ORIGINAL ARTICLE INFECTIOUS DISEASES

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.

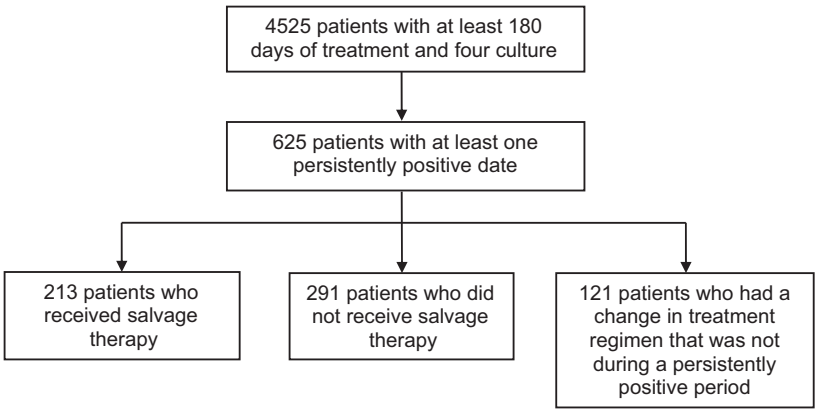

FIG. 1. Cohort selection.

TABLE 1. Clinical characteristics of salvage patients and non-salvage patients

Characteristic	Salvage		Non-salvage		p value
	Number (%)	Median (IQR)	Number (%)	Median (IQR)	
Age (years)		28 (16) (n = 209)		29 (14) (n = 261)	0.77
Male	128 (60%) (n = 213)		174 (60%) (n = 291)		0.95
Number of previous TB treatments		2 (1) (n = 201)		2 (1) (n = 240)	0.46
Baseline body mass index		19.2 (3.5) (n = 124)		19.6 (4.9) (n = 176)	0.31
Bilateral and cavitary disease on chest X-ray	80 (50%) (n = 159)		85 (46%) (n = 184)		0.45
Documented resistance to isoniazid and rifampicin (MDR)	183 (92%) (n = 200)		225 (90%) (n = 250)		0.59
MDR plus resistance to any fluoroquinolone	28 (18%) (n = 157)		48 (24%) (n = 198)		0.14
MDR plus resistance to any second-line injectable	78 (46%) (n = 169)		103 (49%) (n = 210)		0.58
MDR plus resistance to any fluoroquinolone or any second-line injectable (pre-XDR)	85 (50%) (n = 170)		104 (50%) (n = 207)		0.96
MDR plus resistance to any fluoroquinolone and any second-line injectable (XDR)	19 (12%) (n = 156)		39 (20%) (n = 198)		0.06

IQR, interquartile range; MDR, multidrug-resistant; TB, tuberculosis; XDR, extensively drug-resistant.

Salvage therapy was initiated after a median of 11 months (range 7–38 months) after the start of the MDR-TB treatment regimen. Salvage regimens included a median of two new drugs (range 1–6) and nine (range 5–13) total (new plus previously used) drugs (Fig. 2). The most frequently used new drug was moxifloxacin, followed by capreomycin, amoxicillin-clavulanate, kanamycin and clarithromycin (Table 2). Eleven salvage patients received surgery during the 180-day follow-up period; these patients were censused at the surgery date. Nineteen (8.9%) patients died during the follow-up period. Culture conversion occurred in 65 (30.5%) salvage patients. After culture conversion, however, 29 (45%) had at least one subsequent positive culture, and 11 (16.9%) eventually died.

Salvage regimens that included moxifloxacin were significantly more likely to be followed by culture conversion than those that did not (OR 2.1; p 0.02; Table 3). This association was significant even in the subset of 78 patients who received a salvage regimen that contained moxifloxacin as the only new drug. Eight of 16 patients (50%) who received a salvage regimen with moxifloxacin as the only new drug experienced sputum conversion, compared with 13 of 62 (21%) of those who received another new drug (OR 3.8; p 0.02).

