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Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries

A. Trébucq,* V. Schwoebel,* Z. Kashongwe,† A. Bakayoko,‡ C. Kuaban,§ J. Noeske,¶ S. Hassane,# B. Souleymane,# A. Piubello,# F. Ciza,** V. Fikouma,†† M. Gasana,‡‡ M. Ouedraogo,§§ M. Gninafon,¶¶ A. Van Deun,## D. M. Cirillo,*** K. G. Koura,*†††‡‡‡ H. L. Rieder§§§

*International Union Against Tuberculosis and Lung Disease, Paris, France; †Bukavu University, Bukavu, Democratic Republic of Congo; ‡Centre hospitalier universitaire (CHU) Treichville, Abidjan, Côte d'Ivoire; §Bamenda University, Bamenda, ¶Independent Consultant, Yaoundé, Cameroon; #Action Damien, Niamey, Niger; **Action Damien, Bujumbura, Burundi; ††Bangui University, Bangui, Central African Republic; ‡‡National Tuberculosis Programme, Kigali, Rwanda; §§CHU Yo, Ouagadougou, Burkina-Faso; ¶¶National Tuberculosis Programme, Cotonou, Benin; ##Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium; ***Emerging Bacterial Pathogens, Istituto di Ricovero e Cura a Carattere Scientifico San Raffaele Scientific Institute, Milan, Italy; †††Unité mixte de Recherche 216, Institut de Recherche pour le Développement, Paris, ‡‡‡Communauté d'Universités et Etablissements Sorbonne Paris Cité, Université Paris Descartes, Faculté des Sciences Pharmaceutiques et Biologiques, Paris, France; §§§Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland

SUMMARY

SETTING: Nine countries in West and Central Africa.

OBJECTIVE: To assess outcomes and adverse drug events of a standardised 9-month treatment regimen for multidrug-resistant tuberculosis (MDR-TB) among patients never previously treated with second-line drugs.

DESIGN: Prospective observational study of MDR-TB patients treated with a standardised 9-month regimen including moxifloxacin, clofazimine, ethambutol (EMB) and pyrazinamide (PZA) throughout, supplemented by kanamycin, prothionamide and high-dose isoniazid during an intensive phase of a minimum of 4 to a maximum of 6 months.

RESULTS: Among the 1006 MDR-TB patients included in the study, 200 (19.9%) were infected with the human immunodeficiency virus (HIV). Outcomes were as follows: 728 (72.4%) cured, 93 (9.2%) treatment completed (81.6% success), 59 (5.9%) failures, 78 (7.8%) deaths, 48 (4.8%) lost to follow-up. The proportion of deaths was much higher among HIV-infected patients (19.0% vs. 5.0%). Treatment success did not differ by HIV status among survivors. Fluoroquinolone resistance was the main cause of failure, while resistance to PZA, ethionamide or EMB did not influence bacteriological outcome. The most important adverse drug event was hearing impairment (11.4% severe deterioration after 4 months).

CONCLUSIONS: The study results support the use of the short regimen recently recommended by the World Health Organization. Its high level of success even among HIV-positive patients promises substantial improvements in TB control.

KEY WORDS: tuberculosis; multidrug resistance; treatment; short-course; cohort studies

THE EMERGENCE OF RIFAMPICIN (RMP) resistance has created increasing constraints on effective tuberculosis (TB) control. While the 6-month regimen based on RMP and isoniazid (INH) throughout remains the most effective and efficacious standard treatment for RMP-susceptible TB, treatment success for RMP- and INH-resistant cases (i.e., multidrug-resistant TB [MDR-TB]) was only around 50%,[1] further compounded by an excess frequency of relapses.[2] This led the World Health Organization (WHO) to recommend 18 months of treatment beyond culture conversion in its 2006 MDR-TB treatment guidelines.[3] Subsequent updates in 2008[4] and 2011 proposed similar recommendations,[5] but the treatment success rate with this type of regimen remained poor, averaging at about 50%.[6,7]

In 2010, a study from Bangladesh showed a 89% relapse-free success rate using a regimen that lasted only a minimum of 9 months.[8] This encouraged the National Tuberculosis Programmes (NTPs) of Benin, Niger and Cameroon to test a similar 12-month regimen, resulting in 89% success.[9,10] Reassured by these results, nine countries in West and Central Africa—Benin, Burkina Faso, Burundi, Cameroon, the Central Africa Republic (CAR), Côte d'Ivoire, the Democratic Republic of Congo (DRC), Niger and Rwanda—decided to participate in a collaborative observational study conducted by the International

