Drug resistance pattern and outcome of treatment in recurrent episodes of tuberculosis

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أنماط المقاومة للأدوية وحصائل المعالجة في الهجمات المتكررة للسل

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الخلاصة: قد تختلف أنماط المقاومة للأدوية في الحالات المعاودة للسل عن تلك التي تضم سوابق معالجة وفي هذه الدراسة الاستعادية، قارن الباحثون نمط المقاومة للأدوية وحصائل المعالجة بنظام الفئة I من استراتيجية المعالجة القصيرة الأمد تحت الإشراف المباشر (دوتس) لدى 63 من الحالات المتكررة و872 من الحالات الجديدة للسل الرئوي في الفترة بين نيسان/ أبريل 2003 وكانون الثاني/ يناير 2008، في المعهد الوطني للبحوث حول السل وأمراض الرئة في طهران، في جمهورية إيران الإسلامية، واتضح أن المقاومة للإيزونيازيد وللإيثامبوتول كانت أكثر شيوعاً بدرجة يُعْتَدُّ بها في الحالات المتكررة، في حين لم يكن هناك فرق في معدلات المقاومة للريفامبين والبيرازيناميد والستربتوميسين، ولا في معدل الذراري المقاومة لأدوية متعددة. وكانت المقاومة للستربتوميسين هي الأكثر شيوعاً، ولم تكن هناك فوارق يُعتدُّ بها في حصائل المعالجة والوفيات بين المجموعتين. ونتيجةً للتواتُر (للتكرار) المنخفض للمقاومة لأدوية متعددة، فإن الفئة I من استراتيجية المعالجة القصيرة الأمد تحت الإشراف المباشر قد تكون ملائمة للمعالجة التجريبية قبل أن تتوافر نتائج التحسس للأدوية.

ABSTRACT Patterns of drug resistance in recurrent cases of tuberculosis may be different than in those without a history of treatment. In this retrospective study, the drug resistance pattern and outcome of treatment with DOTS category I (CAT I) regimen was compared in 63 recurrent cases and 872 new cases of pulmonary tuberculosis from April 2003 to January 2008 at the National Research Institute of Tuberculosis and Lung Disease in Tehran, Islamic Republic of Iran. Resistance to isoniazid and ethambutol was significantly more common in recurrent cases, but there were no differences in rates of resistance to rifampin, pyrazinamide, streptomycin or the rate of multi-drug resistant strains. Resistance to streptomycin was the most common. No significant differences in treatment outcome and deaths were found between the 2 groups. Due to the low frequency of multi-drug resistance in the recurrent cases, a CAT I regimen may be suitable for empirical therapy before drug sensitivity results become available.

Profils de pharmacorésistance et résultats du traitement des épisodes récurrents de tuberculose

RÉSUMÉ Les profils de pharmacorésistance dans les cas récurrents de tuberculose peuvent être différents de ceux qui n'ont pas d'antécédents thérapeutiques. Dans la présente étude rétrospective, les profils de pharmacorésistance et les résultats du traitement de brève durée sous surveillance directe (DOTS) de catégorie I ont été comparés dans 63 cas récurrents et 872 nouveaux cas de tuberculose pulmonaire entre avril 2003 et janvier 2008 à l'Institut national de recherche sur la tuberculose et les maladies pulmonaires de Téhéran (République islamique d'Iran). La résistance à l'isoniazide et à l'éthambutol était nettement plus fréquente dans les cas récurrents, mais aucune différence n'a été observée dans les taux de résistance à la rifampine, la pyrazinamide, la streptomycine, ni dans le taux des souches multirésistantes. La résistance à la streptomycine était la plus fréquente. Aucune différence significative dans les résultats thérapeutiques et les décès n'a été observée entre les deux groupes. En raison de la faible fréquence de polypharmacorésistance parmi les cas récurrents, le traitement de catégorie I peut convenir en tant que traitement empirique en attendant que les résultats des tests de sensibilité aux médicaments deviennent disponibles.