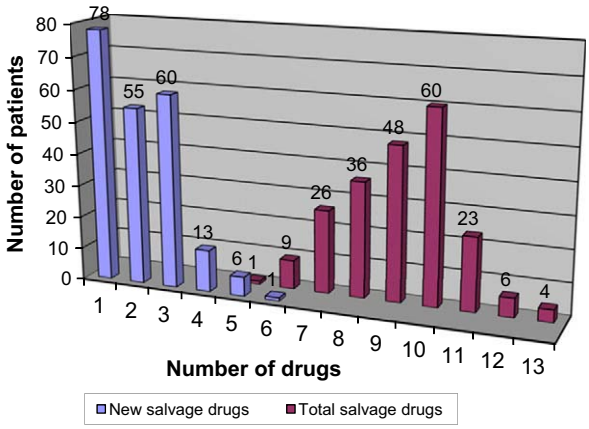

FIG. 2. Number of drugs used in the salvage regimen (n = 213).

TABLE 2. Proportion of patients receiving each tuberculosis drug (n = 213)

Drug	Received before starting salvage therapy	Received as a part of salvage therapy
Moxifloxacin	9.4% (20)	50.7% (108)
Capreomycin	51.2% (109)	33.8% (72)
Amoxicillin-clavulanate	56.3% (120)	23.4% (50)
Kanamycin	53.5% (114)	20.7% (44)
Clarithromycin	5.6% (12)	20.7% (44)
PAS	89.7% (191)	9.4% (20)
Streptomycin	15.0% (32)	9.4% (20)
Pyrazinamide	43.2% (92)	8.9% (19)
Ethambutol	32.9% (70)	7.5% (16)
Clofazamine	51.6% (110)	6.6% (14)
Rifabutin	1.9% (4)	5.6% (12)
Ethionamide/prothionamide	83.6% (178)	4.7% (10)
Isoniazid	5.2% (11)	3.8% (8)
Cycloserine	96.2% (205)	2.8% (6)
Ciprofloxacin/ofloxacin	90.6% (193)	2.8% (6)
Rifampicin	5.2% (11)	2.8% (6)
Levofloxacin	4.2% (9)	0.5% (1)

PAS, para-aminosalicylic acid.

No significant difference was observed in culture conversion by number of new drugs in the salvage regimen or by extent of resistance (Table 3).

Discussion

For MDR-TB patients with persistently positive cultures after 6 or more months of supervised treatment with a tailored regimen of second-line TB drugs, the decision to try a salvage regimen may be controversial because such patients have already received almost all drugs with known activity against *M. tuberculosis*. For this cohort of patients in Peru, the decision to attempt a salvage regimen was largely based on bacteriological response to the initial MDR-TB regimen. It is in this context that we retrospectively evaluated if salvage therapy had been effective and, if so, which drugs were associated with culture conversion.

The two drugs most commonly introduced were moxifloxacin and capreomycin. Both, however, have cross-resistance with other more commonly used TB drugs. Moxifloxacin is a later-generation fluoroquinolone that is known to have significant cross-resistance to early-generation fluoroquinolones such as ciprofloxacin or ofloxacin. Mutations conferring resistance to one fluoroquinolone are thought to confer some level of resistance to all members of the class [16]. Capreomycin is an injectable polypeptide with a structure and mode of action similar to that of the aminoglycosides: kanamycin, amikacin and streptomycin. Several reports have documented various levels of incomplete cross-resistance between capreomycin and kanamycin, the most commonly used injectables for MDR-TB treatment [17,18].

In this Peru cohort, salvage regimens often included drugs of unclear efficacy against *M. tuberculosis* such as amoxicillin-clavulanic acid, clofazimine and clarithromycin. The evidence supporting the use of these drugs in TB patients consists of sometimes conflicting *in vitro* and animal studies [19]. Clinicians also 'recycled' first-line drugs to which the patient had not responded previously—for example, high-dose isoniazid or streptomycin may have been used as part of a salvage regimen when DST indicated that the infecting strain was susceptible to higher concentrations.

