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Aggressive Regimens Reduce Risk of Recurrence After Successful Treatment of MDR-TB

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Background. We sought to determine whether treatment with a "long aggressive regimen" was associated with lower rates of relapse among patients successfully treated for pulmonary multidrug-resistant tuberculosis (MDR-TB) in Tomsk, Russia.

Methods. We conducted a retrospective cohort study of adult patients that initiated MDR-TB treatment with individualized regimens between September 2000 and November 2004, and were successfully treated. Patients were classified as having received "aggressive regimens" if their intensive phase consisted of at least 5 likely effective drugs (including a second-line injectable and a fluoroquinolone) used for at least 6 months post culture conversion, and their continuation phase included at least 4 likely effective drugs. Patients that were treated with aggressive regimens for a minimum duration of 18 months post culture conversion were classified as having received "long aggressive regimens." We used recurrence as a proxy for relapse because genotyping was not performed. After treatment, patients were classified as having disease recurrence if cultures grew MDR-TB or they re-initiated MDR-TB therapy. Data were analyzed using Cox proportional hazard regression.

Results. Of 408 successfully treated patients, 399 (97.5%) with at least 1 follow-up visit were included. Median duration of follow-up was 42.4 months (interquartile range: 20.5–59.5), and there were 27 recurrence episodes. In a multivariable complete case analysis (n = 371 [92.9%]) adjusting for potential confounders, long aggressive regimens were associated with a lower rate of recurrence (adjusted hazard ratio: 0.22, 95% confidence interval, .05–.92).

Conclusions. Long aggressive regimens for MDR-TB treatment are associated with lower risk of disease recurrence.

Keywords. multidrug-resistant tuberculosis; anti-tuberculosis treatment; tuberculosis relapse; tuberculosis recurrence.

Failure, acquired drug resistance, and relapse are the key efficacy measures for the treatment of active tuberculosis. Relapse is defined as tuberculosis disease that occurs after cure or completion of treatment, caused by *Mycobacterium tuberculosis* bacilli that were present at the end of therapy. Current first-line anti-tuberculosis regimens are designed to reduce the chance of relapse for those infected with drug-susceptible strains of tuberculosis, but little is known about how to minimize relapse in patients infected with multidrug-resistant strains of tuberculosis (MDR-TB). Given the high risk of morbidity and mortality among patients with MDR-TB—coupled to high failure rates and financial cost associated with treatment—minimizing MDR-TB relapse should be part of the evaluation of any treatment strategy.

The effects of individual drugs, the total number of drugs, and the total duration of therapy on the risk of relapse in drug-susceptible tuberculosis were established through randomized trials conducted in the latter half of the 20th century [1]. No clinical trials comparing MDR-TB treatment regimens have been completed, hence international treatment recommendations are based on analyses of outcomes reported in observational studies [2–4]. Only a handful of studies have evaluated the impact of specific regimen characteristics on the risk of relapse [5–7]. As the number of persons diagnosed with MDR-TB steadily rises [8], there is a pressing need for additional evidence to determine the optimal number, combination and duration of drugs required to achieve lasting treatment success in these patients.

In a recent study, "long aggressive" regimens were associated with lower risk of tuberculosis recurrence following successful treatment of MDR-TB [6]. "Aggressive" regimens are defined as those in which the intensive phase lasts for at least 6 months following sputum culture conversion and includes at least 5 likely effective medications, and the continuation phase includes at least 4 likely effective medications. Additionally, for a regimen to be classified as aggressive, a second-line injectable agent must be used during the intensive phase, and a fluoroquinolone throughout treatment [2, 9, 10]. In "long aggressive" regimens, treatment continues for at least 18 months following culture conversion [6].

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In the present study, we use data from an MDR-TB treatment program in Tomsk, Russia, to determine if long aggressive regimens were associated with lower risk of disease recurrence in this setting. We use the term "recurrence" instead of "relapse," because we could not distinguish whether tuberculosis disease following successful treatment was caused by the original infecting strain (relapse) or due to infection by a different strain (reinfection).

