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Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients

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SUMMARY

SETTING: Tuberculosis (TB) program, Damien Foundation Projects, Bangladesh.

OBJECTIVE: To summarize the outcome and its determinants of the first treatment for multidrug-resistant TB using a standardized regimen consisting of a minimum 9 months.

DESIGN: This was a prospective, observational study of a gatifloxacin (GFX) based directly observed regimen, mainly with initial hospitalization. The 4-month intensive phase was extended until sputum smear conversion. Patients were monitored using culture for up to 2 years after treatment completion.

RESULTS: Of the 515 patients who met the study inclusion criteria and were successively enrolled from 2005 to 2011, 84.4% had a bacteriologically favorable outcome. Due to extensive disease with delayed sputum conversion, only half of the patients completed treatment within 9 months; however, 95% were able to complete treatment within 12 months. Eleven patients failed or relapsed, and 93.1% of the 435 patients who were successfully treated completed at least 12 months post-treatment follow-up. The strongest risk factor for a bacteriologically unfavorable outcome was high-level fluoroquinolone (FQ) resistance, particularly when compounded by initial pyrazinamide (PZA) resistance. Low-level FQ resistance had no unfavorable effect on treatment outcome. Amplification of drug resistance occurred only once, in a patient strain that was initially only susceptible to kanamycin and clofazimine.

CONCLUSION: The excellent outcome of the Bangladesh regimen was largely maintained. Bacteriological treatment failures and relapses were rare, except among patients with high-level GFX resistance, notably in the presence of PZA resistance.

KEY WORDS: tuberculosis; multidrug resistance; treatment; standardization

THE WORLD HEALTH ORGANIZATION (WHO) has recommended that multidrug-resistant tuberculosis (MDR-TB, defined as resistance to at least isoniazid [INH] and rifampicin [RMP]) be addressed as a public health crisis and that capacity to deliver effective treatment and care be increased.[1] We have previously reported results obtained in Bangladesh with sequentially adapted regimens shortening the treatment duration until we finally arrived at a regimen that required a minimum of 9 months' duration. The results obtained with this regimen based on the core drug gatifloxacin (GFX) were then reported for the first 200 patients.[2]

In the present report, we provide an update of this observational study on treatment outcomes among a cumulative total of more than 500 patients treated with what is colloquially known as the '9-month Bangladesh regimen' and followed for up to 2 years after treatment completion. We demonstrate its continuing success and provide information on the impact of initial fluoroquinolone (FQ) and pyrazinamide (PZA) resistance on treatment outcome.

MATERIAL AND METHODS

Ethical considerations

Ethics clearance was obtained from the Bangladesh Medical Research Council, Dhaka, Bangladesh. Before enrollment, each patient completed and signed an informed consent form in the local language.

Enrollment criteria

All patients with proven or highly likely MDR-TB detected in the Damien Foundation Project area in Bangladesh were eligible; those who received at least one dose of the regimen were enrolled. No age or clinical conditions, apart from overt liver disease, were applied as exclusion criteria. The current population of approximately 30 million persons covered by Damien Foundation on behalf of the

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Bangladesh National Tuberculosis Control Programme is very poor and often presents with advanced disease; however, human immunodeficiency virus (HIV) infection is virtually absent.[2,3] Treatment, food and all other hospitalization costs during the intensive phase were offered free of charge. Hospitalization during the intensive phase was compulsory during the first years, and continued to be practiced for the majority of patients during the first few months of treatment.

Testing at enrollment, during and after treatment

All patients had an initial chest radiograph to determine whether one or both lungs were affected. Sputum was tested using smear microscopy for acid-fast bacilli and cultured on Löwenstein-Jensen (LJ) medium at the local reference laboratory before the start of treatment; during the intensive phase (monthly smear, bi-monthly culture until the end of 2007, monthly thereafter); at 2, 4 and 5 months of the continuation phase; and 6-monthly during the 2 years of follow-up after treatment cessation. Cured patients enrolled up to the end of 2006 had one additional follow-up visit 5 years after treatment cessation.