Despite the limited treatment options, almost one-third of salvage patients experienced sputum culture conversion. In the analysis of specific drugs, only moxifloxacin was significantly associated with culture conversion. This was despite the fact that all of the patients were already receiving an early-generation fluoroquinolone—usually ciprofloxacin (750 mg twice daily) or ofloxacin (400 mg twice daily) (Table 2). One

TABLE 3. Characteristics associated with culture conversion after initiation of salvage therapy*

Characteristic	Conversion	OR (95% CI)	p value
Male	37/128 (29%)	0.8 (0.5–1.5)	0.53
Female	28/85 (33%)		
Age > 28 years	30/100 (30%)	0.9 (0.5–1.7)	0.85
Age ≤ 28 years	34/109 (31%)		
'Pre-XDR' (MDR plus fluoroquinolone or second-line injectable resistance)	25/85 (29%)	0.8 (0.4–1.5)	0.51
Not 'pre-XDR'	29/85 (34%)		
XDR	3/19 (16%)	0.4 (0.1–1.4)	0.14
Non-XDR	45/137 (33%)		
Two or more new drugs in salvage regimen	44/135 (33%)	1.3 (0.7–2.4)	0.39
One new drug in salvage regimen	21/78 (27%)		
Moxifloxacin in salvage regimen			
Yes	41/108 (38%)	2.1 (1.1–3.8)	0.02
No	24/105 (23%)		
Capreomycin in salvage regimen			
Yes	25/72 (35%)	1.3 (0.7–2.5)	0.34
No	40/141 (28%)		
Amoxicillin-clavulanate in salvage regimen			
Yes	16/50 (32%)	1.1 (0.6–2.2)	0.79
No	49/163 (30%)		
Kanamycin in salvage regimen			
Yes	16/44 (36%)	1.4 (0.7–2.8)	0.35
No	49/169 (29%)		
Clarithromycin in salvage regimen			
Yes	14/44 (32%)	1.1 (0.5–2.2)	0.83
No	51/169 (30%)		
PAS included in salvage regimen			
Yes	6/20 (30%)	1.0 (0.4–2.7)	0.96
No	59/193 (31%)		
Streptomycin in salvage regimen			
Yes	7/20 (35%)	1.3 (0.5–3.3)	0.65
No	58/193 (30%)		
Pyrazinamide in salvage regimen			
Yes	4/19 (21%)	0.6 (0.2–1.8)	0.35
No	61/194 (31%)		
Ethambutol in salvage regimen			
Yes	7/16 (44%)	1.9 (0.7–5.2)	0.24
No	58/197 (29%)		
Clofazimine in salvage regimen			
Yes	7/14 (50%)	2.4 (0.8–7.2)	0.11
No	58/209 (28%)		
Rifabutin in salvage regimen			
Yes	5/12 (42%)	1.7 (0.5–5.5)	0.39
No	60/201 (30%)		
Ethionamide/prothionamide in salvage regimen			
Yes	1/10 (10%)	0.2 (0.03–1.9)	0.18
No	64/203 (32%)		

*Drugs used in fewer than 10 patients not included in this table.
MDR, multidrug-resistant; PAS, para-aminosalicylic acid; XDR, extensively drug-resistant.

possible explanation is that some resistance mutations acquired by *M. tuberculosis* during treatment with ciprofloxacin or ofloxacin might not affect the susceptibility to moxifloxacin to the same degree. A recent study of mutations in the *gyrA* and *gyrB* regions shows that different mutations may confer different levels of resistance, though the clinical significance of this is yet to be determined [20]. Another possible explanation is that early-generation fluoroquinolones were unable to penetrate sequestered, fibrotic areas of the lung, such as fibrotic lesions and destroyed tissue, where *M. tuberculosis* can avoid exposure to drugs. This scenario can lead to persistent sputum culture positivity, even in a setting of perfect adherence. In such patients, *M. tuberculosis* may not acquire fluoroquinolone resistance because it is not exposed to drug pressure. Moxifloxacin has excellent penetration into bronchial secretions, and there is some evidence of superior penetration compared to earlier generation fluoroquinolones [21–23].