Correspondence to: Arnaud Trébucq, International Union Against Tuberculosis and Lung Disease, 68 blvd Saint Michel, 75006 Paris, France. e-mail: atrebucq@theunion.org
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Table 1 Clinical, bacteriological and other laboratory examinations at baseline and during treatment*

	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 15	Month 21
Clinical evaluation	x	x	x	x	x	x	x	x	x	x	x	x
Sputum smear	x	x	x	x	xx	x(x)	x(x)	x	x	xx	x	x
Sputum culture	x	x	x	x	x	x	x	x	x	x	x	x
Audiogram	x				x							
Chest X-ray	x									x		
Haemoglobin/platelet/ white blood count	x											
Serum creatinine	x	x	x	x	x							
Serum potassium	x	x	x	x	x							
Thyroid stimulating hormone	x						x					
Serum liver enzymes	x	x	x	x	x		x					
ECG	xx											
Pregnancy test (female)	x											
HIV test	x											

* x(x) = test performed if the smear of the preceding month was positive; xx = test performed twice.
ECG = electrocardiogram; HIV = human immunodeficiency virus.

Union Against Tuberculosis and Lung Disease (The Union; Paris, France) using the 9-month Bangladesh regimen.

MATERIAL AND METHODS

Ethics considerations

The study protocol was approved by The Union Ethics Advisory Group, Paris, France, adapted to each country and cleared by each country's ethics committee; patients provided informed consent.

The study was organised within the framework of the NTPs, without hiring additional personnel or providing incentives for health workers or patients. Treatment was provided free of charge.

Study population

To be eligible for inclusion, patients had to be RMP-resistant on genotypic or phenotypic drug susceptibility testing (DST). For genotypic DST, Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) or line-probe assays were used. INH susceptibility was not a criterion for exclusion. DST was performed almost exclusively among patients who had already been treated for TB (failure, relapse, return after loss to follow-up), and less frequently among new cases. Any patient diagnosed with RMP-resistant TB (RR-TB) in a country was potentially eligible, except in DRC and Côte d'Ivoire, where the study area was restricted to the capital city.

For inclusion in the study patients had to be aged $\geqslant$18 years, agree not to change their place of residence for the duration of treatment and sign a consent form. Patients known to have previously been treated with second-line drugs, to have pre-extensively drug-resistant TB (pre-XDR-TB), i.e., resistance to fluoroquinolones (FQs) or any second-line injectable drug (SLID), or XDR-TB strains (i.e., resistance to both FQs and SLIDs) before enrolment, pregnant women, patients with known intolerance to a study drug, or with a pre-treatment electrocardiogram (ECG) showing a QT interval >500 ms, were not eligible.

Treatment regimen

The intensive phase of treatment consisted of kanamycin (KM), clofazimine (CFZ), normal-dose moxifloxacin (MFX), ethambutol (EMB), high-dose INH (INHh), pyrazinamide (PZA) and prothionamide (PTO) administered daily for 4 months. If the sputum smear examination remained positive at 4 months, the intensive phase was extended by a maximum of 2 months. The continuation phase consisted of normal-dose MFX, EMB, PZA and CFZ administered daily for a fixed period of 5 months. The study regimen therefore differed from the original 'Bangladesh regimen' in that normal-dose MFX was used instead of high-dose gatifloxacin. For those patients who were excluded from the study or who declined to participate, standard treatment according to NTP guidelines or WHO guidelines was recommended.[5]

Patient management

Treatment was daily and directly observed by a health worker throughout the entire duration. Patients were hospitalised, at least during the intensive phase, in Benin, CAR, Burkina Faso, Rwanda, Burundi and Cameroon (383 patients). Ambulatory treatment was provided from the outset in DRC, Côte d'Ivoire and Niger (623 patients). Where possible, food was procured for hospitalised patients and money for transport was given to those on ambulatory treatment. Provision of such enablers depended on the regularity of funding by NTP donors.

Specially prepared patient cards facilitated documentation of patient and disease characteristics, treatment progress, test results (Table 1), adverse events (AEs) and follow-up of drug intake. A portable ECG machine and a portable audiometer were

procured for each team in charge of treatment; each patient underwent an ECG before inclusion and 1 week after initiation of treatment. The team recorded any AE on this card every month, or explicitly specified if there was none.