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Introduction

With 8.8 million new cases and the deaths of 2 million people reported annually worldwide, tuberculosis (TB) is still an important health problem [1,2]. Studies have shown that a previous history of TB treatment, especially irregular drug therapy, is an important risk factor for resistance to anti-TB drugs [3,4]. In most communities, recurrent cases make up the largest proportion of previously treated patients [5]. The pattern of anti-TB drug resistance in this group may be different from that in defaulters and patients with treatment failure. Ideally, drug susceptibility testing should be obtained from all previously treated TB patients. In settings where drug susceptibility results are not routinely available and if country-specific data show low or medium levels of multi-drug resistant TB (MDR), TB cases with a first episode of relapse may receive the DOTS category II regimen (CAT II). This regimen consists of isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), ethambutol (ETB) and streptomycin (STR) for 2 months, followed by the first 4 drugs without STR for 1 month and INH, RIF and ETB for the remaining 5 months [6]. The CAT II regimen is more costly and has more adverse effects than the DOTS category I regimen (CAT I) which consists of 2 months of INH, RIF, PZA and ETB and 4 months of INH and RIF [7].

The incidence of TB in the Islamic Republic of Iran was estimated as 22 per 100 000 people in 2005; 1.9% of confirmed TB patients were recurrent TB cases according to a World Health Organization (WHO) report [2]. Resistance to RIF and concomitant resistance to INH and RIF have the most effect on the outcome of treatment. Therefore information about drug resistance prevalence is necessary for more effective treatment of previously treated cases and for national strategic planning [5]. The aim of the present study was to identify the drug resistance patterns among recurrent and new TB cases and assess the efficacy of the CAT I regimen in these groups.

Methods

Study setting

This retrospective study was conducted at the National Research Institute of Tuberculosis and Lung Disease (NRITLD), Tehran, Islamic Republic of Iran, from April 2003 to January 2008. NRITLD is a specialized centre for TB and lung disease and has a bidirectional relationship with the national TB programme. New cases diagnosed at NRITLD are referred to the national TB programme for supervision of their treatment and the national TB programme refers complex TB cases to NRITLD. This research was reviewed and approved by the ethics committee of the centre.

Sample

Over the study period 63 cases of recurrent pulmonary TB and 872 cases of new pulmonary TB with mycobacteriologic confirmation were diagnosed. All of them were recruited to the study. Recurrent cases were defined as TB patients with previous history of TB who were cured or completed treatment based on WHO definitions. New cases were defined as any pulmonary TB patient with no history of treatment or a history of anti-TB therapy for less than 1 month [6]. All patients were over 14 years of age.

Data collection

Sputum smear and culture testing were performed for all patients. The tests were done at the WHO-approved National Mycobacteriology Reference Laboratory. The laboratory is supervised by the Swedish Institute for Infectious Disease Control and the Research Institute of Tuberculosis of the Japan Anti-Tuberculosis Association. Anti-TB drug susceptibility tests (proportional method) were performed for culture-positive specimens.

Both groups were treated with standard CAT I regimen (see earlier), except for MDR cases or patients with severe adverse drug reactions in which modifications to their drug regimen was necessary. Treatment was initiated as inpatients or outpatients and continued by the national TB programme under the DOTS strategy.

Demographic information (age, sex, nationality and residency), smoking and drug misuse status, drug resistance pattern and outcome of treatment were obtained for both groups. Successful treatment consisted of cure (patient had negative sputum smear at the end of treatment) and treatment completed (patient completed treatment but did not meet the criteria for cure). Treatment failure was defined according to WHO guidelines [6].

Data analysis

For statistical analysis, all data gathered were entered into *SPSS*, version 15. The association between qualitative variables was evaluated by the chi-squared test or Fisher exact test. Student *t*-test and Mann–Whitney tests were used for quantitative variables with normal distribution and non-distributed variables respectively. A P-value < 0.05 was considered statistically significant. Adjusted Mantel–Haenszel test was utilized to exclude covariates.

Results

Background characteristics of the groups

The study sample included 63 (6.7%) recurrent cases and 872 new cases of pulmonary TB from April 2003 to January 2008. The background characteristics, outcome of treatment and drug resistance pattern of both groups are summarized in Table 1. Males were 61.9% of the recurrent cases and 49.4% of new cases, although this difference was not significant. There was no significant difference in the mean

Table 1 Demographic profile and outcome of treatment of new and recurrent tuberculosis cases