Drug susceptibility testing (DST) using the proportion method was performed at the Antwerp Supranational Reference Laboratory (henceforth the 'Antwerp laboratory') on all isolates, using WHO-recommended critical concentrations. INH, RMP, ethambutol (EMB) and streptomycin were tested on LJ medium, while second-line drugs such as kanamycin (KM), ofloxacin (OFX) and ethionamide were tested on Middlebrook 7H11 agar.[4] Test results were not used to modify the standardized regimen. From 2008 onwards, RMP results obtained locally with rapid DST on microscopy slides were used to allow early start of treatment;[5] all isolates were dispatched to the Antwerp laboratory for confirmation or correction of the rapid RMP test results and for extended DST. PZA was tested retrospectively for a subset of the preserved strains by sequencing the *pnc*A gene in the Antwerp laboratory, which also determined the minimum inhibitory concentration (MIC) for GFX (MIC 99 using 0.25, 0.5, 1, 2 and 4 mg/l) of some of the strains, including all those found to be OFX-resistant using the proportion method.

Finally, the Antwerp laboratory compared the pre-treatment strain genotype with that of strains from patients reverting to positive on culture (isolated positives and recurrences) using spoligotyping, with further differentiation using 24-loci mycobacterial interspersed repetitive units-variable number tandem repeat in case of similar spoligotypes.[6,7] After pre-treatment biochemical and hematological screening, only urinary and blood glucose was monitored regularly in dysglycemic patients.

Study exclusion and inclusion criteria

The analysis was restricted to the period from March 2005 (start with this regimen) to 30 June 2011. The closing date allowed completion of treatment and, for most patients, also included the 2-year follow-up period. Patients were excluded from analysis if 1) culture identified only environmental mycobacteria and *Mycobacterium tuberculosis* was never isolated, 2) the patient had a history of previous treatment with second-line drugs, or 3) the Antwerp laboratory failed to confirm RMP- plus INH-resistant TB (i.e., MDR-TB). Patients excluded from the analysis due to missing proof of MDR-TB were treated in an identical manner as those included. Patients excluded for other reasons were given various salvage regimens as deemed appropriate, which are not further elaborated upon here.

Treatment

The same regimen was used throughout the analysis period and comprised high-dose GFX, EMB, PZA, and clofazimine (CFZ) throughout, supplemented during the minimum 4-month intensive phase by KM, prothionamide (PTH), and INH. If sputum smear microscopy results at month 4 were positive, the intensive phase was extended until sputum smears were negative or the patient was declared to have bacteriological treatment failure. The duration of the continuation phase was fixed at 5 months. Treatment was fully supervised throughout, using any available trained and supervised providers. Out-patients attended a Damien Foundation field clinic at least once a month. Further details, such as drug dosages, can be found in the 2010 report.[2]

Treatment outcome definitions

We used the definitions proposed by Laserson et al.,[8] with minor adaptations[2] to fit the shorter treatment duration. Briefly, these were:

Cure: completion of treatment with five or more negative cultures over at least 12 months (follow-up period included[2]) after the last positive culture.

Completion: completion of treatment with documented bacteriological conversion status persisting up to the end of treatment, but fewer than five negative cultures or $<$12 months of observation after the last positive culture.

Failure: one or more positive cultures during treatment after at least 150 days, or death or default with bacteriological evidence of active TB after the first 2 months of treatment, or a medical decision to definitively terminate treatment due to adverse drug reactions.

Relapse: cure or treatment completion, followed by at least one positive culture during post-treatment follow-up, unless the strain was proven to be genotypically different from the initial isolate.

Reinfection disease: recurrent disease with a genotypically different strain.

Death: death from any cause during treatment not meeting the criteria for prior failure.

Default: interruption of treatment for at least 2 months not meeting the criteria for prior failure.

Conversion on culture: two negative cultures taken at least 30 days apart; time to conversion is from start of treatment until the time the first of these two negative specimens was taken.

