Treatment Outcomes of Isoniazid-Resistant Tuberculosis Patients, Western Cape Province, South Africa

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We report treatment outcomes from a retrospective cohort of patients with isoniazid-monoresistant tuberculosis in rural South Africa. Sixteen percent of patients had poor outcomes, 61% of whom progressed to multidrug-resistant tuberculosis. These data reveal the need for early identification and aggressive follow-up of isoniazid monoresistance to increase treatment success.

The current strategy of directly observed treatment, short course, specifies that diagnosis of tuberculosis is made by sputum smear microscopy, and drug susceptibility testing (DST) is reserved for patients who experience treatment failure or are undergoing retreatment [1]. In the absence of routine DST, patients receive an initial regimen of standard 4-drug therapy. The development of rapid diagnostics that allow early detection of multidrug-resistant (MDR) tuberculosis now allows clinicians to adjust initial drug therapy [2]. Multiple studies have shown that outcomes are improved among MDR patients who receive modified regimens [3].

In contrast, the benefits of early detection of isoniazid monoresistance are less clear, and implications for patient outcomes, including progression to MDR, are not known. Although a recent meta-analysis [4] identified multiple studies in which patients with isoniazid-monoresistant tuberculosis had poorer outcomes than did patients with drug-susceptible tuberculosis, other studies reported no differences [5, 6]. Interestingly, in the latter studies, resistance was detected early and drug regimens and duration were modified, suggesting that improved outcomes may reflect the benefits of early diagnosis and tailored therapy.

This heterogeneity in treatment outcomes may also reflect differences in the specific mutations that confer isoniazid resistance. Mutations in *katG*, most commonly at S315T, confer partial loss of isoniazid activation, which is associated with high-level resistance (minimum inhibitory concentration [MIC] of 2–8 μg/mL), whereas *inhA* promoter mutations block isoniazid binding and lead to lower MICs (0.2–0.5 μg/mL) [7]. Patients with *katG* S315T mutations are hypothesized to have worse outcomes than those with *inhA* promoter mutations, especially when isoniazid is used in treatment.

In this retrospective study, we assessed treatment outcomes among patients with isoniazid-monoresistant tuberculosis who received standard therapy and report treatment outcomes stratifying on specific mutations.

METHODS

We enrolled patients who received a diagnosis of isoniazid-monoresistant tuberculosis at 22 clinics in the rural Cape Winelands East and Overberg Districts, Western Cape Province, South Africa, between 28 November 2000 and 28 May 2009. Sputum cultures are tested for isoniazid and rifampin resistance at the National Health Laboratory Services (NHLS) if patients had previously been treated for tuberculosis, had persistently positive results on sputum smears or cultures after 5 months of therapy, were in contact with patients who had confirmed drug-resistant cases of tuberculosis, or at the clinician's discretion. Patients with isoniazid monoresistance received standard 4-drug fixed-dose therapy (Rifafour) for 1 year. Retreatment cases also received streptomycin for the first 2.5–3.5 months. Patients with monoresistant tuberculosis were treated with high-dose isoniazid (10 mg/kg) at the discretion of the treating physician. Box 1 contains definitions of patient treatment history and outcomes.

Using the tuberculosis register of Brewelskloof Hospital, which collects regional data on all patients treated for drug-resistant tuberculosis, we enrolled patients with culture-confirmed isoniazid-monoresistant pulmonary tuberculosis. Patients were excluded if they returned for <1 month of

Received 26 January 2011; accepted 13 May 2011.

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Clinical Infectious Diseases 2011;53(4):369–372

1058-4838/2011/534-0008$14.00
DOI: 10.1093/cid/cir406

Box 1. Summary of Definitions Used [8]

Tuberculosis Treatment History:

- *New case*: A patient who has never had treatment for tuberculosis or who has received tuberculosis treatment for <1 month
- *Retreatment*: A patient who completed a full course of treatment or ≥1 month of treatment previously and returns with positive smear or culture results or has signs of active tuberculosis

Tuberculosis Treatment Outcomes:

- *Treatment completion*: A patient who completed all antituberculosis therapy and has microbiological confirmation of cure or indication in the medical record of receipt of an effective course of treatment
- *Treatment failure*: A patient with persistently positive culture results after 5 months of therapy or progression to MDR tuberculosis
- *Transfer out*: A patient transferred to another reporting unit and for whom the treatment outcome is not known
- *Default*: A patient who missed >20% of their total doses or >2 months of consecutive therapy.
- *Poor treatment outcome*: A patient with treatment failure or death

therapy, had documentation of MDR tuberculosis prior to initiating therapy, or were treated initially with second-line drugs. Brewelskloof Hospital records and clinic medical records were abstracted using a standardized form for patient age, sex, race, and weight; facility; prior tuberculosis history; diagnosis date; acid-fast bacilli sputum grade; treatment initiation and completion dates; drugs and doses used in therapy; DST results; human immunodeficiency virus (HIV) status, CD4 cell count, and antiretroviral therapy (ART) use; end of treatment smear and culture date and results; side effects; and treatment outcome. Microbiological data were confirmed in the NHLS electronic record.

Isoniazid and rifampin DST was performed using the indirect proportion method on Middlebrooks 7H11 agar and spoligotyping of strains and genotyping of mutations was performed, all by standard methods [9]. The study protocol was approved by the Harvard School of Public Health Institutional Review Board and the Stellenbosch University Ethics Committee.

Statistical analyses were performed using SAS, version 9.2. The χ^2 or Fisher exact test was used to examine the relation of categorical predictors to poor versus good treatment outcomes. Multivariate logistic models adjusted for potential confounding and effect modification. A sensitivity analysis included patients who defaulted in the poor outcome group.

RESULTS

We identified 179 patients with pulmonary isoniazid-monoresistant tuberculosis. Twenty-four patients were excluded: 13 returned for <1 month of therapy, 3 received a diagnosis of MDR tuberculosis prior to starting therapy, and 8 received second-line drugs. Of the 155 remaining, mean age was 38.2 +/− 11.8 years, 100 (65%) were male, 85% self-identified as Cape Colored and 15% as Black African, and mean weight was 49.5 +/− 10.6 kg. Thirty-three patients (21%) were HIV positive, and 20 (13%) were not tested for HIV. Among the 31 HIV-positive patients with available CD4 cell counts, the mean was 299. Seventy percent of the patients who met World Health Organization clinical criteria for ART (CD4 cell count, <200) received it. Thirty-six patients (23%) had received a new diagnosis of tuberculosis. Among the 116 (75%) previously treated, all had received standard treatment for drug-susceptible disease; 75 had completed a previous tuberculosis regimen, 38 had defaulted, and 3 had experienced treatment failure.

Of the 90 patients with sputum samples available for sequencing, 37 (41%) had *katG* mutations, 30 (33%) *inhA* promoter mutations, 21 (23%) neither, and 2 (2%) both. Forty percent were Beijing strains.

For 40 patients (26%), a standard 4-drug therapy regimen was initiated, and for 115 (74%) patients, a retreatment regimen was administered. One hundred-eight patients (70%) received high-dose isoniazid; isoniazid dose was increased a mean of 52 days after treatment initiation. No side effects were recorded in the medical records of patients who received high-dose isoniazid. All patients received pyridoxine.

Sixty-five percent of patients completed therapy successfully, 15% experienced therapy failure, 1% died, and 16% defaulted. Of the 23 patients whose therapy failed, 14 progressed to MDR tuberculosis and 9 had persistently positive culture results after 5 months of treatment. Of note, 4%–5% of new smear-positive cases in this region were reported to have poor outcomes [10].

In univariate analyses, we found no association between poor outcomes and specific mutations, HIV status, sex, weight, use of streptomycin or high-dose isoniazid, Beijing strain, and new tuberculosis diagnosis (Table 1). Patients aged 33–43 years had increased odds of a poor outcome, compared with patients aged 44–67 years (odds ratio [OR], 3.6; $P = .07$). Those with smear-positive tuberculosis also had an increased odds of poor treatment outcomes (OR, 5.2; $P = .009$). These associations were essentially unchanged if patients who defaulted were omitted from the analyses or added to the poor outcome group. Among

Table 1. Univariate Analysis of the Association of Patient Characteristics and Poor Treatment Outcomes, Defined as Treatment Failure or Death

Characteristic[a]	Poor outcome with characteristic	Poor outcome without characteristic	Odds ratio	P[b]
KatG 315 mutation (vs other mutations)	9/31	11/40	1.1	.88
HIV positive	5/26	19/82	0.79	.79[c]
Age in tertiles				
44–67 years	5/48	20/78	1.0	…
33–43 years	11/37	14/89	3.6	.07
11–32 years	9/41	16/85	2.4	.62
Weight <50 kg	15/67	7/26	1.2	.73
Female sex	10/50	15/76	1.0	.97
Black African (vs Cape Coloured)	2/15	23/111	0.59	.73[c]
New (vs retreatment)	3/28	21/95	0.42	.28[c]
Beijing strain	8/23	10/36	1.4	.57
Streptomycin	17/93	8/33	0.7	.46
High-dose isoniazid	15/88	10/38	0.58	.23
Initial smear results positive (vs negative)	21/79	3/46	5.2	.009[c]

NOTE. Data are proportion of patients unless otherwise specified. HIV, human immunodeficiency virus.

