

Comparison of the effectiveness of 2 treatment regimens in patients with isoniazid-resistant tuberculosis

P. Tabarsi,¹ P. Baghaei,¹ N. Hemmati,¹ M. Mirsaeidi,¹ M. Kazempour,¹ D. Mansouri¹ and M.R. Masjedi¹

مقارنة بين فعالية نظامين علاجيين لمرضى السل المقاوم للإيزونيازيد

بيام طبرسي، بروانة بقايي، نسيم همتي، مهدي مير سعدي، مهدي كاظم بور، داوود منصورى، محمد رضا مسجدي

الخلاصة: قارن الباحثون بين فعالية نظامين علاجيين أعطيا لـ 42 مريضاً بالسل المقاوم للإيزونيازيد، ممن يترددون على مركز إحالة للسبل في جمهورية إيران الإسلامية. وقد قسّم الباحثون المرضى إلى مجموعتين للدراسة؛ المجموعة الأولى تتألف من 26 مريضاً تلقوا المعالجة المعيارية التي تتضمن الإيزونيازيد والريفامبيسين والبيرازيناميد والإيثيمبتول لمدة ستة شهور، والمجموعة الثانية وتتألف من 16 مريضاً تلقوا نظاماً علاجياً معدلاً يتضمن الريفامبيسين والبيرازيناميد والإيثيمبتول لمدة ستة شهور. ولم يكن هنالك فروق ذات اعتداد إحصائي من حيث العمر والجنس في العينتين المدروستين. وقد شفي 21 مريضاً في العينة التي تلقت المعالجة المعيارية (80.8٪)، وفشلت المعالجة المعيارية لدى 4 منهم (15.4٪)، ومات واحد منهم (3.8٪). أما في النظام العلاجي المعدل فقد شفي جميع المرضى الستة عشرة (100٪). ولم يكن لهذه الفروق أهمية يعتد بها إحصائياً (فكوة الاحتمال $P = 0.194$).

ABSTRACT We compared the effectiveness of 2 treatment regimens for isoniazid-resistant tuberculosis (TB) in 42 patients attending a TB referral centre in the Islamic Republic of Iran. The patients were divided into 2 treatment groups: 26 received the 6-month standard HRZE treatment and 16 received a modified treatment of RZE for 6 months. There were no significant differences in age or sex of the groups. With the standard method of treatment, 21 (80.8%) patients were cured, 4 (15.4%) resulted in treatment failure, and 1 (3.8%) died. In the modified treatment group, 16 (100%) patients were cured. These differences were not statistically significantly different ($P = 0.194$).

Comparaison de l'efficacité de deux schémas thérapeutiques chez des patients atteints de tuberculose à bacilles résistant à l'isoniazide

RÉSUMÉ Nous avons comparé l'efficacité de deux schémas thérapeutiques de la tuberculose à bacilles résistant à l'isoniazide chez 42 patients fréquentant un centre spécialisé dans le traitement de la tuberculose en République islamique d'Iran. Les patients ont été répartis en deux groupes thérapeutiques : 26 ont reçu le traitement HRZE standard de 6 mois et 16 ont reçu un traitement RZE modifié pendant 6 mois. Il n'existait pas de différence significative dans l'âge ou le sexe des patients. Avec le traitement standard, 21 patients (80,8 %) ont guéri, 4 (15,4 %) n'ont pas présenté d'effets et 1 patient (3,8 %) est décédé. Avec le traitement modifié, 16 patients (100 %) ont guéri. Ces différences n'étaient pas statistiquement significatives ($P = 0,194$).

¹Mycobacteriology Research Centre, National Research Institute of Tuberculosis and Lung Disease, Shaheed Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran (Correspondence to P. Tabarsi: tabarsi@nritld.ac.ir).

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Introduction

The World Health Organization (WHO) has recommended measures and treatment methods for tuberculosis (TB) (duration of 6 months) [1]. However, multidrug resistance is increasing around the world, and mono-resistance to isoniazid has a higher incidence [2]. Management and control of mono-resistance to isoniazid is of great significance since it can prevent multidrug-resistant (MDR) TB (resistance to isoniazid and rifampin) [3–6]. Unfortunately, there is no existing specified global solution for the control of mono-resistant (isoniazid) cases or cases resistant to both isoniazid and streptomycin. In some studies, the WHO standard 6-month DOTS regimen, which has been successful thus far, has been introduced as a solution for the treatment of the aforementioned cases [7,8]. Yet in other studies different and longer forms of treatment (9–12 months) have been suggested [9]. A method recommended by the Centers for Disease Control and Prevention and the American Thoracic Society (CDC/ATS) in 1994 is a 6-month treatment regimen with rifampicin, pyrazinamide and ethambutol for cases resistant to isoniazid (with or without resistance to streptomycin) [10].

The purpose of our study was to compare the standard regimen and the modified 6-month regimen recommended by CDC/ATS for the treatment of isoniazid-resistant TB.

Methods

This study was conducted at the Masih Daneshvari Hospital, the national referral centre for TB in the Islamic Republic of Iran. All patients with TB at the centre are tested for *Mycobacterium tuberculosis* using smear, culture and drug susceptibility test (DST). They are admitted to the TB unit

and are monitored for drug resistance and side-effects for a period of 2 weeks. In order to continue their treatment, these patients are either referred to the clinic located in this centre or to their local health centre.