Data management and analysis

Epi Info Version 6.04d (US Centers for Disease Control and Prevention, Atlanta, GA, USA) and later EpiData Version 3.1 (EpiData Association, http://www.epidata.dk, Epidata Association, Odense, Denmark) were used for data capture. Analyses were performed using EpiData Analysis Version 2.2 (EpiData Association) and R Version 3.01 (R Core Team, http://www.R-project.org/, Vienna, Austria). For death and default, the outcome was accepted as recorded. Bacteriologically defined outcomes of cure, completion, failure and relapse were derived from serial culture results using computer algorithms. We used 13 levels to classify outcome. For binomial analysis, we collapsed these into two levels, contrasting 'programmatically favorable' with 'programmatically unfavorable'. 'Programmatically favorable' was defined as bacteriologic conversion persisting through treatment completion or cure without evidence of relapse. 'Programmatically unfavorable' comprised death on treatment, default from treatment, treatment failure, and/or recurrent TB not proven to be reinfection disease or laboratory error due to non-matching genotypes. For further subanalyses, we only considered the outcomes cure/treatment completed vs. failure/relapse, i.e., 'bacteriologically favorable' vs. 'bacteriologically unfavorable'. We determined one-way, two-way, and stratified frequencies for the analysis of categorical variables, with statistical tests, such as χ^2 tests for categorical variables, odds ratios (ORs) or adjusted Mantel-Haenszel ORs, as appropriate. Student's *t*-test was used for continuous variables (univariable). We used stratified Kaplan-Meier estimates of programmatically favorable outcome probability and Cox proportional hazard regression estimates, based on which we calculated probabilities for a programmatically favorable treatment outcome. In the Cox proportional hazard model, we used tests to determine whether the assumption of proportionality was met to decide whether or not adjustment alone was appropriate or required prior stratification for the variable contributing to the violation of the proportionality assumption. To produce the survival function, we used the 'plot.survfit' command in the R-package 'survival' after fitting the Cox proportional hazard model. For this, the hazard ratio (HR) parameters are used (at the average of the included variables), in addition to a non-parametric estimate of the baseline hazard for each level of FQ resistance. To determine risk factors for bacteriologically unfavorable outcomes in a subset of patients (excluding death and default), we used logistic regression modeling.

RESULTS

Patients enrolled and patients available for analysis

Of the 905 patients who had received at least 1 day of treatment, 390 were excluded in the following sequence: 265 were enrolled after 30 June 2011, 32 only had isolates of environmental mycobacteria, 28 had undergone previous treatment with second-line drugs, and 65 did not have laboratory confirmation of both RMP and INH resistance. The remaining 515 patients were included in this analysis.

Cohort analysis of treatment outcome

Overall treatment outcome

Of the 515 patients, 435 (84.5%) had a successful treatment outcome (cured or treatment completed, Table 1); of these, 82.3% ($n = 358$) did not relapse for 24 months, and 93.1% ($n = 405$) for $\geqslant 12$ months after treatment completion. Coverage by post-treatment follow-up culture was 93% complete (data not shown). No additional relapse cases were detected among the 78/89 (88%) patients inactive at 2 years and who were found to be alive at the follow-up visit 5 years after cure.

Subset of patients who died

Twenty-nine (5.6%) patients died on treatment, half within the first 60 days. Of the 15 patients who died after 60 days, one had only a positive diagnostic culture result, one had a single negative culture after the initial positive culture, while the remaining 10 patients had multiple negative (but no positive) cultures before death. Among all 492 patients with information on chest radiographic findings, 83.3% had bilateral disease. This proportion was 96.3% among those who died ($P = 0.11$).

Subset of patients who defaulted

Of the 40 patients who defaulted from treatment, almost half were lost during the first 60 days. All of those who defaulted after 60 days had one or several negative cultures prior to the event, with the exception of one patient who had only a positive diagnostic culture result.

Reinfection disease

Two patients had confirmed reinfection disease during the 2-year follow-up.

Table 1 Treatment outcome among patients with multidrug-resistant tuberculosis. Treatment success comprises cured and treatment completed; all other standard outcomes together constitute non-success

	n (%)	95%CI
Total ($n = 515$)		
Success ($n = 435$, 84.5%)		
Completion	17 (3.3)	2.1–5.2
Cure, 0 months follow-up	4 (0.8)	0.3–2.0
Cure, 6 months follow-up	7 (1.4)	0.7–2.8
Cure, 12 months follow-up	11 (2.1)	1.2–3.8
Cure, 18 months follow-up	36 (7.0)	5.1– 9.5
Cure, 24 months follow-up	358 (69.5)	65.4–73.3
Cured, reinfection disease	2 (0.4)	0.1–1.4
Non-success ($n = 80$, 15.5%)		
Failure	7 (1.4)	0.7–2.8
Death, first 60 days	14 (2.7)	1.6–4.5
Death, after 60 days	15 (2.9)	1.8–4.7
Default, first 60 days	19 (3.7)	2.4–5.7
Default, after 60 days	21 (4.1)	2.7–6.2
Relapse	4 (0.8)	0.3–2.0

CI = confidence interval.

