Factors associated with treatment outcome in 64 HIV negative patients with multidrug resistant tuberculosis

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ABSTRACT

Objectives: In this study we aimed to determine the factors associated with treatment outcome in HIV negative patients with multidrug resistant tuberculosis (MDR TB).

Materials and methods: The study comprised 64 (43 female and 21 male) patients in whom second line TB drugs were administered in directly observed treatment (DOT) programme. Achievement of sputum AFB (acid fast bacilli) negativity in the 3rd month of the treatment was accepted as the bacteriologic response. Treatment outcome of the patients and the factors influencing the bacteriologic response were evaluated.

Results: The mean time of sputum smear negativity was determined as 3±2.2 months. Bacteriologic response was determined in 73.4% of the patients. The mean duration time of the treatment was 16.4±8.2 months. Treatment outcome of the patients was determined as cure in 34 (53.1%), default in 18 (28.1%), treatment failure in 1 (1.6%) and exitus in 3 (4.7%) patients. Also, in 8 (12.5%) patients treatment was incomplete and continued. Adverse effects of the drugs were seen in 39 (60.9%) patients with the most frequency of gastrointestinal disturbance (51.5%), psychiatric disorders (15.6%), dermatological effects (12.5%). In logistic regression analysis only presence of cavity and the extensive disease were found to be associated with poor bacteriologic response (OR=1.5, 95% CI: 1.23-1.82, P=0.01 and OR=2, 95% CI: 1.42-2.79, P=0.00, respectively).

Conclusions: Although radiological findings might affect the bacteriologic response, MDR TB is a treatable disease if regular and appropriate treatment regimen is administered.

KEY WORDS Multidrug resistant tuberculosis (MDR TB); treatment; outcome

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Introduction

Drug resistant tuberculosis is the consequence of poor tuberculosis control programmes and today a global health problem (1,2). Drug resistance develops as a result of spontaneous genetic mutations in Mycobacterium tuberculosis, which are selected if antituberculosis drugs are used inappropriately or inconsistently (3). Multidrug resistant tuberculosis (MDR TB) is defined as resistance to at least two important drugs as isoniazid (H) and rifampicin (R) (4). MDR TB results from an organism that acquires drug resistance either because of inadequate therapy or from transmission of an already resistant organism (5).

Previous studies have shown that patients with drug resistant tuberculosis have lower response rates than those with drug susceptible isolates. Rifampicin and isoniazid are the most active antituberculosis drugs. When R resistance occurs in the presence of resistance to H, the prospects for successful chemotherapy greatly decrease (6-8). MDR TB among previously untreated patients is mostly related to human immunodeficiency virus (HIV) co-infection (9). Also, in patients severely immunosuppressed by HIV infection have lower response rate and high fatality rate than HIV negative cases for MDR TB treatment (6). In this study we aimed to determine the factors associated with treatment outcome in HIV negative patients with MDR TB.

Material and methods

Patients

The study comprised 64 patients hospitalized in a reference

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Table 1. Characteristics of patients with multidrug resistant tuberculosis.

Characteristics	Patients
Age	33.8±10.7 (75-33.8) years
Female	43 (67.2%)
Male	21 (32.8%)
Smoking history (+)	37 (42.2%)
Family TB history (+)	33 (51.6%)
Surgery (+)	6 (9.4%)
*Concomitant disease (+)	14 (21.9%)
Previous TB history	
Relapse	13 (20.3%)
Treatment failure	31 (48.4%)
Irregular treatment	20 (31.3%)
Cavity (+)	51 (79.7%)
Cavity (–)	13 (20.3%)
Limited disease	30 (46.9%)
Extensive disease	34 (53.1%)
Drug resistance	
H+R	18 (28.1%)
H+R+E	11 (17.2%)
H+R+S	11 (17.2%)
H+R+E+S	24 (37.5%)

H, isoniazid; R, rifampicin; E, ethambutol; S, streptomycin; *Concomitant disease, Diabetes mellitus, n=11; Hypertension, n=1; Coronary artery disease, n=1.

hospital between 1998-2006 with a diagnosis of MDR TB. All cases were negative for HIV serologic test. Each patient's demographic profile, medical history, clinical, radiological findings, sputum smear examination, complete blood count, drug susceptibility pattern and previous treatment details were recorded. The characteristics of the patients were shown in Table 1. The diagnoses were performed with the documentation of acid fast bacilli (AFB) through Ziehl-Neelsen (ZN) staining of sputum and the isolation of *Mycobacterium tuberculosis* in sputum culture in liquid medium (BACTEC) and/or Lowenstein-Jensen solid medium. Drug susceptibility test was performed routinely for all cases using Lowenstein-Jensen medium and the method of proportions.