Culture and drug susceptibility testing

Two supranational reference laboratories (SRLs) were involved in the study: in Milan for Côte d'Ivoire and Burkina Faso, and in Antwerp for the seven remaining countries. A specimen of each initial positive culture and of each positive culture after 6 months of treatment were sent to the SRL in charge, where DST was performed phenotypically and/or genotypically (second-line line-probe assay and whole genome sequencing) for RMP, FQs, SLIDs, INH and PTO (*inh*A mutation), only genotypically for PZA (*pnc*A mutations) and only phenotypically for EMB. WHO-recommended critical concentrations were followed for phenotypic testing.[11]

In case of discordance, the SRL result overrode that of the national laboratory, and a phenotypic result at the SRL overrode a molecular result (except for RMP, for which a genotypic result defined inclusion).[12] Altogether, strains from only 585 patients (58%) could be tested at the SRL because airline companies refused to transport any biological specimen with possible pathogenic micro-organisms due to the 2014–2015 Ebola epidemic.

For FQs, a distinction was made between low- (up to and including 2 mg/l) and high-level resistance to ofloxacin (8 mg/l) using the phenotypic method (agar proportion) or, if only molecular tests were available, by identification of specific mutations.[13]

At country level, RR-TB was mostly determined genotypically, while other DST was performed mostly phenotypically. Where FQ or SLID resistance was identified after treatment initiation, the patient was not excluded from treatment, nor was the regimen modified.

Adverse events

AEs, including biological abnormalities detected during routine examinations (Table 1), were recorded monthly and graded using the ANRS (*Agence Nationale de Recherche sur le SIDA*) scale, which includes four grades, ranging from Grade 1 (mild problem without the need for medical intervention) to Grade 4, severe AE (life-threatening or permanently disabling event).[14]

Hearing loss was measured in decibels (dB) using pure tone audiometry. Weighted average hearing loss (WAHL) was calculated using mean hearing loss in both ears across 500 to 4000 Hz frequencies using the following formula: WAHL = hearing loss ('better' ear)*0.7 + hearing loss ('worse' ear)*0.3. The following WAHL grades were used: 0 (normal) <20 dB; 1 (mild): 21–40 dB; 2 (moderate): 41–70 dB; 3 (severe): 71–90 dB; 4 (very severe) >90 dB.[15] Severe deterioration of hearing was defined as a decrease of ⩾2 WAHL grades measured after 4 months of treatment compared to baseline.

Definitions

The latest WHO treatment outcome definitions were used,[16] except for 'cured' and 'treatment failed' because of the short treatment duration. Cure was defined as treatment completed without evidence of failure and ⩾3 consecutive negative cultures taken at least 30 days apart; treatment failed (bacteriological failure) was defined as treatment terminated due to a positive culture after 6 months of treatment (except when preceded by 1 negative and followed by at least 2 negative cultures, i.e., 'isolated positive culture'). Treatment success was defined as the sum of cured and treatment completed. Unsuccessful treatment included death, failure and loss to follow-up.

Body mass index (BMI) groups were defined as follows: <16.0 kg/m^2 severe thinness, 16.0–16.9 moderate thinness, 17.0–18.4 mild thinness, 18.5–24.9 normal, ⩾25.00 overweight; underweight was defined as a BMI of <18.5 kg/m^2.[17]

An analysis of relapses in this study has been deferred until a future publication, when final, validated data have become available.

Data management and analysis

Data were captured in an EpiData Entry database (version 3.1; EpiData Association, Odense, Denmark; http://www.epidata.dk). Data were double-entered and any discordance was resolved by verifying against the original paper record. Analyses were performed using EpiData Analysis Version 2.2.3.187), R, version 3.4 (R Computing, Vienna, Austria; http://www.r-project.org) and Stata, version 14.2 (StataCorp, College Station, TX, USA, 2015). We used univariate and multivariate statistics to determine point estimates, 95% confidence intervals (95%CIs), relative risks (RR), adjusted odds ratios (aORs), *P* values where appropriate, and the Kaplan-Meier survival estimator. We relied largely on χ^2 statistics for cross-tabulations, and occasionally (for multilevel ordinal data) we further evaluated the result obtained using the non-parametric Kruskal-Wallis test. After testing for multicollinearity between variables of interest, multiple logistic regression analysis was conducted using stepwise backward elimination.

