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Outcomes among tuberculosis patients with isoniazid resistance in Georgia, 2007–2009

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SUMMARY

BACKGROUND—The optimal management strategy for patients with isoniazid (INH) monoresistant forms of tuberculosis (TB) has been widely debated. The current daily 9-month regimen of rifampin, pyrazinamide and ethambutol was established based largely on trials in settings with low TB rates and low rates of drug resistance.

OBJECTIVE—To explore the outcomes of patients with INH-monoresistant TB in the country of Georgia, a setting with both high TB rates and drug-resistant forms of the disease.

METHODS—Retrospective record review of all patients diagnosed with smear-positive pulmonary TB resistant to either INH or INH+SM (streptomycin) in Georgia between 2007 and 2009.

RESULTS—Of 8752 patients with pulmonary TB registered in Georgia, 909 were found to have INH or INH+ SM resistance. Treatment outcomes were relatively poor in this group, with only 71% treatment success. Outcomes were significantly worse among patients with older age and a history of previous treatment.

CONCLUSIONS—INH or INH+SM resistance in pulmonary TB patients in Georgia is common. The low rates of treatment success suggest the need for an improved treatment regimen for patients with resistance to these first-line drugs; this need is particularly pronounced among the subset of patients with a history of previous treatment.

Keywords

tuberculosis; INH monoresistance; Georgia, outcomes

DRUG-RESISTANT TUBERCULOSIS (TB) is a significant global problem.[1] Although multidrug-resistant TB (MDR-TB) has been written about extensively, there is a gap in the literature on management of monoresistant forms of TB, particularly isoniazid (INH) resistant TB.[2] INH monoresistance is defined as strains of *Mycobacterium tuberculosis* that have documented resistance to INH;[3] some definitions also include strains of *M. tuberculosis* with resistance to INH and streptomycin (SM), as the addition of SM resistance does not affect current programmatic treatment recommendations.[4]

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INH-monoresistant TB is the most common form of TB monoresistance.[5] The optimal management of INH-monoresistant TB has been widely debated:[6–8] current global recommendations are that INH-monoresistant TB (including INH+SM-resistant strains) should be treated with a 9-month regimen of daily rifampin (R, RMP), pyrazinamide (Z, PZA) and ethambutol (E, EMB; i.e., 9RZE).[9,10] This recommendation is based largely on the results of a prospective clinical study conducted in the United States, in which there were no differences in outcomes between patients with INH monoresistance and those with pansusceptible TB, provided that those with INH monoresistance took their medications daily for the total 9-month course of treatment.[11] The study's applicability to settings outside of the United States, where there are different health care systems and high rates of drug-resistant TB, has been questioned. In contrast to the favorable results of this study, a recent global meta-analysis of outcomes among patients with INH monoresistance found poor treatment outcomes, with failure rates ranging from 18% to 44%.[12]

This article reports the outcomes of patients with INH-monoresistant TB treated under program conditions in the country of Georgia between 2007 and 2009.

SETTING

Georgia is a country in the South Caucasus with a population of 4.5 million. TB rates in Georgia are the fifth highest in the European region, with an estimated 98 cases per 100 000 population.[13] DOTS is the official strategy for TB control in the country, and all patients receive treatment under directly observed therapy (DOT). Rates of anti-tuberculosis drug resistance in Georgia are extremely high, with MDRTB (defined as resistance to at least both RMP and INH) reported in 11% of newly diagnosed patients and 47% of previously treated patients.[14] Rates of INH resistance are also high in Georgia, with INH or INH+ SM occurring in 12.8%, 14% and 12.3% of patients in 2007, 2008 and 2009, respectively. Following World Health Organization (WHO) guidelines, the daily 9RZE regimen is used to treat Georgian patients with INH monoresistance or INH+SM resistance. Of note, all patients in Georgia undergo drug susceptibility testing (DST) at the time of TB diagnosis, and they all receive DOT. Treatment non-a dherence rates are recorded for 10.8% of patients in Georgia.

STUDY DESIGN AND METHODS

Population

A retrospective record review was performed for patients being treated for smear-positive pulmonary TB within the Georgian National TB Program (NTP) between 1 January 2007 and 31 December 2009. Only smear-positive patients were included, as most standard outcomes measures are based on smear microscopy. The WHO-recommended 9RZE regimen was introduced at the national level in 2007. All patients who had smear-positive, pulmonary forms of TB with INH or INH+SM resistance were included in the study. Patients with resistance to INH and another drug besides SM were excluded.