Variable	New cases		Recurrent cases		*P*-value
	No.	%	No.	%	
	(*n* = 872)		(*n* = 63)		
Sex					
Male	431	49.4	39	61.9	NS
Female	441	50.6	24	38.1	
Age [mean (SD)]	51.8 (21.4)		49.9 (20.1)		NS
Nationality					
Iranian	680	78.0	50	79.4	NS
Other	192	22.0	13	20.6	
Smoking					
Yes	232	26.6	29	46.0	0.001
No	640	73.4	34	54.0	0.001
Drug abuse					
Yes	134	15.4	23	36.5	NS
No	738	84.6	40	63.5	
Alcohol use					
Yes	74	8.5	9	14.3	NS
No	798	91.5	54	85.7	
Successful treatment[a]	(*n* = 683)		(*n* = 58)		
Yes	621	90.9	51	87.9	NS
Death					
Yes	56	8.2	7	12.1	NS

[a]*Successful treatment consisted of cure and treatment completed.*
SD = standard deviation; NS = not significant.

age of recurrent cases [49.9 (SD 20.1) range 15–87 years] compared with new cases [51.8 (SD 21.4) range 14–90 years]. Among new cases 78.0% were Iranian and 22.0% were other nationalities, primarily Afghan. In the recurrent group 79.4% were Iranian. Smoking and drug misuse were more common in recurrent cases (46.0% and 36.5% respectively) than new cases (26.6% and 15.4% respectively) ($P = 0.001$).

TB-free duration

In the recurrent group the mean TB-free duration between the 2 episodes of disease was 99 months (median 36 months, range 6–540 months). Over half (53.4%) of the recurring cases occurred during the first 3 years after the previous episode. There was no relationship between the first TB-free period and drug resistance pattern or outcome of treatment ($P = 0.29$ and $P = 0.53$ respectively): mean time between 2 episodes of TB was 10.56 years for recurrent cases without any drug resistance and 6.97 years for recurrent cases with any drug resistance, while for outcome of treatment it was 9.54 and 3.71 years for successfully treated and unsuccessfully treated respectively.

Drug susceptibility

Drug susceptibility testing was performed on 46 culture-positive recurrent cases [16 (25.4%) had negative cultures and data were missing for 1 case]. In the newly occurring group 95 patients had negative cultures and among the culture-positive cases drug susceptibility testing was done for 508 cases (data missing for the remaining cases).

Resistance to first-line anti-TB drugs was found in strains cultured from 22/46 (47.8%) recurrent cases and this was a significantly higher proportion than among newly occurring cases (136/508, 26.8%) ($P = 0.002$). Although resistance to INH and ETB were more common in cultures from recurrent cases than new cases ($P = 0.022$ and $P = 0.012$ respectively), there was no statistical difference in resistance to RIF, PZA and STR. In both groups resistance to STR was the highest among all drugs (28.3% in recurrent and 20.3% in new cases). Two MDR strains were cultured in recurrent cases and 10 in new cases (4.3% and 2% respectively) ($P = 0.262$).

In recurrent cases the CAT I regimen was modified only in 2 MDR cases and another 6 cases due to severe adverse drug reactions, especially drug hepatitis.

Outcome of treatment

Excluding two MDR cases, 87.5% of the recurrent cases were treated successfully with the CAT I regimen.

Table 2 Drug resistance pattern in bacterial strains isolated from culture-positive new and recurrent tuberculosis cases

Variable	New cases (n = 508)		Recurrent cases (n = 46)		P-value
	No.	%	No.	%	
Any drug resistance					
Yes	136	26.8	22	47.8	0.002
No	372	73.2	24	52.2	
Any resistance to:					
Isoniazid	69	13.6	12	26.1	0.022
Rifampin	23	4.5	4	8.7	NS
Pyrazinamide	11	2.2	3	6.5	NS
Ethambutol	17	3.3	5	10.9	0.012
Streptomycin	103	20.3	13	28.3	NS
Multi-drug resistance					
Yes	10	2.0	2	4.3	NS

NS = not significant.

There was no significant difference between the new and recurrent groups in the rates of successful treatment (90.9% and 87.9% respectively) or in the mortality rate (8.2% and 12.1% respectively). Using the Mantel–Haenszel test to adjust for the effect of smoking and drug misuse showed a higher rate of successful treatment in recurrent cases than new cases (P = 0.007, odds ratio = 1.107, 95% confidence interval = 1.078–1.137), but no significant difference in the death rate.

Discussion

Our study compared drug resistance patterns and the efficacy of the CAT I regimen between new and recurrent cases of TB. Resistance to INH and ETB was more common among recurrent cases but there was no difference in rates of resistance to RIF, PZA and STR and in the rate of MDR strains. Resistance to STR was high in our setting (over 20% in both groups). A total of 87.5% of non-MDR recurrent cases were treated successfully with the CAT I regimen. Rates of successful treatment and death were similar between the 2 groups.