METHODS

Study Population and Design

We conducted a retrospective cohort study of adult patients (age ≥ 14) with culture-confirmed MDR-TB who initiated individualized treatment regimens in Tomsk, Russia, between 10 September 2000 and 1 November 2004, and whose outcome at the end of treatment was "cure" or "treatment completion" using internationally accepted definitions for treatment outcomes [11]. Detailed descriptions of enrollment and inclusion criteria, laboratory methods and quality control, treatment, and data collection for this study have been previously reported [10, 12]. All treatment was provided under direct observation. As previously reported, among patients initiating treatment, 66.1% were successfully treated, 8.8% failed, 4.9% died, and 20% defaulted [12]. The rate of recurrent MDR-TB amongst successfully treated patients was 1.7 per 1000 person-months observed (95% confidence interval [CI], 1.1–2.5) over 6 years of follow-up [13]. To analyze recurrence risk, we excluded 9/408 (2.2%) successfully treated patients who had no follow-up data.

Follow-up Investigations

Per Russian national policy, patients were monitored for recurrence by the tuberculosis dispensary for 1 to 3 years post-treatment, with evaluation by a tuberculosis specialist, chest radiography, and sputum smear and culture occurring every 3 to 6 months. Subsequently, patients were followed for an additional three years at primary healthcare facilities through clinical and radiographic examination every 6 months, and, if recurrence was suspected, microbiologic evaluation plus referral back to the tuberculosis dispensary. Incarcerated patients underwent clinical and radiographic evaluation every 6 months, sputum smears if they were coughing, and sputum culture if recurrence was suspected. In Russia, all positive tuberculosis cultures and tuberculosis deaths are reported to the regional tuberculosis dispensary, except for those occurring in prison, which are recorded by the penitentiary system. Thus we collected data from regional tuberculosis dispensary and penitentiary records to ensure we captured all recurrence and death events [13].

Exposure

Our main exposure of interest was treatment with a long aggressive regimen [6]. Because regimens could change throughout the course of therapy, we first determined for each day of treatment whether the prescribed regimen met criteria for being aggressive. Next, months where at least 75% of regimen days met these criteria were classified as months exposed to aggressive regimens. Finally, patients with at least 18 months of treatment following culture conversion meeting these criteria were classified as having received a long aggressive regimen. (We defined sputum culture conversion as two consecutive negative cultures taken at least 30 days apart, with the date of the first negative culture taken as the date of conversion [6, 13].) Cutoffs (75%, and at least 18 months) were chosen a priori to match those used in a previous study [6].

Outcome Definition

We classified patients as having recurrent disease if, during post-treatment follow-up either (1) a sputum culture grew MDR-TB and was followed by another positive culture or death; or (2) they were started on MDR-TB treatment [13].

Statistical Analysis

Patients with recurrent disease contributed person-time until the date of the first recurrence-defining event. Other patients contributed person-time until their last medical evaluation to a maximum of 72 months post-treatment [13].

We sought to determine whether treatment with a long aggressive regimen lowered the risk of disease recurrence compared to treatment with other regimens that varied by composition or duration—hence the reference group for this comparison included patients treated with aggressive regimens for less than 18 months post sputum conversion, and also those whose treatment did not meet criteria for an aggressive regimen. We adjusted for known risk factors for recurrence as well as potential confounders, which we identified based on the data (see below). Known risk factors for recurrence included age, sex, diabetes, prior injectable or fluoroquinolone use, high mycobacterial burden at treatment initiation (sputum smear with 3+ acid-fast bacilli), and extensive pulmonary involvement (baseline chest x-ray showing cavernous, fibrocavernous, caseous, disseminated, or cirrhotic changes).