TB diagnostic laboratory tests

Diagnosis of TB disease was initially made based on clinical presentation and radiographic findings and confirmed in the laboratory using standard smear and culture techniques. Sputum specimens were processed according to WHO recommendations,[15] and were sent for culture and DST against first-line anti-tuberculosis drugs at the National Reference Laboratory.

DST against first-line anti-tuberculosis drugs

DST against the first-line drugs SM, RMP, INH and EMB was performed using the standard culture-based method on Löwenstein-Jensen medium, as reported in other studies,[16] using the absolute concentration method. The critical concentrations used in the standard test were: SM, 4 μg/ml; INH, 0.2 μg/ml; RMP, 40 μg/ml and EMB, 2 μg/ml. The DST plates were examined for interpretation after 28 days of incubation. External quality control of the laboratory was performed by the Supranational Reference Laboratory in Antwerp, Belgium.

Data entry

Basic demographics as well as clinical and laboratory data were obtained through data abstraction from medical charts and entered into a software program, a web-application called SAFE (Satellites For Epidemiology) at the National Center for Tuberculosis and Lung Diseases (NCTBLD), Tbilisi, Georgia. Information on treatment outcomes was collected using the standard reporting and recording form. These forms are filled out for each TB patient at the end of treatment by a TB physician and sent to the regional database manager for quality monitoring and entry into the database.

Definitions

Type of TB case was classified into one of the following categories based on WHO guidelines. New TB cases were defined as patients who had never received treatment or had received <1 month of antituberculosis treatment, while previously treated cases were patients who had been treated for >1 month with first- and/or second-line anti-tuberculosis drugs.[17]

Treatment outcomes were divided into two groups. ‘Successful’ treatment outcomes were those patients meeting WHO definitions of ‘cured’ and ‘treatment completed’. ‘Poor’ treatment outcomes were those patients meeting program definitions of ‘died’ (during treatment), ‘failed’ or ‘defaulted’. The category ‘other’ was used to define all cases that did not fit the above definitions, such as patients for whom it was not known whether or not they had been previously treated; who were previously treated but for whom the outcome of the previous treatment was unknown; and/or who had returned to treatment with smear-negative pulmonary TB or bacteriologically negative extra-pulmonary TB. The term ‘transfer out’ refers to a patient who had been transferred to another recording and reporting unit and whose treatment outcome was unknown. ‘Moved to Category IV’ was applied to all patients who started standard treatment and were switched to treatment with second-line drugs during treatment.[18]

Statistical analysis

Statistical analyses were performed using SAS version 9.1 (SAS Inc, Cary, NC, USA) and Stata Version 9 (Stata Corp LP, College Station, TX, USA). Treatment outcomes among new and previously treated patients with INH or INH+SM resistance were assessed. Trends were investigated using the χ^2 test for trend. Univariable associations were reported and multivariable logistic regression was used to identify independent associations between measured covariates and the probability of a treatment success (i.e., cured or completed treatment). The final multivariable model was constructed first by including all variables considered in the univariable analysis, then by sequentially removing explanatory variables with the greatest *P* value. If the effect size of the other explanatory variables changed by less than 10%, the variable was dropped from the model, otherwise it was retained. Interactions of clinical interest were investigated through the use of likelihood ratio tests.

Ethical approval

The study was reviewed and approved by the Ethical Review Board at the National Center for Tuberculosis and Lung Disease in Tbilisi, Georgia. Institutional review board approval for the US-based investigators (TC and JF) was given by their affiliated institutions.

RESULTS

A total of 8752 smear-positive pulmonary TB patients were registered in Georgia between 2007 and 2009 (72.9% of all TB cases). Of these, 909 had either INH monoresistance or INH+SM resistance and are included in this analysis. Baseline demographics and case definitions for these patients are shown in Table 1.

Treatment outcomes among these patients are shown in Table 2, comparing new and previously treated patients. Among those patients with recorded treatment outcomes (n = 889), the overall probability of treatment success was 71% (data not shown). There was no evidence of temporal trend for changes in the probability of treatment success for new or retreatment patients (P = 0.56 and 0.38, respectively; data not shown). The probability of a successful outcome was significantly higher among patients receiving a first course of treatment (76%) than among those who had been previously treated for TB (58%, P < 0.001).

