a high incidence of adverse gastrointestinal effects, which could promote noncompliance; and the treatment regimen is short-term (only 12 months). Conversely, considering the high cure rate among the patients who used the medications regularly, the SEEtZ regimen, extended to 18 months, represents an option for patients with proven treatment compliance and to whom other, more effective, regimens cannot be administered.

One of the limitations of the present study was that data from one of the three outpatient clinics that treat cases of RHZ regimen failure were not used. This possible selection bias is mitigated, in part, by the homogeneity of the patients, as can be seen in the database searched, according to which the distribution by age and gender, as well as the cure rates, of the patients treated at the outpatient clinic that was not studied was similar to that of the patients included in the present study. Another possible limitation is related to the fact that no susceptibility tests were performed prior to the initiation of treatment. However, because of the magnitude of the observed relationship between

the irregular use of anti-TB drugs and the low cure rate, the occasional cases of primary resistance are not likely to affect outcomes. The potential information bias resulting from the fact that treatment was self-administered is another limitation of the study. If the patients who failed to report their irregular use of anti-TB drugs could have been excluded from the group of patients who used the medications regularly, the cure rate might have been higher than the 88% reported. In addition, there were no available data on potential confounding factors that are currently considered classical, such as level of education, income level, and social class. Data on illicit drug use and HIV infection were not collected, because illicit drug use was uncommon and HIV testing was not routinely available at the time. Finally, because of the retrospective nature of the study, it was not possible to obtain new information that could be useful in examining potential explanatory hypotheses.

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