Time required to complete treatment

Of the 439 patients who completed the prescribed regimen, 50% completed treatment within 272 days (9 months), 75% within 299 days (10 months), 90% within 331 days (11 months), and 95% within 363 days (1 year) (Figure 1). Treatment prolongation was due to extension of the intensive phase among patients with delayed sputum smear conversion. Poor adherence rarely required treatment prolongation, with >90% of patients being at least 95% adherent.

Adverse drug events

Adverse drug events were not systematically recorded, and recording of most events (except for glycosuria) was mostly based on spontaneous reporting by the patient. Vomiting was the most frequently reported adverse event ($n = 111$ patients, 21.6%). Treatment change was required in 12 patients: OFX was substituted for GFX and the treatment extended to 15 months due to diabetes and glycosuria in eight patients, two patients had all drugs temporarily interrupted, and in six patients the KM dose was reduced and stopped in one patient. No failures due to definitive stopping of treatment were declared.

Bacteriologic conversion among patients completing treatment

For a refined assessment of bacteriologic conversion, we excluded 76 patients who died, defaulted, or failed. To ensure the evaluation of the same cohort, only the 217 patients who had both monthly serial culture and microscopy results up to month 4 were included in this subset. Bacteriologic conversion was rapid for culture and lagged for microscopy (Figure 2). At month 2 of treatment, 93% experienced culture conversion, and respectively 73%, 47%, and 27% of patients with scanty/1+ positive, 2+ positive or 3+ positive graded diagnostic sputum microscopy results converted. No relationship was found between the initial grade of microscopy results, smear conversion, and treatment failure or relapse (exact Monte Carlo simulation tests, $P = 0.718$).

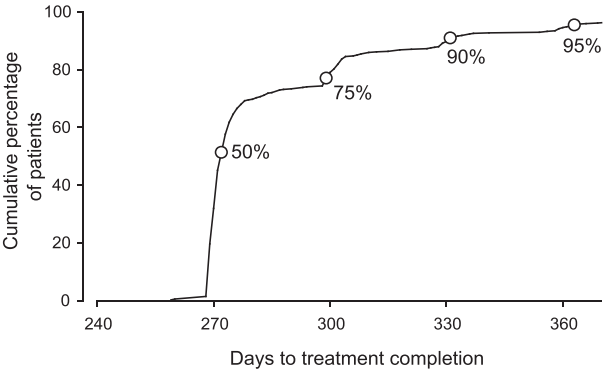

Figure 1 Number of days to treatment completion among the 439 patients who did not end treatment prematurely (due to death, default or treatment failure).

Risk factors for an unfavorable treatment outcome

In univariate analysis (Table 2), patients who were older than the lowest quartile, females (vs. males), and patients with high-level FQ resistance (vs. those with FQ-susceptible TB) had an increased risk of an unfavorable treatment outcome. The unstratified Kaplan-Meier estimate for a programmatically favorable treatment outcome probability among all 515 patients was 84.4% (95% confidence interval [CI] 81.3–87.6). Given that the strongest factor for an unfavorable outcome was high-level FQ resistance, we retained the 501 patients with a known initial FQ DST result. Among the 62 (12.4%) resistant strains, the MIC was determined and dichotomized into 'low-level' (MIC 0.5–1.0 mg/l) and 'high-level' (MIC ⩾2 mg/l) GFX resistance. Six (21%) of the high-level

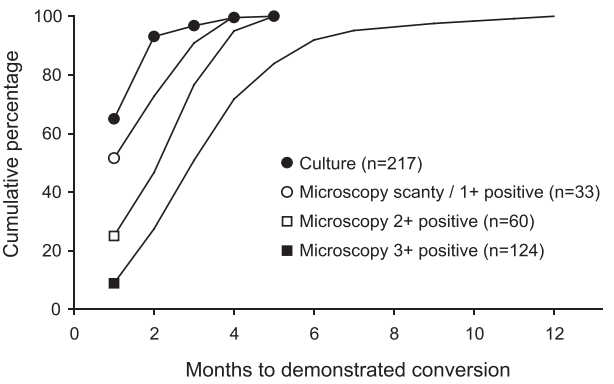

Figure 2 Sputum culture and smear conversion among 217 patients with monthly serial paired culture and microscopy result who neither died, failed nor defaulted. Microscopy results are stratified by diagnostic sputum smear grade.