To identify potential confounders, we first ascertained, among variables that were known or plausible risk factors for recurrence, those that were associated with receipt of long aggressive regimens. Variables evaluated included demographic variables, comorbid conditions (diabetes, baseline renal or hepatic disease, psychiatric illness, and seizure disorders), previous tuberculosis treatment (including exposure to injectable agents or fluoroquinolones in regimens antecedent to the regimen that resulted in successful treatment), clinical indicators of disease severity, adherence to treatment, and duration of treatment. Next, we performed univariable Cox proportional hazards regression to identify variables associated with time to disease recurrence. The variables enumerated above were considered potential confounders if they were associated at $P \leq .20$ in univariable analyses with either receipt of long aggressive regimens (using χ^2, Fisher, or Wilcoxon tests) or with

time to recurrence (using Cox proportional hazards regression). A potential confounder was retained in the multivariable model if, upon its removal, the parameter estimate of long aggressive treatment was changed by more than 10%. All analyses were done using the PHREG procedure in the SAS software (v9.4, SAS Institute Inc., Cary, North Carolina). Primary multivariable analyses were complete case analyses (only included participants with complete data); hence, we performed a sensitivity analysis to assess the impact of missing data, using Markov chain Monte Carlo methods (SAS MI procedure).

Sensitivity Analyses

We undertook a number of sensitivity analyses to evaluate the impact of the following on our results: missing data (described above); the potential for reinfection accounting for some cases of recurrence (described below); inclusion of patients whose original outcome was "treatment completed" (see Online Supplementary); and counting as cases of recurrence, patients that were started on MDR-TB treatment in follow-up without microbiological confirmation of the recurrence episode (see Online Supplementary).

We assessed the potential impact of reinfection on our results because our primary analysis assumed that all cases of recurrence were due to relapse. We hypothesized that as a result of this assumption, our observed association (between long aggressive regimens and recurrence) was weaker than the true association of interest (between long aggressive regimens and relapse). For this sensitivity analysis, we divided our study sample into 2 groups defined by their risk of reinfection after completing treatment and then determined the association between long aggressive regimens and recurrence within each group. We used incarceration status as a proxy for the risk of reinfection because the prevalence of MDR-TB was several fold higher in Tomsk prisons (average annual prevalence ratio comparing prison and civilian sector was 44, between 2002 and 2012 [14, 15]) — hence, patients who had spent time in prison after completing MDR-TB treatment were at a greater risk of reinfection compared to those who had never been incarcerated after completing treatment. If our hypothesis was true, the association between long aggressive regimens and recurrence would be attenuated in the former group compared to the latter group. This was tested in a Cox proportional hazards model with an interaction between long aggressive treatment and incarceration status; this model did not adjust for other variables because of the small number of patients experiencing the outcome. This analysis was restricted to men as no women had been incarcerated.

Exploratory Analysis

In an exploratory post hoc analysis, we sought to determine if there was a trend toward less recurrence with greater duration of aggressive treatment. This analysis was restricted to patients that had been treated with an aggressive regimen for at least 1 month. We grouped these patients into 4 categories of duration of treatment with an aggressive regimen: less than 6 months, 6 to 11 months, 12 to 17 months, and long aggressive (ie, at least 18 months). We calculated the proportion experiencing recurrence within each group and used the Cochrane Armitage test to evaluate the significance of the trend. We calculated univariable hazard ratios (HRs) and 95% CI for recurrence, comparing each category of shorter aggressive treatment to the long aggressive group.

RESULTS

Among 408 patients successfully treated for MDR-TB, 399 had at least 1 follow-up visit and are included in this analysis. Three hundred and fifty-two (88.2%) were treated with an aggressive regimen for at least 1 month following sputum culture conversion, and 111 (27.8%) were treated with a long aggressive regimen (Table 1). Patients with a greater number of previous tuberculosis treatments, prior exposure to injectable agents, and extensively drug-resistant tuberculosis at baseline, were less likely to have received a long aggressive regimen.

