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Predictors of delayed culture conversion in patients treated for multidrug-resistant tuberculosis in Pakistan

F. Qazi[*], **U. Khan**[*], **S. Khowaja**[*], **M. Javaid**[†], **A. Ahmed**[†], **N. Salahuddin**[†], **H. Hussain**[*], **M. C. Becerra**[‡], **J. E. Golub**[§], and **A. J. Khan**[*]

[*] Interactive Research and Development, Karachi, Pakistan;

[†] Indus Hospital, Karachi, Pakistan;

[‡] Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts, USA

[§] Center for Tuberculosis Research, Johns Hopkins School of Medicine, Baltimore, Maryland, USA

Summary

Culture conversion is an interim monitoring tool for treatment of multidrug-resistant tuberculosis (MDR-TB). We evaluated the time to and predictors of culture conversion in pulmonary MDR-TB patients enrolled in the community-based MDR-TB management program at the Indus Hospital in Karachi, Pakistan. Despite strict daily directly observed therapy, monthly food incentives and patient counseling, the median time to culture conversion was 196 days (range 32–471). The cumulative probabilities of culture conversion by 2, 4, 6 and 12 months were respectively 6%, 33%, 47%, and 73%. Smoking, high smear grade at baseline and previous use of second-line drugs delayed culture conversion.

Abstract

La négativation des cultures est un outil de suivi inter-médiaire pour le traitement des tuberculoses à germes multi-résistants (TB-MDR). Nous avons évalué la durée et les facteurs prédictifs de négativation des cultures chez les patients atteints de TB-MDR pulmonaire enrôlés dans le programme de prise en charge basée sur la collectivité de la TB-MDR au niveau de l'Hôpital Indus à Karachi, au Pakistan. En dépit d'un traitement quotidien strictement observé, d'incitants alimentaires men-suels et d'accompagnement des patients, la durée mé-diane avant la négativation des cultures a été de 196 jours (extrêmes 32–471). Les probabilités cumulatives de négativation des cultures aux mois 2, 4, 6 et 12 ont été respectivement de 6%, 33%, 47% et 73%. Le fait de fumer, un degré de positivité élevé des frottis au début ainsi que l'utilisation antérieure de médicaments de deuxième ligne ont retardé la négativation des cultures.

Correspondence to: Fahad Qazi, Interactive Research and Development, Suite 508, Ibrahim Trade Tower, Main Shahrae-Faisal, Karachi, Pakistan. Tel: (+92) 213 432 7697; extn: 2450. Fax: (+92) 213 432 7696. fahad.qazi@irdresearch.org.

Abstract

La conversión de los cultivos constituye un instrumento de análisis provisional del tratamiento de la tuberculosis multidrogorresistente (TB-MDR). En el presente estudio se evaluó el lapso hasta la conversión del cultivo y los factores pronósticos de esta conversión en pacientes con TB-MDR que participaban en un programa de base comunitaria de tratamiento de la TB-MDR del hospital Indus de Karachi, en Pakistán. Pese al estricto tratamiento diario directamente observado, los incentivos alimentarios mensuales y la orientación a los pacientes, el lapso promedio hasta la negativación del cultivo fue 196 días (intervalo 32–471). Las probabilidades acumuladas de conversión del cultivo a los 2, 4, 6 y 12 meses fueron respectivamente 6%, 33%, 47% y 73%. Los factores asociados con el retraso en la conversión del cultivo fueron el tabaquismo, una baciloscopia de alto grado al comienzo del tratamiento y el antecedente de administración previa de medicamentos antituberculosos de segunda línea.

Keywords

MDR-TB; drug-resistant TB; culture conversion; Pakistan

MULTIDRUG-RESISTANT tuberculosis (MDR-TB), which is caused by strains of *Mycobacterium tuberculosis* resistant to both isoniazid (H, INH) and rifampin (R, RMP), requires prolonged treatment with multiple second-line anti-tuberculosis drugs that are more costly and have more side effects than those used to treat drug-susceptible TB. Culture conversion, defined as two consecutive negative sputum cultures following an initial positive culture, is an interim monitoring tool for MDR-TB treatment.[1] Reducing the time to conversion is also an important infection control measure, as culture-positive patients are more likely to transmit TB.[1] Although studies have evaluated factors associated with smear conversion in patients with susceptible TB,[2–4] there are fewer data on culture conversion in patients with MDR-TB.

Pakistan has an estimated 300 000 incident susceptible TB cases and 15 000 MDR-TB cases annually.[5] The practice in many TB centers in Pakistan is to perform cultures every 6 months on patients with MDR-TB, instead of monthly as recommended by the World Health Organization (WHO) guidelines.[1] We sought to examine the time to and predictors of culture conversion in pulmonary MDR-TB patients enrolled in the Indus Hospital TB Control Program in Karachi, Pakistan.

