Outcomes of Multidrug-Resistant Tuberculosis among Binational Cases in El Paso, Texas

Gustavo Ferrer,* Carlos Acuna-Villaorduna, Miguel Escobedo, Esteban Vlasich, and Manuel Rivera

Division of Pulmonary and Critical Care Medicine, Department of Medicine, Cleveland Clinic Foundation, Weston, Florida; Division of Medicine, Washington Hospital Center, Washington, District of Columbia; Centers for Disease Control and Prevention–Texas Department of State Health Services, El Paso, Texas; P. L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, Texas

Abstract. In the United States, multidrug-resistant tuberculosis (MDR-TB) is more commonly seen among foreign-born patients. We report outcomes for 46 patients with MDR-TB who were born in Mexico and treated along the United States–Mexico border. According to our definition, 30 were cured, 3 showed treatment failure, 3 died, and 10 abandoned treatment. Multidrug-resistant tuberculosis can be successfully treated on an ambulatory basis.

INTRODUCTION

The number of tuberculosis (TB) cases in the United States has decreased in the past decade. However, TB cases among foreign-born persons continue to increase.¹ Mexico is the country of origin for 23% of these cases and two-thirds of them occur in the four states bordering Mexico.² Tuberculosis control along the United State–Mexico border is challenging because of high migratory rates (nearly 26 million legal border crossings are reported each year), limited access to health care in the border area and a higher TB incidence in Mexico.² In 1991, The Texas Department of Health in conjunction with the El Paso City County Health Department and the Centers for Disease Control and Prevention created Programa Juntos (Together) with the aim to assist the local health authorities with the treatment of binational TB cases and their contacts in the El Paso, Texas–Ciudad Juárez, Mexico border region. Programa Juntos facilitates laboratory culture diagnostic confirmation and access to therapy.

Multidrug-resistant tuberculosis (MDR-TB) has emerged as a threat to national TB programs worldwide.³ MDR-TB, defined as resistance to at least isoniazid and rifampin, is associated with lower cure rates than susceptible TB and requires longer treatment courses using second-line drugs, which are less efficacious and have more side effects. Rates of MDR-TB are higher in Mexico,⁴ raising concern about transmission of drug-resistant strains during the migratory process. Programa Juntos performs drug susceptibility testing for all newly diagnosed TB patients and provides individualized treatment for MDR-TB when indicated. We report treatment outcomes among binational cases of MDR-TB identified by Programa Juntos in the border area of El Paso–Ciudad Juárez.

METHODS

Binational TB cases were defined as those with culture positive for *Mycobacterium tuberculosis* complex and satisfied one or more of the following requirements: Ciudad Juárez residents that hold visas to remain in El Paso for at least 72 hours; dual residency in El Paso–Ciudad Juárez; live and work on opposite sides of the border; or patients from Mexico seeking care in the United States. Optimum case management requires binational health collaboration. Tuberculosis cases

were referred from public health department clinics (El Paso Health Department Clinic and Servicio de Salud in Juárez). Any TB case diagnosed at these clinics that required binational management get referred. The Servicio de Salud Clinic accounts for approximately 40% of the TB cases in Juárez.

All patients were evaluated by a pulmonologist and clinical data including age, sex, place of birth, previous TB history, alcohol intake, tuberculin skin test result, and conditions associated with TB such as diabetes, renal failure, and use of steroids or silicosis were documented in clinical charts. Human immunodeficiency virus (HIV) status was determined by using an enzyme-linked immunosorbent assay and Western Blot confirmation at the laboratory of the Texas Department of Health. Monthly sputum smears and cultures were obtained throughout the course of therapy and yearly thereafter for two consecutive years. Culture for *M. tuberculosis* was performed by using Middlebrook media.

Drug susceptibility testing was performed at the Texas Department of Health Laboratory by using the proportion method with 7H10 agar plates for isoniazid (0.2 µg/mL and 1 µg/mL), rifampin (1 µg/mL), and ethambutol (5 µg/mL). Isolates resistant to isoniazid and/or rifampin were also tested for susceptibility to streptomycin (2 µg/mL), kanamycin (5 µg/mL), amikacin (5 µg/mL), pyrazinamide (100 µg/mL), ofloxacin (2 µg/mL), capreomycin (10 µg/mL), rifabutin (2 µg/mL), cycloserine (30 µg/mL), and ethionamide (5 µg/mL). Second-line drug susceptibility testing was performed by using the proportion method with 7H10 agar plates and the Bactec 460 method (Becton Dickinson, Sparks, MD).