There were 27 cases of recurrent MDR-TB disease. In 21, drug-susceptibility tests confirmed the recurrent isolate to be MDR-TB. The others were classified as recurrence because they initiated MDR-TB treatment despite negative cultures (n = 2) or non-confirmation of MDR-TB in the recurrence isolate (n = 4). The median time to recurrence was 27.8 months (interquartile range: 14.3–46.8) (see Kaplan–Meier curve, Online Supplementary). In univariable analyses (Table 2), the following baseline variables were positively associated with time to recurrence with a P-value $\leq .20$: illicit drug use, smoking of cigarettes, human immunodeficiency virus, previous tuberculosis-related surgery, high mycobacterial burden, extensive pulmonary involvement, and receipt of less than 80% of prescribed doses. Employment and use of injectable agents in prior episodes were negatively associated with time to recurrence on univariable analyses at this P-value. In the final multivariable model, receipt of a long aggressive regimen was associated with lower risk of recurrence of MDR-TB (Table 2) (adjusted HR: 0.22, 95% CI, .05–.92).

Sensitivity Analyses

To assess the impact of missing data, we first compared the 28 (7.0%) patients excluded and the 371 (93.0%) included in the complete cases analysis (Supplementary Table 1); we did not find significant differences between the two groups. Next, we repeated our multivariable analysis on imputed datasets (Table 2). Long aggressive regimens remained protective against recurrence, but the effect estimate was attenuated and no longer statistically significant.

The next sensitivity analysis assessed the impact of reinfection on our results. We categorized the 138 patients that had spent time in prison after completing treatment as the group at elevated risk of reinfection. Among the incarcerated group,

Table 1. Characteristics of Study Cohort, by Regimen

Variable	Overall	Long Aggressive	Not Long Aggressive	*P* Value
Total	399	111	288	
Median duration of post-treatment follow-up (IQR)	43 (21–59)	44 (22–59)	42 (20–60)	.79
Demographic variables at beginning of treatment				
Age, median (IQR)	32 (25–43)	34 (27–44)	30 (25–43)	.11
Female	67 (16.8)	22 (19.8)	45 (15.6)	.39
Alcohol abuse/dependence	138 (34.6)	44 (39.6)	94 (32.6)	.23
Illicit drug use	70 (17.5)	21 (18.9)	49 (17)	.76
Smoking	333 (84.3)	90 (82.6)	243 (85)	.67
Employed	74 (18.5)	25 (22.5)	49 (17)	.26
Comorbidities at beginning of treatment				
Renal, hepatic, psychiatric, or neurological comorbid condition	277 (69.4)	76 (68.5)	201 (69.8)	.81
Diabetes	16 (4)	5 (4.5)	11 (3.8)	.78 *F*
HIV infection	2 (0.5)	0 (0)	2 (0.7)	1.0 *F*
Prior tuberculosis treatment				
Number of previous tuberculosis treatments, median (IQR)	2 (1–3)	2 (1–2)	2 (1–3)	.03
Previous default	10 (2.5)	1 (0.9)	9 (3.1)	.30 *F*
Previous injectable use	109 (27.9)	21 (19.8)	88 (31)	.04
Previous fluoroquinolones use	48 (12.3)	9 (8.5)	39 (13.7)	.22
Previous tuberculosis-related surgery	42 (10.6)	12 (10.8)	30 (10.5)	1.00
Clinical indicators of disease severity at beginning of treatment				
Low BMI	164 (41.2)	39 (35.5)	125 (43.4)	.18
Poor CXR	144 (36.1)	35 (31.5)	109 (37.8)	.29
Sputum smear AFB 3+	86 (22.2)	18 (16.5)	68 (24.5)	.12
XDR-TB	13 (3.3)	0 (0)	13 (4.5)	.02 *F*
Treatment related variables				
Treatment outcome				
Cured	376 (94.2)	107 (96.4)	269 (93.4)	.36
Treatment completed	23 (5.8)	4 (3.6)	19 (6.7)	
Received <80% of prescribed medication doses	74 (18.6)	21 (18.9)	53 (18.5)	1.00
Duration of treatment, months, median (IQR)	19 (18–21)	20 (18–22)	18 (18–20)	<.001
Received an aggressive regimen for at least 1 mo following sputum culture conversion	352 (88.2)	111 (100)	241 (83.7)	<.001
Duration that patient was treated with an aggressive regimen following sputum culture conversion, months, median (IQR)	16 (9–18)	19 (18–21)	11 (8–16)	<.001

All entries are N (%) unless indicated otherwise.