Table 2 Univariate and multivariate analysis of characteristics of patients with a programmatically favorable outcome vs. those with an unfavorable treatment outcome

	Programmatically unfavorable *n* (%)	Programmatically favorable *n*	Total *n*	Unadjusted	Adjusted (logistic regression)	
				Point OR (95%CI)	Point OR (95%CI)	*P* value
Total	80 (15.5)	435	515			
Age, quartiles, years						
12–22	10 (8.7)	105	115	1	1	
23–30	24 (18.2)	108	132	2.3 (1.1–5.1)	3.8 (1.6–9.4)	0.003
31–42	22 (15.9)	116	138	2.0 (0.90–4.4)	3.6 (1.5–9.0)	0.005
43–76	24 (18.5)	106	130	2.4 (1.1–5.2)	5.0 (2.1–13.1)	0.001
Sex						
Male	48 (13.2)	316	364	1	1	
Female	32 (21.2)	119	151	1.8 (1.1–2.9)	2.8 (1.5–5.1)	0.001
Fluoroquinolone*						
Susceptible	59 (13.4	380	439	1	1	
Low-level resistance†	3 (9.1)	30	33	0.6 (0.2–2.2)	0.91 (0.21–2.8)	0.882
High-level resistance†	15 (51.7)	14	29	6.9 (3.2–15.0)	12.9 (5.0–34.5)	<0.001
Missing	3 (21.4)	11	14	1.9 (0.48–6.5)	3.5 (0.47–20.4)	0.172
Kanamycin*						
Susceptible	78 (15.4)	427	505	1	1	
Resistant	1 (50.0)	1	2	5.5 (0.34–88.5)	1.2 (0.04–34.8)	0.903
Missing	1 (12.5)	7	8	0.78 (0.09–6.5)	0.15 (0.005–2.4)	0.194
Prothionamide*						
Susceptible	63 (16.0)	331	394	1	1	
Resistant	11 (13.3)	72	83	0.80 (0.40–1.6)	0.93 (0.42–1.9)	0.847
Missing	6 (15.8)	32	38	1.0 (0.40–2.5)	1.0 (0.33–2.8)	0.932
Pyrazinamide*						
Susceptible	16 (11.1)	128	144	1	1	
Resistant	18 (17.6)	84	102	1.7 (0.83–3.6)	1.1 (0.47–2.7)	0.783
Missing	46 (17.1)	223	269	1.7 (0.90–3.0)	2.6 (1.3–5.3)	0.006
Extent of radiographic disease						
One lung	9 (11.0)	73	82	1	1	
Bilateral	64 (15.6)	346	410	1.5 (0.71–3.2)	1.7 (0.81–4.2)	0.177
Missing	7 (30.4)	16	23	3.5 (1.2–10.9)	5.4 (1.6–19.1)	0.007

* Drug susceptibility test result of isolate obtained before start of treatment.
† Low-level resistance: minimum inhibitory concentration 0.5–1.0 mg/l; high-level resistance: minimum inhibitory concentration ⩾2 mg/l.
OR = odds ratio; CI = confidence interval.

compared to 22 (67%) of the low-level resistant strains were from patients enrolled before 2008. While the proportion of patients with FQ resistance remained unchanged over the enrollment years ($P = 0.38$), there was a significant increase in high-level resistance among patients with FQ resistance ($P = 0.018$, χ^2 for trend).

We adjusted for age and sex using a Cox proportional hazard model, stratified by FQ resistance. The programmatically favorable outcome probabilities were respectively 87.4%, 90.5% and 51.0% with strains that were respectively fully susceptible, low-level and high-level resistant to fluoroquinolone (Figure 3). The HR of being female was 1.9 (95%CI 1.15–3.1, $P = 0.012$), and for each 1-year increase in age, 1.03 (95%CI 1.01–1.05, $P = 0.0003$). There was no difference in the outcome of patients with low-level FQ-resistant and those with FQ-susceptible TB, while high-level FQ resistance substantially reduced the chance of a successful outcome.

