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Alternative anti-tuberculosis regimen including ofloxacin for the treatment of patients with hepatic injury

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SUMMARY

SETTING: Tuberculosis (TB) clinic of a university-based public hospital in Rio de Janeiro city, Brazil.

OBJECTIVE: To describe treatment outcomes for TB patients with liver injury who received a 12-month regimen of ethambutol (E, EMB) and ofloxacin (O, OFL), including streptomycin (S, SM) for the first 3 months (3SEO/9EO) under routine clinical care conditions.

DESIGN: A retrospective study of a cohort of TB patients prescribed 3SEO/9EO was conducted over a 66-month period. Data were obtained by review of existing medical records. Primary outcomes assessed were cure, treatment failure, treatment default, TB relapse and death.

RESULTS: Outcomes were assessed for 40 patients with hepatic injury who met study criteria. Twenty-three (58%) were male and 13 (33%) were human immunodeficiency virus seropositive. Thirty-four (85%) patients were cured. Three patients (7.5%) defaulted from treatment, and three other patients died (7.5%). There were no treatment failures or relapses during 2 years of follow-up. Clinically recognized drug toxicity occurred in five patients (12.5%), and in each case was attributed to SM.

CONCLUSION: In this series of TB patients with serious liver injury, 3SEO/9EO was well-tolerated, and it was effective in 85% of patients when used under routine clinical care conditions.

KEY WORDS: tuberculosis; treatment outcome; ofloxacin

TUBERCULOSIS (TB) remains a major public health problem worldwide. Globally, there are approximately 8 million incident cases annually, as estimated by the World Health Organization (WHO).[1] Appropriate treatment of persons with active TB is important in limiting the transmission of *Mycobacterium tuberculosis,* and for preventing individual TB-related mortality. For initial treatment of active TB in persons without prior TB treatment, the National TB Program (NTP) of Brazil recommends a standard regimen of rifampin (R, RMP) and isoniazid (H, INH) for 6 months, plus pyrazinamide (Z, PZA) during the first 2 months (2RHZ/4RH).[2] Each of these drugs is associated with hepatotoxicity, which occurs in approximately 10–16% of patients; for 2–6% of cases the replacement of one or more drugs of the standard RHZ regimen is necessary.[3–6] The Brazilian NTP recommends the replacement of the entire standard regimen with an alternative anti-tuberculosis regimen for those patients with 1) pre-existing liver disease associated with serum amino aspartate transferase (AST) activity more than three times the upper limit of normal (ULN) before starting TB treatment, or 2) hepatotoxicity (defined by hepatitis symptoms associated with AST >3 ULN) developing after initiation of standard RHZ treatment and which persists after stopping RHZ and/or is associated with severe TB such that TB treatment cannot safely be withheld during recovery from liver injury.

Prior to 1997, the alternative treatment recommended by the Brazilian NTP for TB patients with liver injury was daily ethambutol (E, EMB) plus ethionamide (Et, ETH) for 12 months, including streptomycin (S, SM) 5 days weekly for the first 3 months.[2] Because of its poor tolerability and perceived poor efficacy, in 1997 the recommended regimen was changed to daily ofloxacin (O, OFL) plus daily EMB for 12 months, with SM given 5 days weekly for the first 3 months (3SEO/9EO).[2] The recommended doses of SM and EMB are respectively 20 mg/kg/day and 25 mg/kg/day for patients weighing ⩽20 kg, 500 mg/day and 600 mg/day for those weighing 20–35 kg, 1000 mg/day and 800 mg/day for patients weighing 35–45 kg, and 1000 mg/day and 1200 mg/day for those weighing >45 kg. The recommended doses of OFL are 400 mg/day for patients weighing ⩽45 kg and 600 mg/day for those weighing >45 kg.[2]

To our knowledge, there is no published clinical experience using 3SEO/9EO for treatment of active TB in patients for whom initial treatment or reintroduction

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of all or part of the standard RHZ regimen is not possible due to severe liver injury.