RESULTS

During the study period, 1769 patients were diagnosed with RR-TB in the nine participating countries. Among these, 316 (18%) were not eligible (38% had been previously treated with SLIDs, 22% were children, 2% were pregnant women, 1% had known

Table 2 Treatment success (completion and cure) versus non-success (all other outcomes) and patient characteristics

	Non-success *n*	Success *n* (%)	Total *n* (% col)
Total	185	821 (81.6)	1006 (100.0)
Country			
Burkina Faso	5	29 (85.3)	34 (3.4)
Burundi	5	56 (91.8)	61 (6.1)
Benin	4	25 (86.2)	29 (2.9)
Democratic Republic of Congo	59	242 (80.4)	301 (29.9)
Central Africa Rep	9	36 (80.0)	45 (4.5)
Cote d'Ivoire	53	207 (79.6)	260 (25.8)
Cameroon	29	147 (83.5)	176 (17.5)
Niger	14	48 (77.4)	62 (6.2)
Rwanda	7	31 (81.6)	38 (3.8)
Sex			
Female	64	275 (81.1)	339 (33.7)
Male	121	546 (81.9)	667 (66.3)
Age groups, years			
18–24	34	152 (81.7)	186 (18.5)
25–34	66	285 (81.2)	351 (34.9)
35–44	42	227 (84.4)	269 (26.7)
45–54	24	117 (83.0)	141 (14.0)
55–64	11	26 (70.3)	37 (3.7)
⩾65	8	14 (63.6)	22 (2.2)
HIV			
Negative	129	677 (84.0)	806 (80.1)
Positive	56	144 (72.0)	200 (19.9)
BMI, kg/m^2			
Severe thinness <16.0	55	156 (73.9)	211 (21.1)
Moderate thinness 16.0–16.9	30	104 (77.6)	134 (13.4)
Mild thinness 17.0–18.4	40	179 (81.7)	219 (21.9)
Normal 18.5–24.9	55	363 (86.8)	418 (41.8)
Overweight ⩾25.0	3	14 (82.4)	17 (1.7)
Subtotal with known BMI	183	816 (81.7)	999
Lung lesions on chest X-ray*			
1 zone	10	62 (86.1)	72 (7.6)
2–3 zones	43	216 (83.4)	259 (27.3)
4–6 zones	119	498 (80.7)	617 (65.1)
Subtotal with known extent on X-ray	172	776 (81.9)	948
Category of patients			
New	26	108 (80.6)	134 (13.3)
First relapse	29	113 (79.6)	142 (14.1)
Several relapses	15	79 (84.0)	94 (9.3)
First failure	62	220 (78.0)	282 (28.0)
Several failures	45	262 (85.3)	307 (30.5)
Return after loss to follow-up	7	18 (72.0)	25 (2.5)
Other	1	21 (95.5)	22 (2.2)

* Each lung is divided into three zones (superior, middle, inferior) by dividing the space between the apex and the hemidiaphragm into three. The extent of lung lesions is defined as the number of zones affected among these six zones.
HIV = human immunodeficiency virus; BMI = body mass index.

XDR-TB, 8% of the patients had social problems, 2% refused to sign the consent form, 29% for unknown reasons but none due to a QT interval >500 ms or known drug intolerance); 426 (24%) did not initiate second-line treatment within the study period (22% died, 50% were untraceable after the diagnosis, 10% were referred to a jurisdiction outside the study catchment area, 5% refused any treatment, 13% for another or unknown reason). A total of 1027 patients (58.1% of those diagnosed) were eligible, accepted to participate and were enrolled between 1 January 2013 and 31 March 2015. Of these, 21 were subsequently excluded because RR-TB was not confirmed. A final total of 1006 patients were eligible for analysis.

The baseline characteristics of the patients with proportions of treatment success in each category are given in Table 2. The male-to-female ratio was 2.0 and the median age was 34 years (range 18–80). All patients were tested for the human immunodeficiency virus (HIV); 200 (19.9%) were positive. Patients were in poor clinical condition: 56.5% were underweight and 21.1% had severe thinness. Radiographically, 65.1% of the patients had extensive lung lesions (more than half of the lungs affected). Most of the patients had previously been treated with first-line anti-tuberculosis drugs, and only 13.3% had not.