All patients had a history of receiving firstline antituberculosis treatment. According to the previous TB history patients were classified as relapse (recurrence of positive smear or culture after achievement of cure), treatment failure (persistent smear or culture positivity in the 5th month of the treatment) and irregular treatment. Patients who met these criteria and also having resistance to both H and R in the drug susceptibility test were diagnosed as MDR TB. Also, the disease was classified as extensive or limited on the basis of the radiological findings. Extensive disease was defined as the infiltrates involving at least 75% of the lung fields or the presence of cavities totaling at least 15 cm in diameter (10).

Treatment regimen

After the diagnosis of MDR TB drugs (para-aminosalicylic acid, cycloserine, ofloxacin, amikacin, prothionamide, thioacetazone, amoxicillin-clavulanate and clarithromycin) were included into the treatment regimen. The administration of all drugs was initiated at the same time with dose intervals adjusted according to the patients' tolerance. All patients took their drugs regularly in directly observed treatment (DOT) programme and hospitalized until sputum AFB smears were negative for 3 consecutive days. Drugs that had serious side effects were withdrawn from the regimen. Surgical resection was considered after 2 months of the medical treatment. Follow up evaluations included sputum smear and culture examinations and the chest radiography obtained every month. Treatment was continued for at least 18 months after the first negative culture had been obtained. Achievement of sputum AFB negativity in the 3rd month of the treatment was accepted as the bacteriologic response (6).

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS Inc, Chicago, IL) for windows release 11.0. The difference between the variables based on bacteriologic response was analyzed by Fisher's Exact test. Logistic regression analysis was performed to determine the factors predicting bacteriologic response. The Odds ratios (OR) and 95% confidence intervals (CI) were determined. A value of $P<0.05$ was considered as statistically significant.

Results

In this study there were 43 (67.2%) female and 21 (32.8%) male patients with a mean age of 33.8±10.7 (75-33.8) years. The characteristics of the patients were shown in Table 1. Patients were classified according to their previous TB history as 13 (20.3%) with relapse, 31 (48.4%) with treatment failure and 20 (31.3%) patients with irregular treatment. Also, 51 (79.7%) patients had cavity and 34 (53.1%) patients had extensive disease whereas, 30 (46.9%) patients had limited disease. Drug susceptibility test was obtained from all patients. Eighteen (28.1%) patients had H+R resistance, 11 (17.2%) had H+R+E resistance, 11 (17.2%) had H+R+S resistance and 24 (37.5%) had H+R+E+S resistance.

Table 2. Drugs used in the treatment of multidrug resistant tuberculosis.

Drugs	Doses
Para-aminosalicylic acid	150 mg/kg /daily
Cycloserine	15 mg/kg/daily
Ofloxacin	14 mg/kg/daily
Amikacin	15 mg/kg/daily
Prothionamide	15 mg/kg/daily
Amoxicillin-clavulanate	2,000-4,000 mg/daily
Clarithromycin	1,000 mg/daily
Thioacetazone	150 mg/daily

Table 3. Adverse effects of the drugs.

Adverse effects	n (%)
Gastrointestinal disturbance	51.5
Psychiatric disorders	15.6
Dermatological disorders	12.5
Neurological disorders	4.7
Ototoxicity	3.1
Arthralgia	3.1
Vertigo	1.6
Hepatitis	1.6
No adverse effect	39.1

Table 4. Treatment outcome of the patients.

Treatment outcome	n (%)
Cure	34 (53.1%)
Default	18 (28.1%)
Continued treatment	8 (12.5%)
Treatment failure	1 (1.6%)
Exitus	3 (4.7%)

The mean duration time of the treatment was 16.4± 8.2 months. The MDR TB drugs and the doses used were listed in Table 2. In our clinic usually we prefer para-aminosalicylic acid, cycloserine, ofloxacin, amikacin, prothionamide and thioacetazone combination (6 drugs) for MDR TB treatment. However in our study only 45 (70.3%) patients received this combination, 14 (21.9%) patients could not receive thiocetazone because of economic problems. Also in 5 (7.8%) patients amoxicillin-clavulanate and clarithromycin were included into this combination if one or more drugs were withdrawn because of side effects. In 39 (60.9%) patients adverse effects of the drugs were seen with the frequency of gastrointestinal disturbance (51.5%), psychiatric disorders (15.6%), dermatological effects (12.5%), neurological disorders (4.7%), ototoxicity (3.1%), arthralgia (3.1%), vertigo (1.6%) and hepatitis (1.6%) (Table 3). In 3 patients cycloserine was withdrawn because of psychiatric and neurological disorders, in 1 patient prothionamide caused hepatitis and the drug was withdrawn, in 2 patients amikacin treatment was not completed because of ototoxicity.