The aim of this study was to describe the outcomes of TB patients who were treated with an alternative anti-tuberculosis regimen of 3SEO/9EO at a public hospital referral center for TB treatment in Rio de Janeiro city, Brazil.

METHODS

Design

We performed a retrospective study of a cohort of adult TB patients (age ⩾18 years).

Setting

This study was conducted at the TB Clinic of Institute of Thoracic Diseases/Clementino Fraga Filho Hospital of the Federal University of Rio de Janeiro (ITD/CFFH/FURJ), a referral center for TB treatment in Rio de Janeiro city, Brazil.

Subject selection and data collection

Name, hospital number and TB treatment regimen(s) prescribed were obtained from the TB Clinic register for all TB patients from 1 January 1998 to 31 June 2003. All other information was obtained by medical record review. Included in this study were all confirmed TB patients who received treatment with 3SEO/9EO according to the treatment guidelines of the Brazilian NTP due to hepatic injury, as described in the patient's chart. Patients were excluded from the study if the 3SEO/9EO regimen was used for ⩽30 days, if there was resistance to either INH or RMP (as in accordance to the NTP guidelines patients with drug resistance were referred to a different TB treatment clinic), if records were not available for review or if no information was available from the follow-up visit 2 years after the end of treatment.

Confirmed TB was considered to be documented growth of *M. tuberculosis* in a clinical specimen or documented presence of granulomatous inflammation on histopathologic study of biopsy tissue. During the first 3 months of TB treatment with 3SEO/9EO, OFL and EMB were administered under direct observation by a member of the TB Clinic staff 3 days per week (Mondays, Wednesdays and Fridays) and were self-administered on the other days of the week. SM was administered 5 days a week: on Mondays, Wednesdays and Fridays at the ITD/CFFH/FURJ TB Clinic and on Tuesdays and Thursdays at the Out-patient Primary Public Health Service clinic nearest to the patient's home. During months 4–12 of treatment, OFL and EMB were self-administered. Dosing of medications was as per the NTP guidelines, as described above. Patients attended monthly follow-up visits at the TB Clinic for clinical evaluation and to receive the exact number of tablets for the next month (30 days) of anti-tuberculosis treatment. Completion of therapy was defined based on calendar time, assuming that patients attending the TB Clinic for the monthly follow-up visit had been taking their treatment. In the routine activities of the ITD/CFFH/FURJ TB Clinic, visits included education about adherence. Patients received incentives (e.g., food voucher, bus token to attend the TB Clinic), and patients who missed clinic visits were contacted by phone or by a home visit. To assess for TB relapse, all patients studied underwent routine annual follow-up, including review of symptoms and chest radiograph, for 2 years after completion of TB therapy.

A patient was considered cured if, after 12 months of treatment, symptoms had resolved and there was complete radiological resolution. Pulmonary TB patients provided a sample of spontaneous sputum for acid-fast bacilli (AFB) smear and culture for TB at the monthly follow-up visit at the TB Clinic for clinical evaluation during TB treatment. In case of clinical or radiographic deterioration in a patient unable to provide sputum spontaneously, sputum induction was carried out. Patients with pulmonary TB and radiological improvement instead of total resolution at the end of treatment were considered cured if they had at least two consecutive samples of sputum (spontaneous or induced) with a negative result for *M. tuberculosis* growth on culture after the fourth month of treatment. Treatment failure of pulmonary TB was defined as persistent AFB smear positive or positive culture for *M. tuberculosis* at 5 months or later during treatment. Treatment failure of extra-pulmonary TB was defined as persistent clinical signs and/or symptoms at 5 months or later during treatment. Relapse was defined as a new episode of respiratory symptoms associated with bacteriologically (smear or culture) positive TB after cure of the first episode. Treatment default was defined as treatment interruption for ⩾2 consecutive months.[2]

For patients with pulmonary TB, the extent of lung field involvement was defined based on chest radiograph description in the medical record. Minimal disease was defined as disease that involved only one lobe and was not cavitary. Extensive disease was defined as disease that was bilateral or involved more than one lobe or was cavitary or miliary. Human immunodeficiency virus (HIV) testing was performed on all patients, as per routine clinical procedures.