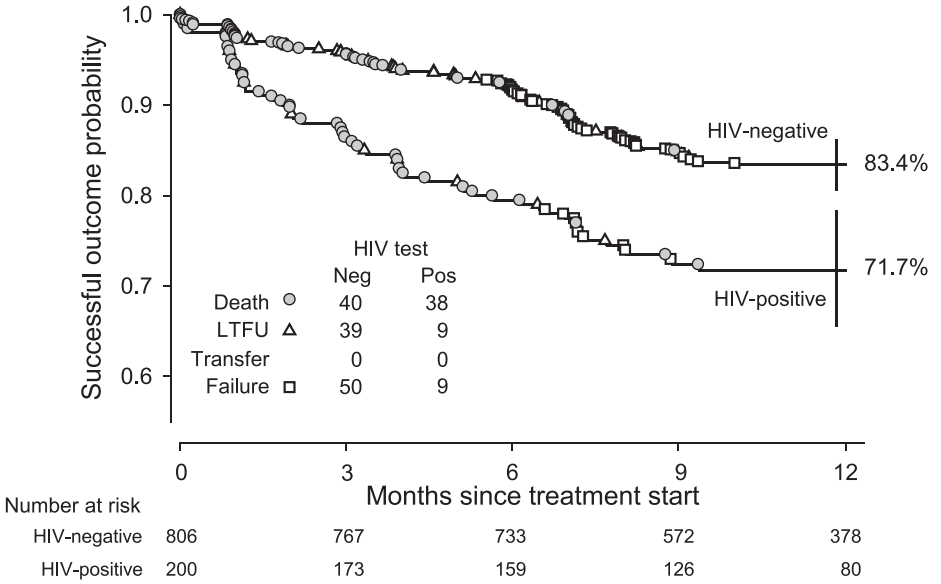

Figure Kaplan-Meyer probability analysis of successful MDR-TB treatment outcome.

Treatment outcomes

In all, 728 (72.4%) patients were declared cured, and 93 (9.2%) treatment completed, giving a success rate of 81.6%. There were 59 (5.9%) failures, 78 (7.8%) patients died and 48 (4.8%) were lost to follow-up.

Treatment success was not significantly different between patients who were initially hospitalised (84.6%) and those treated in ambulatory care from the outset (79.8%). Treatment success was lower in the case of severe thinness due to the increased frequency of death, but did not differ significantly according to sex, age, category of patient and extent of pulmonary lesions.

In Kaplan-Meier survival analysis, patients were stratified by HIV infection. The probability of a successful treatment outcome was lower among HIV-positive than among HIV-negative patients (71.7%, 95%CI 65.6–78.3 vs. 83.4%, 95%CI 80.7–86.1; $P < 0.0001$) (Figure). This was due to the high proportion of deaths among HIV-infected patients (19.0% vs. 5.0%, $P < 0.001$). However, among those patients who survived, treatment success did not differ by HIV status (88.4% vs. 88.9%). The median time to death was not significantly different between HIV-negative and HIV-positive patients (56 days vs. 64 days). Most HIV-infected patients (88.8%) underwent antiretroviral therapy (ART); the proportion who died was similar (18.6% vs. 19.0%), irrespective of whether or not they were on ART.

Among the 999 patients with information on BMI, being underweight was an important risk factor for death among both HIV-infected (29.1% vs. 6.3%; RR 4.6, 95%CI 2.0–10.6) and HIV-negative patients (6.7% vs. 2.6%; RR 2.5, 95%CI 1.2–5.3). The risk of bacteriological failure ($n = 59$) among all patients did not differ significantly by sex, age, HIV status, BMI or extent of lung lesions.

Treatment outcome according to initial drug susceptibility

Overall success differed according to initial FQ susceptibility: 82.0% (468/571) in susceptible and 59.3% (16/27) in resistant strains. Treatment success was higher among those with low-level resistance (6/9, 66.7%) than in those with high-level resistance (10/18, 55.6%), but the difference was not significant (Table 3). Success was barely affected by initial susceptibility to INH, PZA, PTO or EMB. For SLIDs, the success rate was higher in susceptible than in resistant strains (469/580, 80.9% vs. 11/15, 73.3%), but the difference was not statistically significant.

We found no association between drug resistance and loss to follow-up or death.