[a] Patients were included in the analysis if they had a final treatment outcome recorded and a characteristic of interest recorded. The 29 patients who defaulted or transferred out were also considered missing.

[b] χ^2 test, except where otherwise indicated.

[c] Fisher exact test.

patients infected with *katG* S315T mutant strains, treatment with high-dose isoniazid was associated with increased odds of a favorable outcome (OR, 1.87; interaction $P = .14$), whereas there was no difference among those infected with other isoniazid resistance–conferring mutations.

DISCUSSION

Among patients with isoniazid-monoresistant tuberculosis in rural South Africa, we found that 16% of patients had poor outcomes, 61% of whom progressed to MDR tuberculosis. This is not only in marked contrast to the 4%–5% rate of poor outcomes among new, smear-positive tuberculosis cases in these districts [10] but is also markedly worse than the 2%–8% poor outcomes reported from 2 isoniazid-resistant tuberculosis cohorts in the United States and Europe [5, 6]. The high proportion of treatment failure underscores the importance of early identification and close monitoring of patients with isoniazid-resistant tuberculosis and suggests the need for tailored regimens to improve outcomes.

We found no evidence that specific isoniazid resistance–conferring mutations were associated with worse treatment outcomes. Patients with *katG* mutations who received high-dose isoniazid had better outcomes than did those who received standard dose isoniazid, although this finding did not reach statistical significance, possibly as a result of small sample size. We also found that smear-positive tuberculosis was associated with poor outcomes, consistent with the idea that patients with smear-positive tuberculosis have a greater extent of disease and more cavitary lesions than do patients with smear-negative tuberculosis [11]. HIV positivity did not predict worse tuberculosis treatment outcomes, perhaps because the HIV-positive patients had a relatively high mean CD4 cell count, and the majority with CD4 cell counts <200 were receiving ART. Recent studies have shown that outcomes of patients receiving ART during tuberculosis treatment are similar to those of HIV-negative patients, including patients with drug-resistant tuberculosis [9, 12]. Patients aged 33–43 years experienced worse outcomes than did the oldest patients, perhaps as a result of poorer compliance, as evidenced by a higher percentage default in this age range.

Our study is limited by its retrospective design and lack of a drug-susceptible tuberculosis arm. Although the tuberculosis control program in this region reports new, smear-positive case outcomes, these patients may have less underlying pulmonary damage and better adherence to treatment than this isoniazid-monoresistant cohort, of whom 75% were retreatment cases. Last, we did not have follow-up information on patients beyond their 1 year in treatment and may, therefore, have overestimated success rates, because we did not consider those who relapsed after the end of the treatment period.

Even with these limitations, this cohort of patients with isoniazid-monoresistant tuberculosisis is, to our knowledge, the largest studied to date and the first with specific resistance genotypes from a resource-limited setting. Our study reveals the need among patients with isoniazid-monoresistant tuberculosis

for early identification with rapid diagnostics, such as a line probe assay, and aggressive follow-up given their risk of progression to MDR and treatment failure. Current line probe assays detect only a portion of the isoniazid resistance–conferring mutations, however, so improved rapid methods are needed. Our study also underscores the importance of adherence during the first episode of drug-susceptible tuberculosis infection to avoid acquisition of isoniazid resistance. Specific interventions, including the effectiveness of higher dose isoniazid, need additional study in this population.

Acknowledgments

We would like to thank Molly Franke, Christie Jeon, Carole Mitnick, Andre van der Kouwe, and Kathleen Wirth for their assistance and feedback on this project.

Financial support. This work was supported by the Burroughs Wellcome Fund/American Society of Tropical Medicine and Hygiene Postdoctoral Fellowship in Infectious Diseases (K. R. J.), National Institutes of Health (T32 AI07387 to K. R. J.), and Division of Research Development Research Travel Grant, Stellenbosch University, South Africa (K. R. J).

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed in the Acknowledgments section.

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