During the same period in Georgia, outcomes for INH- and INH+SM-resistant patients being treated with 9REZ were poorer than those for patients with INH-susceptible disease being treated with the standard 6-month drug regimen (2HREZ/4HR*): new patients with INH-susceptible disease had an 83% probability (3124/3759) of treatment success (P < 0.001); while retreatment patients with INH-susceptible disease had a 67% (608/906) probability of treatment success (P = 0.008). The percentage of default among the two groups was similar, with 20.6% defaulters among those with INH- or INH+SM-resistant disease and 15.6% among those with INH-susceptible disease (data not shown).

Multivariable analysis

A multivariable analysis was performed to identify risk factors for poor treatment outcomes among patients with INH- or INH+SM-resistant disease. The final model included the following variables: Logit P(Y = 1, successful treatment outcome) = β_0 + β_1 retreatment status + β_2 age + β_3 extra-pulmonary disease + β_4 employment status+ β_5 prison + β_6 baseline SM resistance + β_7 (retreatment status × baseline SM resistance). In this multivariable analysis, increasing age was an independent risk factor for poor treatment outcome (adjusted odds ratio [aOR] 0.98, 95% confidence interval [CI] 0.97–0.99). We found effect modification of the relationship between retreatment status and baseline SM resistance. Retreatment status was associated with poor treatment outcome, but retreatment cases with baseline SM resistance actually appeared to fare better than retreatment cases without baseline SM resistance (aOR 0.57 vs. aOR 0.30, respectively). The final multivariable model with aOR and 95%CI is shown in Table 3.

DISCUSSION

This retrospective record review conducted among patients with INH- or INH+SM-resistant TB in Georgia between 1 January 2007 and 31 December 2009 has several interesting findings. First, 10% (909/8752) of smear-positive pulmonary TB patients in Georgia demonstrated INH or INH+SM resistance during this period. Although a proportion of these

*H = isoniazid. Numbers before the letters indicate the duration in months of the phase of treatment.

patients had previously been treated for TB, the majority were newly diagnosed. This suggests ongoing primary transmission of INH- and INH+SM-resistant strains of TB in Georgia, and is cause for concern.

Second, compared with individuals with INH-susceptible TB, those with INH or INH+SM resistance had significantly worse outcomes, even when treated with a WHO-recommended regimen. This may be due to several factors, including the extended length of the 9RZE regimen and the need for it to be taken daily, both of which may be associated with reduced adherence. It also suggests that, in contrast to studies performed in settings with low background rates of drug-resistant TB, INH or INH+SM resistance may require a different treatment strategy among patients in epidemiologic settings where drug-resistant TB is more common, such as Georgia. Finally, the findings may also suggest inherent differences in the health care system between Georgia and the United States, such as the greater number of medical providers and a lower disease burden on public TB programs in the United States, leading to different results in the two settings. It should be noted, however, that all patients enrolled in the study received their daily medication under DOT.

An interesting finding was that among retreatment patients with INH resistance, those with additional SM resistance had better treatment outcomes compared to retreatment patients with INH resistance alone. The reasons for better outcomes among this subgroup with additional resistance is not clear, but could be explained by increased fitness costs in mycobacteria when resistance to both INH and SM occurs, although this was not observed among previously untreated patients.

Finally, we found that even among those patients with INH- or INH+SM-resistant disease, treatment outcomes were worse among certain subgroups, specifically older patients and those with a history of prior treatment for active TB. These findings suggest that a different therapeutic strategy may be needed among patients with INH or INH+SM resistance who have been treated previously. A history of previous treatment may be associated with a longer period of illness, worse lung parenchymal damage, and overall poorer health status. Furthermore, patients with a history of previous treatment may be more likely to default from treatment, particularly when given a regimen of a longer duration. Finally, patients with a previous history of TB may be more likely to have minority subpopulations of mycobacteria with additional resistance to other first-line agents (i.e., heteroresistance or polyclonal infection).[19,20] This would be difficult to detect in a single clinical sample, but could contribute to a poorer treatment response and eventually be picked up as apparent ‘acquisition’ of MDR-TB. All of these possibilities merit further evaluation.