To further isolate factors that may have influenced the probability of an unfavorable bacteriological treatment outcome, we excluded 14 patients without a FQ DST result, 439 with FQ-susceptible TB, 2 who died and 7 who defaulted. Among the remaining 53 patients, we compared 44 patients with a bacteriologically favorable outcome to 9 with a bacteriologically unfavorable outcome (6 failures and 3 relapses). We included age, sex and the initial DST results for KM, PTH and PZA, dichotomized into 'resistant' and 'not demonstrated to be resistant' (Table 3). In the univariate analysis, sex, and high-level FQ and PZA resistance increased the risk of an unfavorable outcome. In the stepwise elimination process of the multivariate model, removal of all factors except for GFX and PZA DST results improved the model, with ORs for an unfavorable bacteriological outcome of high-level vs. low-level FQ resistance of 13.0 (95%CI 1.9–262, $P = 0.025$) and for PZA resistance of 9.2 (95%CI 1.3–187, $P = 0.055$). Eight of the nine unfavorable outcome cases compared to 17/44 favorable, had known PZA resistance.

Acquisition of drug resistance

Of the 11 patients with treatment failure or relapse,

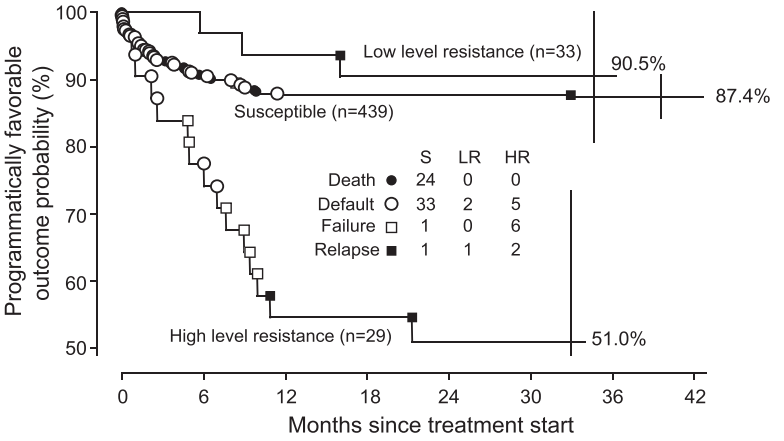

Figure 3 Programmatically favorable treatment outcome probability derived from a Cox's proportional hazard model among 501 patients, stratified by initial fluoroquinolone susceptibility test result, adjusted for age and sex. S = susceptible to ofloxacin and/or GFX at the standard critical concentration; LR = low-level resistance (GFX MIC 0.5–1.0 mg/l); HR = high-level resistance (GFX MIC ⩾2 mg/l); GFX = gatifloxacin; MIC = minimum inhibitory concentration.

two had FQ-susceptible TB at start of treatment and at the time of recurrence. One was a failure case, and was grossly non-adherent during the intensive phase; the second, classified as a relapse, might have been a case of reinfection with a strain identical to that of her sister who died due to advanced MDR-TB shortly before the recurrence was diagnosed. There was thus no evidence of acquisition of FQ resistance.

KM: both patients with initial KM resistance also had initial high-level GFX resistance (primary extensive drug resistance with the same strain as the index case[9]). One of the patients had relapse-free cure up to the 24-month follow-up with the unmodified regimen, while the other patient, who had the same resistance pattern, failed on standard treatment. One patient acquired KM resistance. She initially had high-level GFX-resistant TB that was susceptible to only CFZ and KM.

Other drugs: there was no evidence of acquisition of PZA or PTH resistance; however, PZA sequencing was not repeated for the two patients with FQ-susceptible recurrence. For all other drugs mentioned,

Table 3 Characteristics of patients with a bacteriologically unfavorable outcome (treatment failure or relapse) compared to patients with a bacteriologically favorable outcome. Analysis restricted to patients with tuberculosis due to a strain not fully susceptible to fluoroquinolones and who did not die or default from treatment