METHODS

We abstracted retrospective data of MDR-TB patients treated in the Indus Hospital TB Control Program in Karachi, Pakistan, between January 2008 and June 2010. All patients received free, individualized regimens that included second-line drugs procured from the local market. Treatment adherence was monitored by trained treatment supporters and promoted through free monthly household food rations for a family of five. Personalized counseling was provided for each patient every month, and more frequently if indicated.

Research ethics committees at the Johns Hopkins School of Medicine and Interactive Research and Development approved this study protocol.

Study participants included patients enrolled with culture-confirmed pulmonary MDR-TB who had at least 1 month of follow-up recorded. Culture conversion was defined as the first of two consecutive negative sputum cultures.[6] Sputum smears and cultures were performed at baseline and on monthly follow-up visits over the course of treatment. Smear microscopy was performed using Ziehl-Neelsen staining methods. All baseline culture and drug susceptibility testing were performed on liquid culture media using the BACTEC Mycobacterial Growth Indicator Tube 960 (BD Diagnostics, Sparks, MD, USA) at the Indus Hospital bio-safety level 3 laboratory (BSL-3), which completed external quality assurance testing by the WHO Supranational Reference Laboratory (SRL) network in November 2008, and at the Borstel SRL in Germany prior to that date.

Analysis

We conducted survival analysis to identify predictors of time to conversion using a Cox proportional hazards model. The final multivariate model included candidate variables that were known to be independently associated with culture conversion or those that predicted conversion at $P < 0.20$, using backward stepwise regression. P values and 95% confidence intervals (95%CI) were reported using a level of significance at ⩽0.05. Data were analyzed using Stata/IC 11.0 (Stata Corp, College Station, TX, USA).

RESULTS

Eighty-five patients had culture-confirmed pulmonary MDR-TB. The mean age was 29.7 (standard deviation 12.6) and 50 (59%) were females. Sputum isolates from 14 patients were resistant to INH, RMP, ethambutol (E, EMB), pyrazinamide (Z, PZA), and streptomycin (S, SM), 3 to HREZ, 9 to HRSZ, 4 to HRES, 5 to HRE, 21 to HRS, 12 to HRZ and 17 to HR. Twenty-three isolates were resistant to fluoroquinolones (FQs); one was resistant to injectables and two were resistant to other second-line agents such as ethionamide (ETH), cycloserine (CS) and para-amino salicylic acid (PAS).

The baseline regimens were as follows: 57 patients (67%) received kanamycin (KM), ofloxacin (OFX), CS, ETH, PAS, vitamin B6 (B6); 20 (24%) received KmMxfCsEthPASB6 (Mxf = moxifloxacin); 4 (5%) received KmOfxCsEthB6; 1 received KmCsEthPASB6; 2 received KmOfxEthPASB6; and 1 received KmMxfEthPASB6. All regimens included ⩾4 effective drugs based on DST results as per WHO guidelines. All patients with FQ resistance were put on a 5-drug regimen, and Mxf was included in the baseline regimen in place of OFX whenever available. The cumulative probabilities of culture conversion by month 2, 4, 6, 12 and 18 are shown in Table 1.

The median time to culture conversion was 196 days (range 32–471). Table 2 shows the significant results of the univariate and final multivariate model for culture conversion. Current smokers had a 0.08 times greater likelihood (hazard; 95%CI 0.01–0.49, $P = 0.006$) of culture conversion compared to never smokers. Patients who had previously received second-line drugs had a 0.20 times greater likelihood (95%CI 0.05–0.92, $P = 0.04$) of culture conversion compared to those who had not. Patients whose smear grading was negative at baseline had a 6.8 times greater likelihood (95%CI 1.37–33.6, $P = 0.02$) of culture

conversion compared to patients who had a smear grading of '3+' (>9 acid-fast bacilli/high-power field).

DISCUSSION

The median time to culture conversion in Karachi, Pakistan (196 days) was 3–4 months longer than reported by MDR-TB programs in Latvia (60 days) and KwaZulu-Natal, South Africa (85 days),[7,8] but similar to Kanpur, India,[9] where a randomized control trial of high-dose INH for MDR-TB treatment found a median time to culture conversion of 6.6 months in the placebo group (only receiving second-line treatment for MDR-TB).

The delay in culture conversion in the Indus Hospital program exists despite strong social support to patients, regular psychological counseling and the use of community treatment supporters for directly observed therapy. Current smoking, high smear grade at start of treatment and previous use of second-line drugs were strong predictors of delayed time to culture conversion in our cohort.

