Multidrug-Resistant Tuberculosis (TB) Resistant to Fluoroquinolones and Streptomycin but Susceptible to Second-Line Injection Therapy Has a Better Prognosis than Extensively Drug-Resistant TB

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Multidrug-resistant tuberculosis (TB) strains resistant to the fluoroquinolones and streptomycin but susceptible to second-line injection treatment would not be defined as extensively drug-resistant TB. In a cohort of 174 patients with multidrug-resistant TB, we demonstrated that 12 patients with multidrug-resistant TB strains resistant to the fluoroquinolones and streptomycin had significantly better initial and long-term outcomes, compared with 10 patients with extensively drug-resistant TB.

Drug-resistant tuberculosis (TB) has reached new levels of concern because of the recent identification of strains that are resistant not only to rifampin and isoniazid (multidrug-resistant [MDR] TB) but also to any fluoroquinolone (FQN) and at least 1 of the second-line injectable agents (amikacin, kanamycin, and/or capreomycin); this type of drug-resistant TB has been designated extensively drug-resistant (XDR) TB [1–4]. The first cluster of XDR TB was seen among patients with AIDS in the KwaZulu-Natal Province of South Africa and was associated with a high and rapid fatality rate [3]. A survey by the World Health Organization has identified XDR TB in at least 49 countries [5]. In the United States, the Centers for Disease Control Prevention estimated that, in 2007, 3% of patients with MDR TB would qualify as having XDR TB [6].

Authorities originally defined XDR TB as Mycobacterium tuberculosis strains resistant to at least isoniazid and rifampicin (among the first-line drugs) plus resistance to at least 3 of the following 6 classes of second-line drugs: aminoglycosides, polypeptides, FQNs, thioamides, cycloserine, and para-aminosalicylic acid [7]. However, in the current definition, there is greater emphasis on the second-line injectable agents—excluding streptomycin (STM)—because they are more reliably tested and more active than other second-line drugs [1, 2].

This retrospective study was approved by the Institutional Review Board of National Jewish Health. We previously reported that, among a cohort of 205 patients with MDR TB [8], 174 had isolates that underwent sufficient drug-susceptibility testing (i.e., of the FQNs ciprofloxacin and/or ofloxacin and of the second-line injectable agents capreomycin, amikacin, and/or kanamycin) to determine whether the patients also qualified as having XDR TB according to the current definition [9]. The 10 patients (6%) whose isolates fulfilled the criteria for XDR TB had significantly lower initial and long-term success rates and worse survival, compared with the 164 patients who had MDR TB only [9]. Because the current definition of XDR TB is not predicated on whether there is resistance to STM, we analyzed the same cohort of patients to determine whether MDR TB strains resistant to FQN and STM but susceptible to all 3 second-line injectable agents had similarly poor outcomes as those seen among our patients with XDR TB. In our cohort of 174 patients, 12 patients fulfilled the criteria for having MDR TB resistant to FQN and STM. Thus, accounting for the 12 patients with MDR TB resistant to FQN and STM and the 10 patients with XDR TB from the cohort of 174 patients, there remained 152 patients with MDR TB only, defined as MDR TB with any pattern of resistance other than that for MDR TB resistant to FQN and STM or that for XDR TB (table 1).

We then compared the initial and long-term outcomes in the 12 patients with MDR TB resistant to FQN and STM with those in the previously reported 10 patients with XDR TB. As shown in table 1, the initial treatment outcome demonstrated 10 successes and 1 failure (with 1 indeterminate outcome) for the 12 patients with MDR TB resistant to FQN and STM. By contrast, among the 10 patients with XDR TB, there were 3 successes and 5 failures (with 2 indeterminate outcomes). For long-term treatment outcome, there were 9 successes and 3
failures among patients with MDR TB resistant to FQN and STM and 2 successes and 8 failures among patients with XDR TB. Fisher’s exact test yielded $P = .04$ and $P = .03$ for differences between the group with MDR TB resistant to FQN and STM and the group with XDR TB for initial and long-term success rates, respectively. Similar test results were statistically insignificant when the patients with MDR TB resistant to FQN and STM were with compared with the patients with MDR TB only ($P > .45$). Therefore, the patients with MDR TB resistant to FQN and STM had significantly better initial and long-term outcomes than did the patients with XDR TB, despite comparisons with relatively small sample sizes.