	Bacteriologically unfavorable *n* (%)	Bacteriologically favorable* *n*	Total *n*	Unadjusted Point OR (95%CI)	Adjusted (logistic regression) Point OR (95%CI)	*P* value
Total	9 (17.0)	44	53	—		
Age						
Median and above	3 (11.1)	24	27	1		
Below median	6 (23.1)	20	26	2.4 (0.53–10.8)	1.3 (0.18–9.5)	0.817
Sex						
Male	3 (8.1)	34	37	1		
Female	6 (37.5)	10	16	6.8 (1.4–32.2)	1.9 (0.26–14.4)	0.515
Fluoroquinolone						
Low-level resistant*	1 (3.2)	30	31	1		
High-level resistant†	8 (36.4)	14	22	17.1 (2.0–150.7)	14.7 (1.3–607.3)	0.064
Kanamycin						
Not resistant‡	8 (15.7)	43	51	1		
Resistant	1 (50.0)	1	2	5.4 (0.30–95.1)	0.78 (0.01–33.9)	0.892
Prothionamide						
Not resistant	7 (16.7)	35	42	1		
Resistant	2 (18.2)	9	11	1.1 (0.20–6.3)	2.2 (0.13–75.6)	0.588
Pyrazinamide						
Not resistant	1 (3.6)	27	28	1		
Resistant	8 (32.0)	17	25	12.7 (1.5–110.8)	6.9 (0.84–150.3)	0.110

* GFX MIC 0.5–1.0 mg/l.
† GFX MIC ⩾2 mg/l.
‡ Susceptible or not tested.
OR = odds ratio; CI = confidence interval; GFX = gatifloxacin; MIC = minimum inhibitory concentration.

DST results could be compared in strains before and after treatment for all recurrences. Among the entire cohort, only a single instance of acquired drug resistance (to KM) could thus be demonstrated. However, the strain remained susceptible to AMK (*rrs*1402 mutation), and the patient was cured after retreatment based on this drug and bedaquiline, which was also used to cure the patient with primary extensively drug-resistant TB (XDR-TB) who failed the short regimen. Not a single XDR-TB case from the entire cohort thus remains.

DISCUSSION

This analysis covers more than 500 patients treated with the fully standardized '9-month Bangladesh regimen'. The results reported in 2010[2] for some 200 patients have only marginally deteriorated, with a favorable outcome in roughly 85%. It appears that low-level initial FQ resistance had no diminishing influence on the favorable outcome, while high-level resistance did. The increasing ratio of high- to low-level FQ resistance since our first report explains the higher percentage of bacteriologically unfavorable outcomes. With only 1 relapse among patients with initial FQ-susceptible TB (which may have been a case of reinfection), 1 among patients with low-level FQ-resistant TB, and 2 among patients with high-level FQ-resistant TB, it would appear that adjusting the treatment duration based on smear conversion was highly successful. That the excellent results are not due to missing failures and relapses is indirectly demonstrated by the identification of eight bacteriologically unfavorable outcomes among the 29 patients with high-level initial FQ resistance. False-negative cultures due to persevering CFZ deposits appearing in the sputum for several years are also unlikely. The LJ culture medium used inactivates at least 4 mg/l of this drug (unpublished data), and an additional follow-up of the first 2 years' cohorts did not find any additional relapse 5 years after treatment cessation. Even patients with high-level FQ resistance had a 50% chance of a favorable outcome, and the odds improved further if there was no demonstrated PZA resistance. The success of the regimen is based on the core drug GFX, which has shown a very favorable area under the curve to MIC ratio,[10] an indicator that likely best explains why the high dose of GFX employed was able to overcome low-level FQ resistance. A second companion drug in addition to PZA was CFZ, which has recently been found to have superb relapse-preventing properties in murine models,[11] and a predictor of survival in the treatment of extensive drug resistance in South Africa.[12]

The 9-month regimen was well tolerated, and serious events requiring a regimen change were rare. Despite the shortening of the duration of PTH intake, one fifth of patients still reported vomiting. Although KM was administered for only half the WHO-recommended duration,[13] and hearing loss was clinically infrequent, the drug remains a matter of potential concern. Dysglycemia proved of minor relevance in this young, underweight population.[14]

While clinical trials test efficacy under controlled conditions, our observational study provides information on in-the-field effectiveness under routine service conditions. Nevertheless, it seems inconceivable that patients who actually failed treatment would not have shown up as relapses during the rigorous follow-up period that covered $\geqslant 2$ years in $>80\%$ of the patients. Given the large number of patients and the close to 10 years' experience, the underlying efficacy of this regimen is now firmly established. What needs to be further demonstrated is the extent to which these results hold in populations with HIV infection, a complication assumed to be absent among our patients, or in settings with a high prevalence of resistance to second-line injectable drugs.