This study had some limitations. First of all, our centre is a national referral centre for TB patients in the Islamic Republic of Iran, so further prospective studies in the wider community are necessary. Lack of information about HIV status was the second limitation, although the prevalence of coinfection with HIV and TB was low in the country in the period of study (2.2% in new cases of TB) [8]. The most important limitation was the difficulty of following most patients for a long period after completion of treatment due to address changes or emigration.

In low TB incidence communities, the most frequent cause of recurrence is true relapse or treatment failure [9,10], whereas in high TB incidence populations reinfection is the most common mechanism for recurrence of disease [11,12]. Therefore, efficacy of the CAT II regimen in recurrent cases may be dependent on the frequency of drug-resistant strains in the community, the primary mechanisms of recurrent disease and the efficiency of the national TB programmes [5]. There are no randomized clinical trials to support STR consumption in the CAT II regimen or the superiority of CAT II over CAT I among relapse cases.

Resistance to RIF may occur with use of first-line anti-TB drugs in a subpopulation with a high frequency of INH resistance and lead to the generation of MDR-TB strains [13]. However, resistance to RIF or both RIF and INH have the greatest effect on the outcome of treatment [14].

National TB programmers need data about country-specific drug resistance patterns to inform decisions on each country's standard treatment regimens for defined patient groups [6]. Many studies have shown that resistant strains are more frequent in TB patients with a history of treatment than in new TB cases [10] but that the rate of this resistance varies among communities. In addition, in most studies, recurrent cases were not analysed separately from other previously treated patients. In a study in Malawi 81% of recurrent cases were sensitive to first-line anti-TB drugs [15]. However, there was resistance to at least 1 anti-TB drug among 85.9% and 84.4% of TB cases with a history of treatment in Tashkent (Uzbekistan) and Baku (Azerbaijan) respectively [16]. In another study performed from 2003 to 2004 in our centre, 78% of previously treated patients (recurrent and others) had any resistance to first-line anti-TB drugs [17]. In the present study, we found resistance to at least 1 first-line anti-TB drug in 47.8% of recurrent cases.

Drug resistance surveys often show that TB patients relapsing have a medium or low likelihood of harbouring MDR stains; such patients can receive a

re-treatment regimen of first-line drugs [6]. Previous studies showed different results for the efficacy of the CAT II regimen. In 2003 Salaniponi et al. demonstrated a 65% success rate with the CAT II regimen in Malawi but the frequency of STR resistance was low in their setting and 81% of strains were sensitive to first-line anti-TB drugs. However, the mortality rate was as high as 25% [16]. In similar studies, success rates were estimated as 74.8% and 64.9% in Morocco and Turkey respectively [14,18].

In our study, recurrent cases (excluding the 2 MDR cases) were treated with the CAT I regimen, with an 87.5% success rate. In the recurrent patients who were fully sensitive to first-line anti-TB drugs the success rate reached 95.5%. This was significantly higher than that reported by Espinal et al., although their analysis did not separate the patients with recurrence from the patients with treatment failure [19]. We cannot justify the efficiency of the CAT II regimen in our patients as it was not used, but the CAT II regimen does not have any additional benefits in cases with sensitive strains and, on the basis of the drug resistance patterns, it is probably suboptimal in patients harbouring resistant strains.

In a study in Thailand, MDR-TB was found in 80% of treatment failed cases but the frequency of MDR was as low as 8% in recurrent cases [20]. In our study, we found only 2 MDR-TB cases among recurrent cases (4.6%) and there was no statistical difference between the proportion of new and recurrent cases in the frequency of RIF resistance or of MDR strains.

The high frequency of STR resistance in our setting is notable and it might be related to use of this drug in the treatment of brucellosis, which is an endemic disease in the Islamic Republic of Iran [21].

In summary, our study showed a need to perform drug sensitivity testing for recurrent TB cases. Moreover resistance to STR is common in our setting. The CAT I regimen was effective for treatment of non-MDR recurrent cases. Due to the low frequency of MDR among this group, the CAT I regimen may be suitable for empirical therapy before drug sensitivity test results become available. Further studies in different communities, with consideration of long-term outcomes of treated patients, are necessary to investigate the best approach to the management of patients with recurrent TB.

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