The study was approved by the Ethics Committee of the Federal University of Rio de Janeiro in March 2003.

Statistical analysis

The results were analyzed using SPSS version 11.0 (SPSS Inc, Chicago, IL, USA). Successful outcome was considered to be cure without relapse during the 2-year follow-up period. Unsuccessful outcomes were treatment failure, treatment default, cure with relapse or death. The χ^2 test was used in the analysis of dichotomous variables and Fisher's exact test when

appropriate. The odds ratio (OR) of the association between variables that might affect treatment outcomes and treatment outcomes with 95% confidence interval (CI) was calculated. A value of 5% was considered statistically significant.

RESULTS

Over a 66-month period, 940 patients were admitted to the ITD/CFFH/FURJ TB Clinic with a diagnosis of TB. Sixty patients (6.4%) received one or more doses of 3SEO/9EO as an alternative to the standard treatment regimen (2RHZ/4RH). Medical records were reviewed for each of the 60 patients. Twenty patients were excluded from the study: two patients received ⩽30 days of 3SEO/9EO, as they tolerated the re-introduction of the standard RHZ regimen, and 18 patients had drug-resistant TB. Forty patients were included in the study and the treatment outcomes were evaluated. A flow diagram of the study population is shown in the Figure.

The baseline characteristics of the study population are shown in Table 1. In 30% (12/40) of the patients, 3SEO/9EO was prescribed as the initial anti-tuberculosis treatment regimen because of pre-existing liver disease associated with AST >3 ULN (seven cases of alcoholic cirrhosis, four cases of cirrhosis attributed to hepatitis C virus and one case of autoimmune cirrhosis). In 70% (28/40) of cases, 3SEO/9EO was prescribed because patients presented severe liver injury related to standard RHZ drugs associated with AST >3 ULN and did not tolerate re-introduction of the RHZ regimen. Among these patients, 96.4% (27/28) developed hepatitis (7 patients with history of chronic alcohol consumption and 20 with unknown risk factors for hepatotoxicity) and 3.6% (1/28) developed cholestasis besides hepatitis.

Among the patients who received RHZ therapy prior to initiation of 3SEO/9EO therapy, 71.4% (20/28) received RHZ for ⩽30 days, of whom 25% (5/20) received RHZ for <15 days. Twenty-five per cent (7/28) of the patients received >30 days of RHZ (median 90 days) prior to 3SEO/9EO initiation. For the remaining patient (3.6%), the exact length of time on RHZ treatment was not assessed.

Thirty-four patients (85%) were considered cured according to the study definition. All 34 patients were followed for 2 years after completing their treatment and no cases of relapse occurred during this period. Three patients (7.5%) defaulted from treatment and were lost to follow-up, and three patients (7.5%) died. Two deaths were attributed to respiratory failure secondary to chronic obstructive pulmonary disease, and one death was attributed to hepatic failure.

Table 2 shows the effect of various factors on treatment outcome, dichotomized to 'successful' versus 'unsuccessful' for all patients. In our sample, seropositive HIV status (OR 2.4, 95%CI 0.5–12.5, $P = 0.37$) as well as no previous use of standard RHZ therapy (OR 2.8, 95%CI 0.5–14.6, $P = 0.34$) were not statistically significantly associated with unsuccessful outcome.