In this retrospective cohort study, we included patients infected with TB who were referred to this centre between the years 2003 and 2005 and whose DST showed resistance to isoniazid (with or without resistance to streptomycin).

Two treatment methods were undertaken for these patients:

- The first group continued their treatment at the health centres with the standard 6-month regimen: 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) and 4 months of isoniazid and rifampin.
- The second group continued their treatment at the hospital clinic and their regimen was modified to RZE for a total period of 6 months (6RZE).

Patients were followed up for 1 year after their treatment was completed. The treatment outcomes were analysed based on WHO guidelines (Table 1) [1].

All data were entered into SPSS, version 11.5, for statistical analysis. The chi-squared test was used for categorical variables, and whenever necessary the Fisher exact test was used. P -value < 0.05 was considered statistically significant.

The Scientific and Ethics Committee of the National Research Institute of Tuberculosis and Lung Disease approved the study protocol.

Results

We identified 42 isoniazid-resistant patients and these were included in the study. The first group comprised 26 patients who received standard treatment and the second

Table 1 Outcome definitions in smear-positive tuberculosis patients [1]

Outcome	Outcome definition
Cured	Patient who is sputum smear-negative in the last month of treatment and on at least 1 previous occasion.
Treatment completed	Patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure.
Treatment failure	Patient who is sputum smear-positive at 5 months or later during treatment.
Died	Patient who dies for any reason during the course of treatment.
Defaulted	Patient whose treatment was interrupted for 2 consecutive months or more.
Transferred out	Patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known.

group had 16 patients, who were given the modified treatment. Demographic and bacteriological data for both groups are shown in Table 2. The HIV test was negative for all patients. Mean age in the first group was 53 [standard deviation (SD) 23] years and in the second group 40 (SD 9.28) years. In both groups, 50% of patients showed resistance to both isoniazid and streptomycin.

Table 2 Demographic and bacteriological data of the 2 treatment groups

Variable	Standard regimen (n = 26)		Modified regimen (n = 16)	
	No.	%	No.	%
Sex				
Male	18	69.2	13	81.3
Female	8	30.8	3	18.7
Smear				
Negative	2	7.7	0	–
Positive	24	92.3	16	100.0
Culture				
Negative	0	–	0	–
Positive	26	100.0	16	100.0
Resistant to:				
Isoniazid	13	50.0	8	50.0
Isoniazid & streptomycin	13	50.0	8	50.0
HIV test				
Negative	26	100.0	16	100.0
Positive	0	–	0	–

Regarding age and sex, there were no significant differences between the 2 groups ($P > 0.05$).

Treatment results are shown in Table 3. There were no significant differences between the 2 groups ($P = 0.194$).

Discussion

A number of regimens for treating isoniazid-resistant TB have been recommended, even though the ideal regimen and the duration are still under discussion [11–13].

In the past few years, several reports concluded that the standard 4-drug treatment over 6 months is sufficient for the treatment of TB resistant to isoniazid [14,15]. However, in the recently published guidelines, continuation of pyrazinamide treatment for 6 months is recommended [16].

The treatment effectiveness of these recommended regimens has not yet been fully identified. For instance, the effectiveness of a 12-month treatment regimen with rifampin and ethambutol has not yet been examined. In the study by Bai et al., the success rate of the 6-month standard treatment regimen in isoniazid-resistant cases was reported to be 94.4% [17]. The success rate in our study was 80.8% and that of the 6-month RZE treatment regimen was 100%, similar to the findings of Nolan and Goldberg [15].

Table 3 Treatment outcome in the 2 treatment groups

Outcome	Standard regimen		Modified regimen		Total	
	No.	%	No.	%	No.	%
Complete recovery	21	80.8	16	100.0	37	88.1
Treatment failure	4	15.4	0	–	4	9.5
Death	1	3.8	0	–	1	2.4
Total	26	100.0	16	100.0	42	100.0

P = 0.194.

In the present study, during the 1-year follow-up period, in the group receiving RZE, there were no cases of reactivation or death. This disagrees with the results of Bai et al., who confirmed the effectiveness of the standard treatment [17], but our study showed a 15.4% failure rate for the standard treatment, higher than for the modified regimen (6RZE) although no statistically significant differences were found. It has been shown that comparing the treatment of cases with isoniazid-resistant TB (a factor in the failure of the standard treatment regimen and increases in the reactivation rate) with cases sensitive to the 4 drugs is important [14]. Moreover, the development of MDR-TB in isoniazid-resistant TB patients with incomplete treatment, and particularly in patients with cavitary TB and bilateral infiltrative lesions, has been reported more often [11]. In a study by Stewart and Crofton, it is reported that resistance to isoniazid can cause significant differences in the results of treatment [18].

Even though there was no significant difference between the 2 treatment regi-

mens in our study, the 1 death and the high rate of treatment failure in patients treated with the standard regimen could indicate that the standard regimen in cases with isoniazid-resistant TB is not entirely effective. Therefore, routine sensitivity tests, especially in the first 2 months of treatment, and the use of appropriate treatment regimens are important in order to achieve complete recovery of patients.

Conclusion

Our study shows that there were no significant differences between the success rates of the modified regimen (6RZE) and the standard regimen in the treatment of isoniazid-resistant TB cases. There is a need however for more studies with larger sample sizes in order to more accurately determine the effectiveness of different treatment regimens. Considering the high rate of treatment failure, it is recommended that in isoniazid-resistant TB cases, especially in cavitary TB and bilateral lesions, the modified regimen (6RZE) be used.

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