The risk of bacteriological failure among all patients was significantly higher among patients with initial resistance to FQs (37.0% vs. 5.4%; RR 7.0, 95%CI 3.8–12.8), to INH (6.8% vs. 1.0%; RR 6.8, 95%CI 0.95–49.0) and to PTO (10.4% vs. 2.6%; RR 4, 95%CI 0.92–17.0). It did not differ significantly according to resistance to SLIDs, EMB or PZA.

In multiple logistic regression analysis conducted among patients with treatment success vs. bacteriological failures (excluding deaths and loss to follow-up) and taking into account HIV, age, sex and drug resistance (to FLQ, INH, PTO and PZA), only resistance to FQs (adjusted odds ratio [aOR] 10.0, 95%CI 4.1–24.3) remained significantly associated with risk of failure ($P < 0.001$) and association with INH resistance (aOR 5.7, 95%CI 0.8–42.9) was of borderline significance ($P = 0.09$).

Table 3 Success and bacteriological failure according to initial drug susceptibility among patients with DST results

	Patients with DST result	Success			Bacteriological failure		
	n	*n* (%)	RR (95%CI)*	*P* value	*n* (%)	RR (95%CI)*	*P* value
Isoniazid							
Tested	658			0.079			0.024
Susceptible	100	88 (88.0)	1		1 (1.0)	1	
Resistant	558	450 (80.6)	0.92 (0.84–1.00)		38 (6.8)	6.8 (0.95–49.0)	
Fluoroquinolone							
Tested	598			0.011			$<10^{-4}$
Susceptible	571	468 (82.0)	1		31 (5.4)	1	
Low-level resistant	9	6 (66.7)	0.81 (0.51–1.3)		2 (22.2)	4.1 (1.2–14.6)	
High-level resistant	18	10 (55.6)	0.68 (0.45–1.03)		8 (44.4)	8.2 (4.4–15.2)	
Second-line injectables							
Tested	595			0.466			0.932
Susceptible	580	469 (80.9)	1		42 (7.2)	1	
Resistant	15	11 (73.3)	0.91 (0.67–1.2)		1 (6.7)	0.92 (0.14–6.3)	
Pyrazinamide							
Tested	375			0.502			0.141
Susceptible	182	144 (79.1)	1		9 (4.9)	1	
Resistant	193	158 (81.9)	1.03 (0.94–1.1)		17 (8.8)	1.8 (0.81–3.9)	
Ethambutol							
Tested	101			0.329			0.291
Susceptible	29	24 (82.8)	1		1 (3.4)	1	
Resistant	72	53 (73.6)	0.89 (0.72–1.1)		7 (9.7)	2.8 (0.36–21.9)	
Prothionamide							
Tested	201			0.201			0.042
Susceptible	76	63 (82.9)	1		2 (2.6)	1	
Resistant	125	94 (75.2)	0.91 (0.79–1.05)		13 (10.4)	4 (0.92–17.0)	

* RR for success or failure among those with a DST result.
DST = drug susceptibility testing; RR = relative risk; CI = confidence interval.

Amplification of resistance

Of the 570 patients with initial FQ susceptibility, 8 (1.4%) acquired high-level FQ resistance. All had initial INH resistance, one was also SLID resistant and four were PZA-resistant; only one patient was HIV-positive. Of the nine patients with initial low-level FQ resistance, two acquired amplification to high-level resistance.

Six patients had resistance amplification for SLIDs; all strains were initially resistant to INH, four to PZA and three to FQs.

One patient acquired resistance to PZA (1/182, 0.5%). There was no detected amplification of resistance to INH.

Adverse events

Clinical examinations were performed monthly and biological examinations (serum liver enzymes, creatinine, etc.) were done as scheduled (Table 1) among >80% of patients. An AE (or biological abnormality) was reported in 89.2% of the patients (Table 4). The most severe AE recorded during treatment was Grade 1 or 2 for most patients (78.5%); 71 (7.1%) had Grade 3 AE and 36 (3.6%) had Grade 4 AE.

Gastro-intestinal disorders were the most frequent complaint (57.1%), and occurred within the first 2 months in 75% of the patients. These were generally mild, except in two patients who had a Grade 4 AE; PTO had to be stopped after 55 days in only one patient. Hepatic, neurological, osteoarticular and renal disorders affected respectively 48.8%, 26.9%, 18.2% and 15.7% of the patients, but were graded 3 or 4 in less than 0.5% (Table 4).