Patients with MDR-TB were started on a regimen that included at least three drugs to which the strain of *M. tuberculosis* was found to be susceptible. Treatment was provided as an outpatient procedure under directly observed therapy (DOT) as recommended by the American Thoracic Society for management of tuberculosis in the United States; social workers supervised and administered the medications.⁵ Oral medications were administered from Monday through Saturday and injectable medications were administered from Monday through Friday. Regimens were determined in a case-by-case basis by a binational TB committee that included a physician with experience in treatment for MDR-TB. Initial regimens were based on the history of drugs taken by each patient. Commonly, regimens included injectable medications (amikacin, kanamycin, or capreomycin) at a dose of 15 mg/kg without exceeding 1 gram; fluoroquinolones (ciprofloxacin, 1 gram or levofloxacin, 1 gram); and oral bacteriostatic agents (ethionamide, 500 mg and cycloserine, 500 mg) in conjunction

*Address correspondence to Gustavo Ferrer, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Cleveland Clinic Foundation, 2950 Cleveland Clinic Boulevard, Weston, FL 33331. E-mail: ferrerg@ccf.org

with vitamin B6 (100 mg). Ethambutol and pyrazinamide were used depending on previous use history and susceptibility results. Regimens were modified based on the susceptibility results and administered for at least 12 months after the initial sputum culture conversion.

Outcomes are reported according to the recommendations of the World Health Organization⁶ (cure, failure, default, or death). Cure was defined as persistent conversion of sputum cultures for at least one 1 year after initiation of therapy, and failure was defined as at least two positive cultures during the last year of treatment or clinical deterioration leading to treatment interruption. The study was reviewed and approved by the Institutional Review Board Committee at Texas Tech University Health Sciences Center in El Paso.

RESULTS

During January 1994–December 2007, Programa Juntos treated 613 patients with smear-positive pulmonary TB. Forty-eight (7.8%) patients had MDR-TB; all were born in Mexico. Of these patients, 35 (73%) were male, their mean age was 45 years, and 37 (77%) had a history of TB. Sixteen (33%) patients had concomitant medical conditions; 13 had diabetes and 1 each had silicosis, aplastic anemia, and renal failure, respectively. All patients were negative for HIV infection.

Patients were resistant to a mean of 3.75 drugs. Thirteen (27%) patients had isolates with resistance to ethambutol, 10 (21%) with resistance to pyrazinamide, 19 (40%) with resistance to streptomycin, 11 (23%) with resistance to ethionamide, 25 (52%) with resistance to rifabutin, and 2 (4%) with resistance to ofloxacin. No isolates were found to be resistant to kanamycin, amikacin, capreomycin, or cycloserine. Thus, no cases of extremely drug resistant TB were found.

Of 48 patients with MDR-TB, 2 were transferred to another facility at their request. Of the remaining 46 patients, 30 (65%) were cured according to our definition, 2 (4%) had treatment failure, 3 (6%) died during treatment, and 11 (24%) defaulted; 4 left the study before starting treatment and 5 left the study within the first 6 months of therapy. Clinical characteristics of patients are shown in Table 1.

Patients were given regimens with a median of 5 drugs (range = 4–7 drugs). Mean duration of treatment was 14 months (range = 1–27 months). Among the 42 patients given second-line drugs, these regimens included fluoroquinolo-

nes for 41 patients (ciprofloxacin for 20 patients, levofloxacin for 20 patients, and ofloxacin for 1 patient); amikacin for 31 patients; ethambutol for 20 patients; pyrazinamide for 11 patients; capreomycin for 31 patients; streptomycin for 5 patients; ethionamide for 18 patients; cycloserine for 31 patients; and clofazimine, kanamycin, and para-aminosalicylic acid for 1 patient.

Among 30 patients with a final outcome of cured, the proportion of patients with negative acid-fast bacilli sputum smears was 12 (40%) after one month of treatment, 20 (67%) after two months of treatment, and 24 (80%) after three months of treatment. The proportion of patients with negative TB culture was 8 (27%) after one month of treatment, 11 (37%) after two months of treatment, and 18 (60%) after three months of treatment.