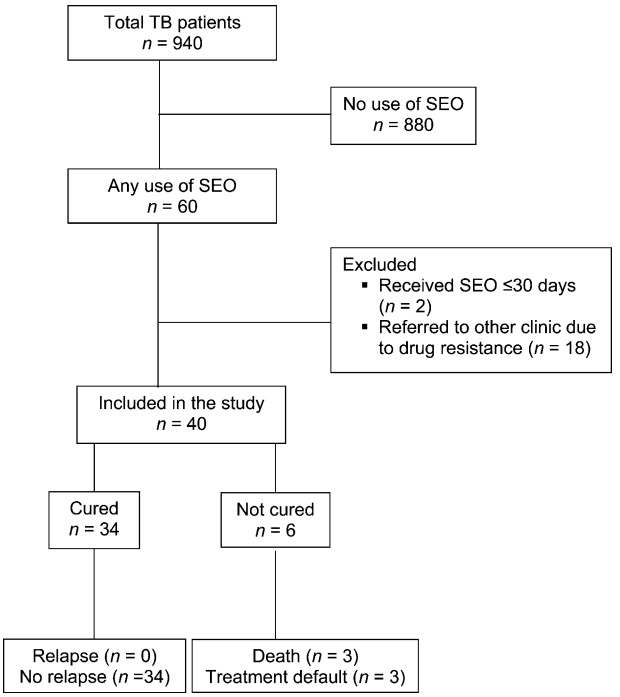

Figure Flow diagram of the study population. TB = tuberculosis; SEO = streptomycin, ethambutol, ofloxacin.

Table 1 Baseline characteristics of the study patients

	Study population ($N = 40$)	
Characteristics	*n*	%
Sex		
Male	23	57.5
Female	17	42.5
Total	40	100
Race		
White	17	42.5
Colored	23	57.5
Total	40	100
HIV status		
Negative	27	67.5
Positive	13	32.5
Total	40	100
Disease site		
Pulmonary	25	62.5
Extra-pulmonary	15	37.5
Total	40	100
Initial anti-tuberculosis treatment		
SEO	12	30.0
RHZ	28	70.0
Total	40	100
Liver toxicity to RHZ regimen		
Symptoms and AST >3 ULN	27	96.4
Cholestasis and AST >3 ULN	1	3.6
Total	28	100

HIV = human immunodeficiency virus; SEO = streptomycin, ethambutol, ofloxacin; RHZ = rifampin, isoniazid, pyrazinamide; AST = serum amino aspartate transferase; ULN = upper limit of normal.

Table 2 Comparison of outcomes for the study patients

	Unsuccessful (n = 6) n (%)	Successful (n = 34) n (%)	OR (95%CI)	P value
Sex			1.6 (0.3–8.4)	0.69
Male	4 (66.7)	19 (55.9)		
Female	2 (33.3)	15 (44.1)		
HIV status			2.4 (0.5–12.5)	0.37
Positive	3 (50.0)	10 (29.4)		
Negative	3 (50.0)	24 (70.6)		
Disease site			1.8 (0.4–9.4)	0.65
Extra-pulmonary	3 (50.0)*	12 (35.3)		
Pulmonary	3 (50.0)	22 (64.7)		
Extent of pulmonary TB†			1.7 (0.2–14.4)	1.00
Advanced	2 (66.7)	12 (54.5)		
Minimal	1 (33.3)	10 (45.4)		
Prior RHZ			2.8 (0.5–14.6)	0.34
No	3 (50.0)	9 (26.5)		
Yes	3 (50.0)	25 (73.5)		
Prior RHZ ⩾15 days			3.5 (0.6–18.8)	0.21
No	4 (66.7)	12 (35.3)		
Yes	2 (33.3)	21 (61.8)		
Unknown	0 (0)	1 (2.9)		
Prior RHZ >30 days			1.1 (0.1–8.2)	1.00
No	5 (83.3)	27 (79.4)		
Yes	1 (16.7)	6 (17.7)		
Unknown	0 (0)	1 (2.9)		

* Treatment default.
† 25 cases of pulmonary TB.
OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus; TB = tuberculosis; RHZ = rifampin, isoniazid, pyrazinamide.

Clinically recognized treatment-related toxicity was described for five patients receiving 3SEO/9EO (12.5%). In each case, toxicity had been attributed to SM by the treating clinician. One patient had a local inflammatory reaction at the site of injection, two patients had dermatitis and two had vestibular syndrome. Premature discontinuation of SM was necessary in one case of vestibular syndrome. There was no recognized toxicity attributed to OFL or EMB.