We also used logistic regression to compare initial and long-term treatment outcomes between groups, with use of time with TB before first visit to National Jewish Health as a covariate. The odds of initial treatment success for the group with MDR TB only, relative to the group with MDR TB resistant to FQN and STM, was 0.9 (95% CI, 0.1–8.7), and the odds of initial treatment success among the group with XDR TB, relative to the group with MDR TB resistant to FQN and STM was 0.04 (95% CI, 0.003–0.5). For long-term outcome evaluations, the odds of success were 1.5 (95% CI, 0.4–6.3) among the group with MDR TB only, relative to the group with MDR TB resistant to FQN and STM, and 0.07 (95% CI, 0.009–0.5) among the group with XDR TB, relative to the group with MDR TB resistant to FQN and STM. Thus, whereas the group with MDR TB resistant to FQN and STM and the group with MDR TB only had similar initial and long-term outcomes, patients in the former group had significantly better initial and long-term outcomes than did the XDR TB group. We cannot rule out the possibility of unmeasured confounders in our results; however, other measured variables (i.e., age, surgical intervention, FQN use, drug resistance rate, and the number of drugs previously used) were also examined using logistic regression and did not appear to be confounders.

Despite their relative inconvenience for administration, injectable agents are important for the treatment of drug-resistant TB. Cross-resistance between kanamycin and amikacin is seen because of the similarity in their structures [10]. Of interest, in a study involving 240 patients with MDR TB and 48 patients with XDR TB, capreomycin resistance was solely associated with worse outcomes and with higher failure and death rates, compared with capreomycin susceptibility [11]. Although it is unclear whether the poor outcomes associated with capreomycin resistance occurred because other injectable agents to which the isolates remained susceptible were not used or were minimally used, there was no difference in outcomes between those isolates that were susceptible and those that were resistant to either amikacin or kanamycin [11]. In a recent study from Peru that demonstrated relatively good outcomes in patients with XDR TB who were intensely treated, an injectable agent was given for prolonged periods (for a median duration of nearly 15 months), and capreomycin was given to more than one-half of the patients [12].

In summary, in our relatively small cohort of patients, MDR TB isolates resistant to FQN and STM but susceptible to all 3 second-line injectable agents did not seem to confer the poor prognosis seen with XDR TB, presumably because of the availability and use of the second-line injectable agents. This was supported by the fact that all 12 patients with MDR TB resistant to FQN and STM received at least 1 of the other 3 second-line injectable agents to which their M. tuberculosis isolate remained susceptible. Thus, based on these retrospective findings, in patients with MDR TB that is also resistant to FQN and STM, the second-line injectable agents would appear to be an im-

### Table 1. Comparison of the initial and long-term treatment outcomes among patients with multidrug-resistant (MDR) tuberculosis (TB) only, MDR TB with resistance to fluoroquinolones (FQN) and streptomycin (STM), and extensively drug-resistant (XDR) TB.

<table>
<thead>
<tr>
<th>Variable</th>
<th>MDR TB only (n = 152)</th>
<th>MDR TB resistant to FQN and STM (n = 12)</th>
<th>XDR TB (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients who had a successful initial outcome</td>
<td>108/120</td>
<td>10/11</td>
<td>3/8</td>
</tr>
<tr>
<td>Initial treatment success rate, % (95% CI)</td>
<td>0.9 (0.8–0.95)</td>
<td>0.8 (0.6–0.93)</td>
<td>0.3 (0–1)</td>
</tr>
<tr>
<td>Proportion of patients who had a successful long-term outcome</td>
<td>109/132</td>
<td>9/12</td>
<td>2/10</td>
</tr>
<tr>
<td>Long-term success rate, % (95% CI)</td>
<td>0.8 (0.7–0.89)</td>
<td>0.8 (0.6–0.93)</td>
<td>0.2 (0–0.6)</td>
</tr>
</tbody>
</table>

**NOTE.** Initial treatment success was defined as at least 3 consecutive negative sputum culture results over a period of at least 3 months during treatment. Long-term success was based on the most recent clinical information available on the patients with regard to whether they had active disease, as previously defined [8]. The total numbers of patients in each of the 3 groups do not always match their respective denominators in calculating the success rates because of insufficient data. 95% CIs are based on the Wilson score method.
portant part of the treatment regimen. This finding needs fur-
ther corroboration from other studies.

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