The most frequent serious AE was hearing loss, with Grade 3 or 4 WAHL (>70 dB) in 71 (7.1%) patients in the total cohort; only 1% of the patients

Table 4 Distribution of patients according to the most severe AE or biological abnormality recorded during treatment for multidrug-resistant tuberculosis by grade of severity

Type	No AE *n* (%)	Grade 1 *n* (%)	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)
Any type	109 (10.8)	510 (50.7)	280 (27.8)	71 (7.1)	36 (3.6)
Gastro-intestinal	432 (42.9)	444 (44.1)	126 (12.5)	2 (0.2)	2 (0.2)
Hepatic	515 (51.2)	344 (34.2)	117 (11.6)	25 (2.5)	5 (0.5)
Neurological	735 (73.1)	208 (20.7)	58 (5.8)	4 (0.4)	1 (0.1)
Osteoarticular	823 (81.8)	142 (14.1)	41 (4.1)	0 (0)	0 (0)
Renal	848 (84.3)	127 (12.6)	28 (2.8)	1 (0.1)	2 (0.2)
Hearing loss	560 (55.7)	302 (30.0)	73 (7.3)	45 (4.5)	26 (2.6)

AE = adverse event.

already had Grade >2 WAHL at baseline. Of the 491 patients with audiometry results available at both month 0 and month 4 of normal hearing or Grade ⩽2 WAHL at baseline, 56 (11.4%) had severe hearing deterioration at month 4. This deterioration was not significantly associated with previous anti-tuberculosis treatment, but was much more frequent in older patients (fourth quartile ⩾42 years 23.6% vs. 7.1%; RR 3.3, 95%CI 2.0–5.4) and in HIV-positive than in HIV-negative patients (23.6% vs. 8.7%; RR 2.7, 95%CI 1.7–4.4).

Five patients suffered from Grade 4 hepatic disorder: one died, the remaining four were cured. Two patients had Grade 4 renal disorder, and one died. One patient had Grade 4 neurological complaint, and one had self-limited toxic epidermal necrolysis: both were cured.

An ECG was performed at treatment initiation in 98% of the patients, and after 1 week of treatment in 78%. No cardiological problem above Grade 2 was reported. A QT interval >500 ms (529) was reported at treatment initiation in one patient who, by error, was not excluded; he still had >500 ms QT after 1 week and was cured. A QT interval >500 ms after 1 week was reported for three other patients, whose treatment was not stopped: 2 were cured and 1 died of unknown causes.

DISCUSSION

The 82% success rate in this study approaches the results obtained in Bangladesh (85%) (although relapses have not yet been ascertained),[18] Cameroon (89%)[9] and Niger (89%),[10] where regimens modelled on the 'Bangladesh regimen' have been evaluated. These results are substantially superior to the 50% success rate reported with the longer WHO-recommended regimens.[6,7] The role of each individual drug and their interaction in the 9-month regimen remains unknown, but it seems likely that the major contribution lies in the high efficacy and sterilising power of fourth-generation FQs[19,20] and possibly CFZ;[21] furthermore, fewer patients abandon treatment prematurely, likely because it is shorter and better tolerated.

The regimen was also effective in HIV-infected patients: while death was substantially more frequent among such patients, the regimen proved microbiologically equally efficacious among those who survived.

Few factors other than HIV infection were identified as being likely to adversely affect treatment outcomes. These notably included low BMI, large radiographic extent of pulmonary lesions and older age. All of these increased the risk of death independently of HIV status, but not did not affect the microbiological effectiveness of the regimen.

The strongest risk factor for unsuccessful treatment and failure was FQ resistance. It was not possible to test all strains against each drug, due to a large extent to the difficulty in transporting specimens in the wake of the Ebola epidemic, but this is unlikely to have introduced selection bias. A lower success rate due to more frequent failures in patients with FQ resistance was also observed in Bangladesh, Cameroon and Niger. However, failures were more frequent in our study (5.9%) than in Bangladesh (1.4%) or in Niger (no failure among 65 patients), where high-dose gatifloxacin was used. Unlike in Bangladesh, the frequency of failure was higher not only for high-level but also for low-level FQ resistance. Furthermore, we had eight cases (1.4%) with acquired high-level FQ resistance in our study, a substantial difference from the single case documented in Bangladesh.[18] Although this has yet to be proven, a case for systematic use of high-dose FQ can likely be made.