Despite previous use of second-line drugs, there was no evidence that resistance to FQs was a factor in delayed culture conversion, potentially due to a stronger 5-drug regimen that included Mxf. More evidence is required to determine the bioavailability of local drugs and their effect on outcomes of MDR-TB management, including the time to culture conversion.

CONCLUSIONS

Despite strong programmatic management with close treatment support and monthly food incentives, the time to culture conversion for MDR-TB patients on locally procured medicines was delayed due to smoking, high smear grade at baseline and prior treatment with second-line drugs.

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Table 1

Cumulative probability of culture conversion

Month	CPCC (95%CI)
2	0.06 (0.02–0.14)
4	0.33 (0.24–0.46)
6	0.47 (0.36–0.59)
12	0.73 (0.60–0.84)
18	0.78 (0.66–0.89)

CPCC = cumulative probability of culture conversion; CI = confidence interval.

Table 2

Hazard ratios of culture conversion

		Univariate analysis		Multivariate analysis*	
Categories	***n***	**Hazard ratio (95%CI)**	***P* value**	**Hazard ratio (95%CI)**	***P* value**
Sex					
Male	35	Reference		Reference	
Female	50	1.93 (1.05–3.54)	0.03	1.78 (0.84–3.77)	0.13
Age, years					
≤40	71	Reference		Reference	
>40	14	0.48 (0.20–1.14)	0.10	0.36 (0.11–1.15)	0.09
BMI, kg/m^2					
18.5–24.9	22	Reference			
<18.5	53	0.87 (0.46–1.64)	0.67		
≥25	4	0.75 (0.17–3.29)	0.7		
Smear grading at baseline					
3+ (>9 AFB/HPF)	18	Reference		Reference	
2+ (1–9 AFB/HPF)	13	1.3 (0.46–3.75)	0.62	2.09 (0.63–7.01)	0.23
1 + (10–99 AFB/100 HPF)	42	1.09 (0.47–2.53)	0.84	0.99 (0.34–2.87)	0.99
Scanty (1–9 AFB/100 HPF)	4	1.15 (0.23–5.64)	0.87	6.96 (0.83–58.0)	0.07
Negative	5	5.04 (1.26–20.1)	0.02	6.8 (1.37–33.6)	0.02
Number of first-line drugs to which isolate is resistant					
5 drugs	14	Reference		Reference	
4 drugs	16	1.02 (0.38–2.74)	0.97	1.35 (0.41–4.39)	0.62
3 drugs	38	0.98 (0.42–2.31)	0.97	1.56 (0.55–4.39)	0.40
2 drugs	17	0.75 (0.66–4.64)	0.26	2.66 (0.80–8.80)	0.11
Prior second-line drugs					
Not received	74	Reference		Reference	
Received	11	0.39 (0.12–1.24)	0.11	0.20 (0.05–0.92)	0.04
Pattern of lung lesion					
Non-consolidative	64	Reference			
Consolidative	21	1.25 (0.66–2.39)	0.49		

		Univariate analysis		Multivariate analysis*	
Categories	***n***	**Hazard ratio (95%CI)**	***P* value**	**Hazard ratio (95%CI)**	***P* value**
Extent of lung lesion					
Unilateral	36	Reference		Reference	
Bilateral	49	0.92 (0.52–1.64)	0.79	1.00 (0.49–2.04)	0.99
Cavitation					
No cavitation	51	Reference		Reference	0.29
Cavitation	34	0.66 (0.36–1.22)	0.19	0.68 (0.34–1.38)	
Diabetes					
RBS <200 mg/dl	77	Reference		Reference	
RBS >200 mg/dl + symptoms	8	1.54 (0.65–3.64)	0.32	3.05 (0.97–9.60)	0.06
Smoking					
Never smoked	78	Reference		Reference	
Current smoker	6	0.20 (0.05–0.83)	0.03	0.08 (0.01–0.49)	0.006
Former Smoker	1	0.89 (0.12–6.49)	0.91	0.94 (0.10–9.02)	0.96
Fluoroquinolone resistance					
Susceptible	62	Reference		Reference	
Resistant	23	0.58 (0.28–1.21)	0.14	0.47 (0.19–1.16)	0.10
Delay in treatment from diagnosis					
<3 months	41	Reference			
≥3 months	44	0.63 (0.35–1.15)	0.13		

*Multivariate model includes categories that had $P < 0.20$ using the backward stepwise method and those that were known to be independently associated with culture conversion.

CI = confidence interval; BMI = body mass index; AFB = acid-fast bacilli; HPF = high-power field; RBS = random blood sugar.

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