Low BMI defined as <18.5 kg/m^2 for women and <20 kg/m^2 for men.

Poor CXR defined as cavernous (ie, cavitary), fibrocavernous (ie, cavitary disease with volume loss due to fibrotic changes), caseous (thick walled cavities with satellite nodules), disseminated, or cirrhotic (bronchiectasis with nodular opacities) changes.

All *P*-values for categorical variables from continuity-adjusted Chi-Square or Fisher's exact test; *P*-values for continuous variables from Wilcoxon test. *F* = *P*-value from Fisher's exact.

Variables with missing data (no. of patients): smoking status (3), diabetes (1), HIV (1), number of previous tuberculosis treatments (4), previous injectable use (9), previous fluoroquinolone use (9), previous tuberculosis-related surgery (1), low BMI (1), smear (12), adherence (1).

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; CXR, chest x-ray; HIV, human immunodeficiency virus; IQR, interquartile range; XDR-TB, extensively drug-resistant tuberculosis.

all of whom were male, 34 (24.6%) were treated with long aggressive regimens, compared to 55 (28.4%) among male patients that had not been incarcerated in the follow-up period ($P = .53$). The association between long aggressive regimens and recurrence was attenuated among those imprisoned during post-treatment follow-up (unadjusted HR: 0.73, 95% CI, .22–2.61) compared to those that had not spent time in prison after completing treatment (unadjusted HR: 0.55, 95% CI, .06–4.89). The difference was not statistically significant (*P*-value for interaction term = .80).

Additional sensitivity analyses are reported in Supplementary Table 2. Exclusion of patients classified as treatment completed, or of patients in whom recurrence of MDR-TB was not microbiologically confirmed, provided results very similar to our primary multivariable analysis.

Exploratory Analysis

The post hoc analysis to explore the association between duration of aggressive treatment and risk of recurrence was restricted to the 352 patients exposed to an aggressive regimen for at least 1 month. Despite differing in duration of exposure to an aggressive regimen, the 4 groups were similar in duration of treatment overall (Table 3). The HR for recurrence fell with increasing duration of aggressive treatment. The trend for less recurrence

Table 2. Crude and Adjusted Hazard Ratios for Recurrence of Disease Following Successful Treatment of Multidrug-Resistant Tuberculosis

Variable	Crude HR (95%CI)	Adjusted HR (95%CI)	
		Complete Case, N = 371	Multiple Imputation, N = 399
Demographic variables at beginning of treatment			
Age, per 1 y increase	1.00 (.97–1.04)	1.01 (.97–1.05)	1.00 (.96–1.04)
Female	0.76 (.26–2.21)	1.22 (.39–3.81)	1.05 (.35–3.2)
Alcohol abuse/dependence	1.23 (.56–2.69)	. . .	. . .
Illicit drug use	1.93 (.81–4.56)[a]	. . .	. . .
Smoking	4.85 (.66–35.81)[a]	. . .	. . .
Employed	0.29 (.07–1.23)[a]	. . .	. . .
Comorbidities at beginning of treatment			
Renal, hepatic, psychiatric, or neurological comorbid condition	0.65 (.30–1.40)	. . .	. . .
Diabetes	0.81 (.11–5.98)	0.87 (.10–7.22)	0.91 (.11–7.52)
Prior tuberculosis treatment			
Number of previous tuberculosis treatments	1.17 (.91–1.52)	. . .	. . .
Previous default	2.22 (.30–16.49)	. . .	. . .
Previous injectable use	0.46 (.16–1.34)[a]	0.35 (.11–1.16)	0.36 (.10–1.26)
Previous fluoroquinolone use	0.85 (.25–2.82)	1.54 (.40–5.97)	1.35 (.34–5.44)
Previous tuberculosis-related surgery	2.33 (.94–5.78)[a]	. . .	. . .
Clinical indicators of disease severity at beginning of treatment			
Low BMI	1.41 (.66–2.99)	. . .	. . .
Poor CXR	1.92 (.90–4.09)[a]	1.83 (.77–4.37)	1.79 (.79–4.04)
Sputum smear AFB 3+	1.85 (.83–4.13)[a]	1.65 (.69–3.96)	1.56 (.65–3.72)
Treatment related variables			
Received <80% of prescribed medication doses	1.85 (.81–4.24)[a]	. . .	. . .
Treated with aggressive regimen for at least 18 mo following the first sputum conversion	0.44 (.15–1.28)[a]	0.22 (.05–0.92)[b]	0.44 (.15–1.28)[c]