The mean time of sputum smear negativity was determined as 3±2.2 months. In our manuscript 34 (53.1%) patients were cured and the cure was defined as negative smears and cultures throughout treatment for at least 18 months. Treatment outcome of the other patients was determined as default in 18 (28.1%), treatment failure in 1 (1.6%) and exitus in 3 (4.7%) patients. Also, 8 (12.5%) patients in whom bacteriologic response was achieved in the 3rd month had incomplete treatment (Table 4).

Patients who received MDR TB treatment for at least 3 months were evaluated and the achievement of sputum AFB negativity in the 3rd month was accepted as the bacteriologic response. In our study bacteriologic response was determined in 47 (73.4%) patients. Older age (P=0.04), absence of cavity (P=0.011) and extensive disease (P=0.000) were found higher in patients with bacteriologic response (Table 5).

In logistic regression analysis only presence of cavity and the extensive disease were found as the predictors of bacteriologic response (OR=1.5, 95% CI: 1.23-1.82, P=0.01 and OR=2, 95% CI: 1.42-2.79, P=0.00, respectively). However age, sex, previous TB history and drug resistance pattern did not show any association with the bacteriologic response (Table 6).

Discussion

MDR TB is a growing public health problem in all over the world. The treatment of MDR TB is very important because of the risk of transmitting virtually untreatable drug resistant disease. Many factors may affect the treatment outcome. In our study cure was achieved in 34 (53.1%) patients and bacteriologic response was determined as 73.4%.

Treatment response rates in MDR TB were determined different in the previous studies. HIV positive patients were found to have lower response rate than HIV negative patients (6). Park *et al.* evaluated 173 patients with MDR TB of whom over half were known to be HIV infected. They found mortality significantly greater for HIV positive patients than for HIV negative group (11). In another study of Park *et al.*, only 63 HIV negative patients with MDR TB were analyzed and 82.5% of the patients were found to have microbiologic responses (6). In addition, Goble *et al.* reported an overall response rate of 56% and the mortality 22% in 171 patients with MDR TB (10), whereas Telzak *et al.* found 96% clinical response in 25 HIV negative MDR patients (12). In our study as all of the patients were HIV negative, we could not have the chance to compare the HIV negative and the HIV positive patients.

Table 5. Difference between the variables based on bacteriologic response.

Factors	Bacteriologic response (+)	Bacteriologic response (-)	P
Age	35.36±11	29.82±8.6	0.04*
Female	32	11	0.512
Male	15	6	
Smoking (-)	29	8	0.485
Smoking (+)	18	9	
Concomitant disease (-)	35	15	0.206
Concomitant disease (+)	12	2	
Family TB history (-)	23	8	0.894
Family TB history (+)	24	9	
Surgery (-)	42	16	0.491
Surgery (+)	5	1	
Cavity (-)	12	1	0.011*
Cavity (+)	35	16	
Limited disease	30	0	0.000*
Extensive disease	17	17	

*Statistically significant.

Table 6. Factors associated with bacteriologic response in logistic regression analysis.

Factors	OR	95% CI	P
Age	0.94	0.88-1	0.07
Sex	1.16	0.36-3.74	0.79
Cavity	1.5	1.23-1.82	0.01*
Radiology	2	1.42-2.79	0.00*
Previous TB history	0.97	0.2-4.53	0.46
Drug resistance	0.86	0.55-1.34	0.51

*Statistically significant.

Tahaoglu *et al.* reported bacteriologic response rate of 95% in MDR TB and a successful outcome achieved in 73% of cases with medical therapy alone. Also they found resistance to more than five drugs associated with poor outcome, whereas younger age and absence of ofloxacin in the previous treatments were found as associated with successful outcome (13). In our study presence of cavity and extensive disease were found to be associated with bacteriologic response. Chan *et al.* analyzed the outcomes in 205 patients with MDR TB and compared the results with the previous series. They found greater long-term success rates, 75% versus 56%, and lower tuberculosis death rates, 12% versus 22%, than the earlier study. They also reported surgical resection and fluoroquinolone therapy associated with improved microbiological and clinical outcomes (14). All of our patients had ofloxacin in the MDR treatment and this may be an important reason for the high rate of bacteriologic response.

MDR TB treatment is both toxic and expensive. The drugs have many side effects which cause to interrupt the therapy. In our patients gastrointestinal disturbance (51.5%), psychiatric disorders (15.6%) and dermatological effects (12.5%) were determined as the most frequent adverse effects. Also Torun *et al.* evaluated 263 patients for the adverse effects of MDR TB treatment retospectively. They found ototoxicity (41.8%), psychiatric disorders (21.3%), gastrointestinal disturbance (14.0%) as the most frequent side effects. These effects led the clinicians to withdraw one or more drugs from the treatment regimen in 146 (55.5%) cases (15).

In conclusion, although radiological findings might affect the bacteriologic response, MDR TB is a treatable disease if regular and appropriate treatment regimen is administered. However treatment is difficult because of toxicity of the drugs and the length of the therapy.

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