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Salvage therapy for multidrug-resistant tuberculosis

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Abstract

Treatment of multidrug-resistant tuberculosis (MDR-TB), defined as *Mycobacterium tuberculosis* resistant to both isoniazid and rifampicin, is challenging under the best of circumstances, and particularly in resource-limited settings. For patients who remain persistently sputum-culture-positive despite therapy with second-line TB drugs, treatment options are limited, especially if disease is too advanced for resective surgery. Salvage therapy refers to the design of a regimen combining new and previously used drugs in a final effort to attain sputum conversion before declaring treatment to have failed. We retrospectively evaluated the outcomes of salvage therapy in 213 Peruvian patients. Salvage regimens included a median of two new drugs (range 1–6) and nine (range 5–13) total (new plus previously used) drugs. The most frequently used new drug was moxifloxacin, followed by capreomycin, amoxicillin-clavulanate, kanamycin and clarithromycin. Culture conversion occurred in 65 (30.5%) patients. Salvage regimens that included moxifloxacin were significantly more likely to be followed by culture conversion (OR 2.2; p 0.02). Later-generation fluoroquinolones such as moxifloxacin should be used in salvage therapy but also in the initial treatment of MDR-TB, if the best clinical strategy is to use the most effective drugs when the patient has the best chance for cure. New TB drugs are most likely to be initially used in salvage patients, in conditions similar to those described here. Close bacteriological monitoring of these patients will be essential, as useful information about the best way to use these new drugs can be gained from analysis of salvage therapy cohorts.

Keywords: Culture conversion, moxifloxacin, multidrug-resistant tuberculosis, Peru
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Introduction

Treatment of multidrug-resistant tuberculosis (MDR-TB), defined as *Mycobacterium tuberculosis* resistant to both isoniazid and rifampicin, is challenging under the best of circumstances, and particularly in resource-limited settings. Even with a well-designed regimen [1–3], excellent adherence, and good adverse event management [4–6], MDR-TB treatment can be expected to fail to achieve durable culture conversion in a certain proportion of patients [7]. Most MDR-TB patients who eventually go on to cure have sputum cultures that convert from positive to negative by the 6th month of treatment [5,8]. For patients who remain persistently sputum-culture-positive despite therapy with second-line TB drugs, treatment options are limited, especially if disease is too advanced for resective surgery. In these patients, salvage therapy refers to the design of a regimen combining new and previously used drugs in a final effort to attain sputum conversion before declaring treatment to have failed.

Since 1996, the Peru National TB Programme has been diagnosing and treating thousands of MDR-TB patients using an innovative model of community-based care [5,9]. Within this large number of closely monitored, highly adherent MDR-TB patients, we identified a cohort of persistently positive patients who received salvage therapy. We evaluated the outcome of salvage therapy in these patients and compared the frequency of culture conversion associated with specific drugs.

Study Population and Methods

We studied adults in Peru who initiated a tailored MDR-TB regimen between 28 August 1996 and 1 April 2007. The Peru MDR-TB treatment programme has been described elsewhere, including the procedures used for identifying MDR-TB suspects [10–12], designing MDR-TB treatment regimens [3], delivering community-based MDR-TB treatment [4], and performing smear, culture and susceptibility testing [13]. Drug susceptibility testing (DST) was performed routinely at the initiation of MDR-TB treatment. The design of tailored treatment regimens followed international guidelines for the management of drug-resistant TB [1,2,14]. Drugs were chosen hierarchically from the following groups: first-line drugs (ethambutol or pyrazinamide), second-line injectables (kanamycin or capreomycin), fluoroquinolones (ciprofloxacin or ofloxacin), and oral second-line drugs [ethionamide, cycloserine and para-aminosalicylic acid (PAS)]. If this did not result in a regimen that included at least five drugs likely to be effective, drugs of unclear efficacy (e.g. clofazimine, amoxicillin-clavulanate) were also included. For design of salvage regimens, there was no strict protocol, but physicians generally followed the same principles, giving highest priority to drugs that the patient had never received previously. Every effort was made to include a fluoroquinolone (usually moxifloxacin) and an injectable (usually capreomycin) because these drugs were less likely to have been used in MDR-TB treatment.

According to the Peruvian national treatment protocol, all MDR-TB patients were asked to submit sputum specimens for culture on a monthly basis during treatment. Culture and first-line DST were performed at the national reference laboratory. National protocols did not include guidelines for when to request second-line DST in patients who were persistently culture-positive. During the study period, second-line DST was available, but took months because cultures had to be shipped to a supranational reference laboratory in Massachusetts, USA. For purposes of analysis, all DST results available up to the start of the follow-up period were included; if a drug ever tested resistant, it was considered resistant. All bacteriological results were regularly collected and entered into a web-based database that contained information about all TB drugs received, including the dose, start date and end date for each drug [15].

We first identified persistently positive periods within the series of culture results of each individual patient. These were defined as 180-day periods at any time during treatment with at least four positive sputum cultures, separated by at least 14 days. A persistently positive date was defined as the date of the last positive culture in a persistently positive period. Salvage therapy was defined as the use of at least one new, never-used drug added to the regimen of a patient within 30 days before or after a persistently positive date. The following did not meet the definition of salvage therapy: (i) a dose increase, (ii) the use of a drug previously taken by the patient during the tailored MDR-TB regimen, or (iii) a drug that was started within 90 days before or after resective surgery. If several drugs had been started within 30 days of each other, they were considered to be part of a single salvage regimen for the purpose of analysis. For the small number of patients who received more than one course of salvage therapy, we used the first one for the analysis, assuming that subsequent salvage therapy would be much less likely to be successful after a failed course of salvage therapy. A switch between ethionamide and prothionamide was not considered an addition of a new drug because there is no evidence of difference in activity between the drugs. A switch from an early-generation quinolone (ciprofloxacin, ofloxacin) to a later-generation fluoroquinolone (levofloxacin, moxifloxacin), however, was considered an addition of a new drug because there was a theoretical improvement in anti-TB activity.

Culture conversion was defined as three consecutive negative culture results at least 14 days apart. Sputum samples were collected for culture every month according to programme guidelines, but the exact interval between cultures could vary a few days in either direction depending on the schedule of the patient. If a patient received resective surgery during the 180-day follow-up period, he or she was censused on the date of surgery. We calculated OR with chi-squared tests (SAS, version 8.02, Cary Institute, NC, USA) to determine the associations between specific drugs and culture conversion among salvage patients. All reported p-values are two-sided. This study was approved by the Harvard Medical School Committee on Human Studies.

Results

A total of 4525 individuals initiated a tailored MDR-TB regimen during the study period and had at least one 180-day period that included four culture results available for analysis. Of 625 (13.8%) patients who had at least one persistently positive episode, we identified 213 patients who received at least one course of salvage therapy and 291 patients who never received salvage therapy. The remaining 121 patients had a documented change in treatment regimen, but not around the time of a persistently positive episode (Fig. 1). Clinical characteristics and resistance patterns of salvage and non-salvage patients are shown in Table 1.