Low BMI defined as <18.5 kg/m^2 for women and <20 kg/m^2 for men.

Poor CXR defined as cavernous (ie, cavitary), fibrocavernous (ie, cavitary disease with volume loss due to fibrotic changes), caseous (thick walled cavities with satellite nodules), disseminated, or cirrhotic (bronchiectasis with nodular opacities) changes.

Variables with missing data (N): smoking status (3), diabetes (1), HIV (1), number of previous tuberculosis treatments (4), previous injectable use (9), previous fluoroquinolone use (9), previous tuberculosis-related surgery (1), low BMI (1), smear (12), adherence (1).

Complete case analysis from participants with data on all variables evaluated for inclusion in the final multivariable model (see "Methods" section).

Multiple imputation analysis using Markov chain Monte Carlo methods (see "Methods" section).

Proportional hazards assumption was verified for all variables in both univariable and multivariable analyses.

HIV was not included in multivariable model as only 2 patients were HIV-positive. Crude HR (95%CI) for HIV was 52.23 (6.24–437); XDR was not included in the multivariable model as none of the 13 patients with XDR-TB experienced recurrence.

Abbreviations: AFB, acid-fast bacilli; BMI, body mass index; CI, confidence interval; CXR, chest x-ray; HIV, human immunodeficiency virus; HR, hazard ratio; XDR-TB, extensively drug-resistant tuberculosis.

[a] Crude *P*-value ≤ .20.

[b] Adjusted *P*-value = .04.

[c] Adjusted *P*-value = .13; NB: The reported univariable and multivariable HR are identical due to rounding.

with increasing duration of aggressive treatment had an associated *P*-value of .03 (Cochrane Armitage test).

DISCUSSION

Among patients successfully treated for MDR-TB in Tomsk, Russia, treatment with long aggressive regimens was associated with a 78% reduction in the risk of disease recurrence. We also found an attenuated association among patients at elevated risk of reinfection, suggesting that the association between long aggressive regimens and relapse—which is the true measure of treatment efficacy—is stronger than our observed association between these regimens and recurrence. Our findings add to a growing body of evidence demonstrating that aggressive regimens are associated with improved MDR-TB treatment outcomes, namely, a shorter time to culture conversion [16], greater probability of treatment success and survival [9, 10], and lower risk of disease recurrence [6].

In our study, the association between long aggressive regimens and lower risk of recurrence remained after we adjusted for correlates and measures of bacillary burden. While this clearly suggests that a long aggressive regimen may be protective, it is very difficult to know what aspect of the regimen—the number of effective agents, the combination of drugs used and their synergy with each other, or the duration of treatment—contributed most to the marked reduction in risk of disease recurrence.