Later-generation fluoroquinolones such as levofloxacin, gatifloxacin and moxifloxacin have lower MICs for *M. tuberculosis* than early-generation fluoroquinolones such as ciprofloxacin or ofloxacin, and have been found to have superior sterilizing ability in mouse models [16,24]. Levofloxacin is the biologically active enantiomer of ofloxacin; levofloxacin essentially contains double the active enantiomer of an equivalent dose of ofloxacin. The early bactericidal activity of moxifloxacin, gatifloxacin, and high-dose levofloxacin appear to be higher than that of ciprofloxacin and ofloxacin [25–27].

There have been few clinical studies comparing the outcomes of later-generation fluoroquinolones with that of early-generation fluoroquinolones in the treatment of MDR-TB. Levofloxacin-containing regimens appeared to achieve better outcomes than ofloxacin-containing regimens in a retrospective study of MDR-TB treatment in Hong Kong [24]. Gatifloxacin-containing regimens seemed to achieve better outcomes than ofloxacin-containing regimens in a study in Bangladesh [28]. And an individual patient data meta-analysis of 9153 patients with MDR-TB showed better outcomes with regimens that used later-generation fluoroquinolones compared with ofloxacin-containing regimens [29]. In our study, all patients who received moxifloxacin as part of salvage therapy had previously received early-generation fluoroquinolones without achieving culture conversion.

The improvement in culture conversion achieved with moxifloxacin-containing salvage regimens raises the question of whether later-generation fluoroquinolones should be used in the initial treatment of MDR-TB rather than being reserved for salvage therapy. If moxifloxacin had been used in the initial MDR-TB treatment regimen, some patients might have gone on to cure without ever needing a salvage regimen. 'Saving' drugs for future use is a poor clinical strategy in the treatment of MDR-TB; rather, the most effective drugs—those offering the best chance for cure—should be used in the initial regimen designed to treat a patient with MDR-TB. This is particularly relevant to a drug like moxifloxacin, because *M. tuberculosis* that acquires mutations in the *gyrA* or *gyrB* regions during failed treatment with early-generation fluoroquinolones probably has reduced susceptibility to later-generation fluoroquinolones as well.

Surgical resection, such as pneumonectomy or lobectomy, is an important salvage intervention that was not evaluated in this study. Sputum-negative patients may undergo resection of residual lesions to prevent relapse, while sputum-positive patients may undergo resection of active lesions as a rescue strategy. Resective surgery is complicated, but has been shown to be feasible in resource-limited settings, resulting in a higher incidence of sustained sputum culture conversion than that of the salvage chemotherapy found in our study [30]. For this reason, the ideal strategy for persistently positive patients who are surgical candidates may be to combine salvage chemotherapy with surgical resection.

This was a retrospective study without a strict protocol for the initiation of salvage therapy or for monitoring of drug resistance acquisition at regular intervals. As DST was not regularly performed during treatment, we could not assess the effect of changes in second-line drug resistance on the effectiveness of salvage therapy. Salvage therapy did not include linezolid, which has since demonstrated strong evidence of efficacy, including one clinical trial [31]. Some drugs were used much more infrequently than others, resulting in a smaller sample size for comparison. For these reasons, a lack of association with conversion should not be considered definitive evidence that a specific drug has no *in vivo* activity against *M. tuberculosis*. There could have been unmeasured confounding in the initial comparison; we were not able to perform a multivariable analysis to assess confounding. The sample size also limits detection of effect estimates greater than two, which were of borderline significance. This may be the reason for no significant association between culture conversion and either the number of drugs in the salvage regimen or the extent of baseline resistance.

Despite these limitations, this study suggests that salvage therapy based on a careful history of bacteriological response to treatment can sometimes be effective, even in extensively treated patients. A number of new drugs have been or are expected to be approved for treatment of MDR-TB. Initial use, such as in compassionate-use cohorts, will include patients in conditions similar to those described here. Close bacteriological monitoring will be essential, as useful information about the best way to use new drugs may be gained from analysis of salvage therapy cohorts.

Contribution to Authorship

KJS, MCB and CDM were responsible for the conception and design. KJS, SSA and CDM performed the analysis and interpretation. Drafting the manuscript for important intellectual content was carried out by KJS, MCB, FA, CAB and CDM.

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Transparency Declaration

The authors declare no conflicts of interest.

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