CONCLUSIONS

This study has some major limitations, primarily related to its retrospective design. In addition, it was conducted in a population of patients with pulmonary TB receiving care from the NTP in Georgia and thus may not be generalizable to other populations. A number of the variables had missing data, especially concerning employment status. In addition, data on some covariates, such as adherence and socio-economic status, were not collected. This will be remedied in future work. Finally, the health care systems in the United States, where the 9-month regimen was studied most extensively, and Georgia are different, and differences in outcomes may not reflect a difference in efficacy of the regimen, but rather in the way it was delivered. Many countries with the highest burdens of TB and drug-resistant TB often have health care systems that differ widely from the US system. Thus, whether a problem in efficacy or delivery, this study raises concerns about the currently recommended 9-month treatment regimen outside of the United States.

Despite its limitations, this study has important findings. The ongoing transmission of INH and INH+SM resistance in Georgia suggest the need for an aggressive control strategy based on increased case detection and successful management of those with these forms of disease. The currently recommended treatment regimen may not be adequate in Georgia, as patients in this study were found to have a high probability of poor outcome, significantly worse than those with pan-susceptible disease. Among patients with INH- or INH+SM-resistant disease, those with a history of previous treatment did worse, suggesting that a more aggressive treatment strategy may be needed to improve outcomes among these groups of individuals. It is clear that more work is needed in managing patients with INH and INH+SM resistance, particularly in countries with high rates of drug-resistant TB. We hope that this study will guide future research into how best to manage patients with INH-resistant TB.

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Table 1

Baseline characteristics of patients with INH monoresistance or INH+SM resistance enrolled in the Georgian NTP, 2007–2009

	n (%)
Total	909
Sex	
Male	711 (78)
Age, years, median [IQR]	35 [26–47]
Case definitions	
New	655 (72)
Previously treated	81 (32)
Relapse	67
Failure	6
Default	44
Other	133
Chronic	3
Transfer	1
Baseline resistance	
INH monoresistance	
New	208
Previously treated	79
INH+SM resistance	
New	447
Previously treated	175

INH = isoniazid; SM = streptomycin; NTP = National Tuberculosis Control Program; IQR = interquartile range.

Table 2

Outcomes recorded for new and previously treated tuberculosis patients with INH monoresistance or INH+SM resistance enrolled in the Georgian NTP, 2007–2009 (n = 889)

Outcome	Previously treated *n* (%)*	New *n* (%)*
Successful	145 (58)	486 (76)
Cure	110	361
Completed	35	125
Unsuccessful	103 (42)	32 (24)
Default	51	77
Death	11	19
Failure	17	20
Transfer to Category IV regimen†	14	28
Transfer out	10	11
Unrecorded	6	14
Total with recorded outcomes	248	641

*Percentages with specific outcomes are calculated considering only the total number of individuals with recorded outcomes as the denominator.

†Patients whose drug susceptibility testing results changed from susceptible to resistant.

INH = isoniazid; SM = streptomycin; NTP = National Tuberculosis Control Program.

Table 3

Univariable and multivariable associations with successful treatment outcome

		Univariable		Multivariable	
Variable	***n***	**OR (95%CI)**	***P* value**	**aOR (95%CI)**	***P* value**
Male	889	0.79 (0.55–1.13)	0.19	—	—
Age, per year	889	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)*	0.002*
Retreatment	889	0.45 (0.33–0.61)	<0.001	0.30 (0.17–0.53)*	<0.001*
Baseline SM resistance	889	1.09 (0.80–1.49)	0.57	0.87 (0.58–1.31)	0.51
Extra-pulmonary	889	10.16 (1.36–75.51)	0.02	6.03 (0.79–46.01)	0.08
Internally displaced person	855	1.04 (0.50–2.21)	0.91	—	—
Employed	830	1.69 (1.02–2.80)	0.04	1.42 (0.84–2.39)	0.19
Prisoner	862	0.85 (0.57–1.27)	0.43	0.81 (0.52–1.25)	0.34
Retreatment × baseline SM resistance		—	—	2.18 (1.09–4.39)*	0.03*

OR = odds ratio; CI = confidence interval; aOR = adjusted OR; SM = streptomycin.