Table 3. Association Between Duration of Exposure to an Aggressive Regimen and Recurrence

	Duration of Exposure to an Aggressive Regimen, in Months			
	<6	6–11	12–17	≥18
Number experiencing recurrence/Total (%)	2/8 (25%)	8/90 (8.9%)	10/143 (7%)	4/111 (3.6%)
Univariable hazard ratio (95% CI) comparing risk of recurrence to patients treated with long aggressive regimens	6 (1.1–33.0)	2.4 (.7–8.0)	2.0 (.6–6.3)	Reference
Median total duration of treatment, months (IQR)	18 (18–22)	18 (18–19)	18 (18–20)	20 (18–22)

Analysis restricted to 352 patients that were treated for at least 1 month with an aggressive regimen.

Abbreviations: CI, confidence interval; IQR, interquartile range.

In this study we were unable to assess whether the number of effective agents was important throughout the MDR-TB regimen or only during some periods. Similarly, we were unable to determine if the 18-month minimum duration was essential to receive a benefit. Although our expoloratory analysis (Table 3) suggests outcomes were better when aggressive regimens were used for at least 18 months, inference is limited because it is a post hoc and unadjusted analysis. We are mindful of data showing low rates of recurrence among MDR-TB patients receiving treatment for anywhere between 9 and 15 months [7, 17–19]; in 3 of these studies, intensive phase regimens consisted of 7 drugs (a second-line injectable agent, a fluoroquinolone, prothionamide, clofazimine, isoniazid, ethambutol, and pyrazinamide) [17–19]. Although it is difficult to directly compare the results of these cohorts with our own findings, they raise the possibility that early aggressive treatment with more than 5 drugs could be an essential component for reducing the duration of treatment without increasing the risk of relapse. This question will ultimately need to be addressed through controlled trials, such as the STREAM study, seeking to reduce MDR-TB treatment duration [20]. Also needed are studies evaluating the potential contribution of drugs that were not available for use in the Tomsk program, such as bedaquiline, delamanid, linezolid, and clofazimine.

Our study had a number of strengths and limitations. Strengths of the study include the availability of detailed data on socioeconomic status and treatment adherence that allowed us to assess potential confounding by these factors. Furthermore, few patients (7%) were excluded due to missing data, and we verified our conclusions through sensitivity analyses on imputed data sets. An additional strength is that, despite the absence of genotyping, we were able to explore how the use of recurrence as a proxy for relapse could affect inference about the efficacy of long aggressive regimens.

A number of limitations should also be considered when interpreting our results. First, even among patients who did not receive long aggressive regimens, 84% were treated with an aggressive regimen for at least 1 month following culture conversion, and 25% of this group received aggressive regimens for at least 16 months post-conversion. This similarity between those treated with long aggressive regimens and the reference group to whom they were compared biased our study towards showing no association between long aggressive regimens and recurrence. A second important limitation is that the association between long aggressive regimens and lower risk of recurrence was not statistically significant in our sensitivity analysis on imputed data sets. Although this could have resulted from inadequate power, it could also indicate bias in the primary analysis. Nonetheless, the effect estimate from the sensitivity analysis (adjusted HR 0.44, 95% CI, .15–1.28) was very close to that reported in a study of MDR-TB patients in Peru, in which treatment with a long aggressive regimen was associated with a 60% reduction in recurrence (adjusted HR, 0.40, 95% CI, .17–.96) [6]. A third limitation, due to the small number of patients who experienced the outcome of interest, is that we did not adjust for potential confounders in the analysis that explored the impact of reinfection on our results. Hence, we cannot rule out the possibility that the attenuated effect of long aggressive regimens among the group at elevated risk of reinfection is due to confounding. A fourth limitation, discussed in detail above, is that our study design could not separate the importance of duration from the number of effective agents.

CONCLUSION

Results from the first randomized trials evaluating treatment regimens for MDR-TB are years away. In the meantime, there is a pressing need to expand access to MDR-TB treatment and improve outcomes. Our study adds to a growing body of evidence that individualized aggressive regimens improve treatment outcomes for MDR-TB, particularly among populations where previous exposure to second-line drugs is common.

Supplementary Data

Supplementary materials are available at http://cid.oxfordjournals.org. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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