DISCUSSION

This study expands our knowledge of the tolerability and treatment outcomes of 3SEO/9EO as used in Brazil for the treatment of TB patients with severe liver injury. Specifically, this regimen was well-tolerated and had acceptable treatment outcomes when used under pragmatic clinical care conditions. Although toxicity and risk factors for toxicity associated with the standard first-line anti-tuberculosis regimen (RMP, INH, PZA ± EMB) are well-described, there is relatively little information about the toxicity and effectiveness of alternative anti-tuberculosis regimens in patients with chronic liver disease and/or patients who develop acute liver injury while receiving standard first-line treatment.[4–7] This information is important, especially in some resource-limited settings in which algorithm-based approaches may be more feasible than implementation of highly individualized drug challenges and treatment regimens, which can involve extensive clinician and patient time as well as frequent laboratory testing. All studied patients had been treated under existing Brazilian NTP guidelines with respect to initiation of 3SEO/9EO. While we recognize that this aspect of our study may not be generalizable outside Brazil, our findings are nevertheless likely to have broader applicability and interest, as they apply to patients in whom a first-line TB regimen cannot be used for whatever reason. It is important to note that RMP, which plays a critical role in TB treatment, is less hepatotoxic than INH and PZA and can safely be used in many patients who develop toxicity to the RHZ combination, although this is not addressed in the context of the current Brazilian NTP guidelines.

OFL was used because of its availability in Brazil in 1997 when the NTP recommendations were changed. Fluoroquinolone antibiotics are active against *M. tuberculosis*, and OFL has gained general acceptance mainly for the treatment of multidrug-resistant TB.[8–10] A notable feature of human clinical studies and experience with OFL-based regimens for TB treatment has been the tolerability and safety of OFL in the presence of liver disease.[11,12] Similarly, in our cohort in which OFL was used for up to 12 months, there was no recognized toxicity due to OFL. The newer fluoroquinolones, including moxifloxacin and gatifloxacin, have more potent in vitro activity against *M. tuberculosis*.[13] One can speculate that, in the 3SEO/9EO regimen, replacement of OFL with a newer fluoroquinolone might improve the regimen's effectiveness.

In our study, the odds of an unsuccessful outcome were not statistically different for patients who received none versus any standard RHZ-based TB treatment prior to SEO-based treatment. This finding was unexpected, given the potent bactericidal activity of RHZ-based regimens during the first few weeks of TB treatment. On the other hand, this finding may have been due to the small sample size, to chance alone or to factors not related to the antimicrobial activity of RHZ, as the 'unsuccessful' outcomes (3 treatment defaults and 3 deaths not considered due to TB) were not clearly attributable to TB disease activity.

Interestingly, treatment outcomes with the 3SEO/9EO regimen were generally similar to or more favorable than the standard regimen treatment outcomes reported by the Rio de Janeiro City TB Program in 2002 (cure 70%, default 17%, failure 2%, death 35%), and for the TB Clinic of ITD/CFFH/FURJ during the same time period (cure 79%, default 13%, failure 3%, death 5.7%).[14] One possible explanation for this unexpected finding is that, until 2001, fewer than half of TB patients were treated with directly observed therapy (DOT) at the Rio de Janeiro City TB Program or the ITD/CFFH/FURJ program. Before 2001, DOT was generally used only for individuals considered to be at high risk for treatment default. In contrast, all patients treated with the 3SEO/9EO regimen received

three of the five weekly doses by direct observation during the first 3 months of treatment. Furthermore, individuals with acute liver injury due to standard first-line TB treatment were hospitalized during the first week of 3SEO/9EO treatment. Therefore, in the 3SEO/9EO cohort, close interaction between patients and health workers and better patient perception of the necessity of treatment completion might have contributed to better adherence and favorable treatment outcomes.