Two patients were considered to be treatment failures. These patients had persistent positive sputum smears and cultures after 12 months of therapy despite receiving 4 medications with known *in vitro* activity. Both patients were receiving regimens that included ciprofloxacin (1 gram), capreomycin (1 gram), cycloserine (500 mg), and ethionamide (500 mg).

DISCUSSION

We report a cohort of patients born in Mexico who had MDR-TB treated along the United States–Mexico border with individualized regimens on an ambulatory basis. Four retrospective cohorts of MDR-TB patients have been reported in the United States,^{7–10} with cure rates between 40% and 67%. Conditions such as co-infection with HIV⁷ and resistance to pyrazinamide and ethambutol¹¹ have been associated with treatment failure. Use of fluoroquinolones,¹² treatment for more than 18 months, and DOT throughout treatment has been shown to improve outcomes.¹³ We found a 65% cure rate, which may have been caused by several factors, such as an HIV-negative population, low rates of pyrazinamide and ethambutol resistance, use of fluoroquinolones and implementation of DOT, and individualized regimens as recommended by the World Health Organization (23 of 30 patients who were cured received at least 18 months of treatment).

Strikingly, we had 2 patients who showed treatment failures for MDR-TB treatment despite good compliance with regimens containing four drugs to which the strain of *M. tuberculosis* was known to be susceptible. The clinical relevance of drug susceptibility testing for second-line drugs has not been well studied.¹³ We hypothesize that these strains of *M. tuberculosis* probably had minimum inhibitory concentrations close to the drug concentrations defining drug resistance, which may explain their poor antimicrobial response.

Our results also show that MDR-TB patients can be successfully treated as outpatients using by DOT. Nevertheless, we acknowledge that our default rate (24%) was high in comparison with those in other studies. This finding is worrisome because use of second-line drugs can lead to emergence of extremely drug-resistant TB. We believe that our high default rate might be related to some unique characteristics of our cohort, which was composed of binational cases in continuous cross-border mobility. However, it is also known that MDR-TB patients are at risk for default because of prolonged treatments and side effects associated with them. A recent meta-analysis involving 33 MDR-TB cohorts worldwide found an overall default rate of 12%.¹⁴

TABLE 1

Characteristics of patients with multidrug-resistant tuberculosis, El Paso, Texas*

Characteristic	Cure (n = 30)	Treatment failure/death (n = 5)	Default (n = 11)
Male	20 (66)	3 (60)	10 (91)
Previous treatment for tuberculosis	24 (80)	4 (80)	9 (82)
Alcoholism	4/28 (14)	1 (20)	2/9 (22)
Diabetes	11/29 (38)	1 (20)	3/10 (30)
EMB resistance	8 (27)	3 (60)	2 (18)
PZA resistance	8 (27)	1 (20)	1 (9)
STM resistance	11 (37)	3 (60)	4 (36)
Treatment > 18 months	23 (77)	2 (40)	NA
Mean number of drugs to which resistance was observed	3.83	4.20	3.18

*Values are no (%) unless otherwise indicated, EMB = ethambutol; PZA = pyrazinamide; STM = streptomycin; NA = not available.

We found a moderate prevalence of MDR-TB (7.8%) among patients with TB treated in Programa Juntos. This finding might indicate a selection bias because some of our patients were referred from health centers of El Paso–Ciudad Juárez because of failure to respond to treatment. Nonetheless, Rates of MDR-TB in the State of Chihuahua are as high as 9% among new TB patients,⁴ which might explain our findings. In conclusion, MDR-TB patients can be successfully treated on an ambulatory basis along the United States–Mexico border. However, measures should be taken to improve adherence to therapy. Future studies should address the effect of treating binational cases to stop foreign-born TB transmission.

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Authors' addresses: Gustavo Ferrer, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Cleveland Clinic Foundation, Weston, FL, E-mail: ferrerg@ccf.org. Carlos Acuna-Villaorduna, Allentown, PA, E-mail: carlosvillaorduna@hotmail.com. Miguel Escobedo, El Paso–Centers for Disease Control and Prevention Quarantine Station, El Paso, TX, E-mail: mxe8@cdc.gov. Esteban Vlasich, El Paso, TX, E-mail: esteban.vlasich@dshs.state.tx.us. Manuel Rivera, P. L. Foster School of Medicine, Texas Tech University Health Sciences Center, El Paso, TX, E-mail: manuel.rivera@ttuhsc.edu.

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