Conflict of interest: none declared.

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RESUME

CONTEXTE : Programme de lutte contre la tuberculose (TB), projets de la Fondation Damien, Bangladesh.

OBJECTIF : Résumer les résultats du premier traitement de la TB multirésistante avec un protocole standardisé court de 9 mois et les facteurs déterminant ces résultats.

SCHÉMA : Etude d'observation prospective. Protocole basé sur la gatifloxacine (GFX), sous observation directe, avec le plus souvent une hospitalisation initiale. La phase intensive d'au moins 4 mois était étendue jusqu'à conversion du frottis de crachats. Les patients ont été suivis par culture jusqu'à 2 ans après l'achèvement du traitement.

RÉSULTATS : Sur 515 patients enrôlés avec succès de 2005 à 2011 qui répondaient aux critères d'inclusion de l'analyse, 84,4% ont eu un résultat bactériologique favorable. Seulement la moitié des patients a pu terminer son traitement en 9 mois — les autres patients ayant une atteinte étendue avec une conversion de frottis retardée — mais 95% l'ont achevé en 12 mois. Onze patients ont eu un échec du traitement ou ont rechuté (93,1% des 435 traités avec succès ont bénéficié d'au moins 12 mois de suivi post-traitement). Le facteur de risque le plus important pour un résultat bactériologique défavorable était un niveau élevé de résistance à la fluoroquinolone (FQ), particulièrement quand elle était aggravée par une résistance initiale au pyrazinamide (PZA). Un niveau faible de résistance à la FQ n'avait pas d'effet négatif sur l'issue du traitement. Une amplification de la pharmacorésistance est survenue une seule fois chez un patient dont la souche était initialement sensible seulement à la kanamycine et à la clofazimine.

CONCLUSION : L'excellent résultat du protocole du Bangladesh pourrait être largement maintenu. Les échecs bactériologiques du traitement et les rechutes ont été rares, sauf parmi les patients ayant une résistance élevée à la GFX, notamment en présence de résistance au PZA.

RESUMEN

MARCO DE REFERENCIA: El programa contra la tuberculosis (TB) de la Fundación Damien en Bangladesh.

OBJETIVO: Compendiar los desenlaces terapéuticos de un primer tratamiento de la TB multidrogorresistente con un régimen normalizado como mínimo durante 9 meses y definir los factores que determinan los desenlaces.

MÉTODO: Fue este un estudio prospectivo descriptivo. El tratamiento consistió en un régimen directamente observado basado en gatifloxacino (GFX), en la mayoría de los casos con una hospitalización inicial. La fase intensiva del tratamiento tuvo una duración mínima de 4 meses, la cual se prolongó hasta la conversión de la baciloscopia del esputo. Se practicaron cultivos de seguimiento hasta 2 años después de la compleción del tratamiento.

RESULTADOS: De los 515 pacientes que cumplían con los criterios de inclusión y se incorporaron sucesivamente al estudio entre el 2005 y el 2011, el 84,4% presentó un desenlace bacteriológico favorable. Debido a una enfermedad extensa con retraso en la conversión del esputo, solo la mitad de los pacientes completó el tratamiento en 9 meses, pero el 95% lo había logrado a los 12 meses. Se presentaron 11 fracasos o recaídas (93,1% de los 435 pacientes con un tratamiento exitoso completaron como mínimo 12 meses de seguimiento posterapéutico). El principal factor de riesgo de presentar un desenlace bacteriológico desfavorable fue la resistencia de alto grado a las fluoroquinolonas (FQ), sobre todo cuando se complicó con una resistencia inicial a pirazinamida (PZA). La resistencia de bajo grado a las FQ no produjo un efecto desfavorable en el desenlace terapéutico. Solo se observó amplificación de la farmacorresistencia en un paciente, cuya cepa inicialmente era sensible solo a kanamicina y clofazimina.

CONCLUSIÓN: Es muy posible mantener los excelentes desenlaces del régimen de Bangladesh. Los fracasos terapéuticos y las recaídas definidos bacteriológicamente fueron raros, excepto en los pacientes con una resistencia de alto grado a GFX, sobre todo cuando coexistía una resistencia a PZA.