Our study has important limitations. This is a retrospective study and treatment was provided under pragmatic clinical 'non-study' conditions. Therefore, monitoring for drug-related side effects and treatment response were not uniform across all patients. Importantly, sub-clinical drug toxicity or side effects not reported by patients may not have been captured in our study. We cannot exclude the possibility that unreported drug toxicity was a factor in treatment default by three patients. In addition, the relatively small numbers of patients included in our study prevented a detailed analysis of factors associated with various outcomes.

We conclude that, in this series of TB patients with serious liver injury, 3SEO/9EO was well tolerated and was effective in 85% of individuals.

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RÉSUMÉ

CONTEXTE : Clinique de Tuberculose (TB) d'un hôpital universitaire dans la ville de Rio de Janeiro au Brésil.

OBJECTIF : Décrire les résultats du traitement des patients tuberculeux avec atteinte hépatique qui ont reçu un régime de 12 mois d'éthambutol (E) et d'ofloxacine (O), accompagné de streptomycine (S, SM) pendant les 3 premiers mois (3SEO/9EO), dans des conditions de soins cliniques de routine.

SCHÉMA : Etude rétrospective d'une cohorte de patients TB ayant reçu 3SEO/9EO, menée au cours d'une période de 66 mois. Les données ont été obtenues en revoyant les dossiers médicaux existants. Les résultats principaux évalués ont été guérison, échec du traitement, abandon, rechute de TB et décès.

RÉSULTATS : Les résultats ont pu être évalués chez 40 patients avec atteinte hépatique qui répondaient aux critères de l'étude. Il s'agissait de 23 hommes (58%) et de 13 séropositifs pour le virus immunodéficience humaine (33%). La guérison a été obtenue chez 34 patients (85%). Il y a eu trois abandons (7,5%) et trois décès chez d'autres patients (7,5%). On n'a pas noté d'échec du traitement ou de rechute au cours d'un suivi de 2 années. Une toxicité cliniquement reconnue due aux médicaments est survenue chez cinq patients (12,5%) et a été dans chaque cas attribuée à la SM.

CONCLUSION : Dans cette série de patients TB dont l'atteinte hépatique était sévère, le régime 3SEO/9EO a été bien toléré et s'est avéré efficace chez 85% des patients lorsqu'il était utilisé dans des conditions de soins cliniques de routine.

RESUMEN

MARCO DE REFERENCIA: El consultorio de tuberculosis (TB) de un Hospital Universitario del sector público en la ciudad de Río de Janeiro, en Brasil.

OBJETIVO: Describir el desenlace terapéutico de pacientes tuberculosos con afectación hepática, quienes recibieron un tratamiento durante 12 meses con etambutol (E) y ofloxacino (O), el cual asociaba además estreptomicina (S, SM) durante los primeros 3 meses (3SEO/9EO). El tratamiento se administró en condiciones de atención clínica sistemática.

MÉTODOS: Fue este un análisis retrospectivo de cohortes de pacientes con TB quienes recibieron 3SEO/9EO. La duración del estudio fue de 66 meses. Los datos se obtuvieron a partir de las historias clínicas. Los criterios primarios de evaluación fueron curación, fracaso terapéutico, abandono del tratamiento, recaída de la TB y defunción.

RESULTADOS: Se evaluó el desenlace clínico de 40 pacientes con lesión hepática, quienes cumplieron con los requisitos de inclusión en el estudio. Veintitrés pacientes (58%) fueron hombres y 13 (33%) presentaron serología positiva para el virus de la inmunodeficiencia humana. Treinta y cuatro pacientes (85%) alcanzaron la curación. Tres pacientes (7,5%) abandonaron el tratamiento y otros tres fallecieron (7,5%). No se presentaron fracasos terapéuticos ni recidivas durante los 2 años del seguimiento. En cinco pacientes (12,5%) ocurrió toxicidad medicamentosa determinada clínicamente, la cual se atribuyó en todos los casos a la SM.

CONCLUSIÓN: En esta serie de pacientes tuberculosos con afectación hepática grave, el tratamiento 3SEO/9EO presentó una buena tolerabilidad y fue eficaz en el 85% de los pacientes tratados en condiciones de atención clínica sistemática.