As resistance to SLIDs was very rare ($n = 14$) among those with a result, an interpretation of its effects would not be meaningful. Most of the strains tested were resistant to INH (85%), and success was similar regardless of DST pattern. This is consistent with the effectiveness of high-dose INH (10 mg/kg) used in the regimen. The failure rate appeared to be somewhat higher in the case of INH resistance and independently of FQ resistance. This may be partly due to high-level INH resistance, but insufficient data precluded outcome analysis by INH resistance level.

The higher (non-significant) failure rates in patients with PZA or PTO resistance are likely due to the fact that these patients had a much higher probability of harbouring FQ-resistant strains, as was the case in Bangladesh. Indeed, when FQ resistance was taken into account in multivariate analysis, resistance to PZA, EMB or PTO was not found to be independently associated with treatment outcomes. In its latest guidelines, the WHO recommended not to use the 9-month regimen if resistance to one of these three drugs was proven or highly suspected.[22] Recent studies have shown that if these recommendations were followed, in some settings fewer than 5% of cases would be eligible for the short regimen.[23,24] PZA resistance identified by molecular testing is commonly around 50% among MDR-TB cases in various settings;[25,26] similarly, in our study, it was 51%. The restrictions imposed on the indication for the short-course MDR-TB regimen among patients with an FQ-susceptible strain are not supported by our data, and the indication for this regimen could be substantially larger than is currently proposed.[27]

The regimen was generally well tolerated. Very severe AEs were rare (1%, not including hearing loss). The combination of MFX and CFZ is suspected of inducing QT prolongation,[28,29] and we identified three patients with QT prolongation (two were cured, and one died due to unknown causes). The frequent gastric disorders reported in the early months of

treatment were likely due to PTO, and can be reduced by appropriate measures, such as by taking a light meal before drug intake. The most serious problem was hearing loss,[30] which was frequent despite halving the duration of the intensive phase compared to some other WHO-approved regimens. HIV-infected patients in particular experienced hearing loss for reasons not fully understood. Our comprehensive observations reinforce the recommendation to closely monitor hearing during treatment and to develop further research into anti-tuberculosis treatment regimens that do not require the inclusion of aminoglycosides or polypeptides.

The limitations of our study are mainly related to its observational nature. Because the study began in 2013 when screening and management of drug-resistant TB was in an early development phase in most countries, a backlog of chronic patients may have existed. The resulting selection bias is likely to be small, however, as all RR-TB patients diagnosed in the nine participating countries were assessed consecutively for eligibility during the enrolment period. During the study period, 24% of the patients diagnosed with RR-TB did not initiate second-line treatment, and among these at least 50% were untraceable. Although we cannot exclude some selection bias, such high figures are in fact unfortunately quite common and are not specific to our study. In its 2014 global tuberculosis report, the WHO estimated that 29% of diagnosed MDR-TB cases did not begin treatment.[31] Similarly, for 29% of the 316 patients who were ineligible for this study, we were not able to record the reason. Not all monthly cultures could be obtained everywhere, and the relative frequency of failures may thus have been slightly overestimated due to the lack of formal identification of isolated positive cultures. Some examinations such as audiometry could not be performed for every patient. Largely due to the Ebola epidemic, only 58% of the patients had initial DST at an SRL, which limits this part of the analysis. However, as non-availability of initial specimens was random, it is very improbable that the missing data have introduced any significant bias. Such difficulties reflect the real-life situation of an NTP, but are unlikely to undermine the validity of our results.

CONCLUSION

The possibility of offering a short, highly effective treatment regimen for MDR-TB patients, irrespective of HIV status, represents a significant improvement in TB control. One of the main challenges, notably in the light of the large number of pills that patients must ingest every day, is the regularity of drug intake, for which directly observed treatment is likely a key component in reducing the risk of acquiring XDR-TB. It is gratifying to see that the good treatment outcome of this multi-country study, managed as an integral part of NTP activities, suggests that this challenge has been addressed adequately. As a consequence, the case management of MDR-TB patients continued unchanged after the study, demonstrating the feasibility and ease of scaling up the implementation of the regimen.

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RÉSUMÉ

CONTEXTE : Neuf pays d'Afrique de l'Ouest et du Centre.

OBJECTIF : Evaluer les résultats et les effets secondaires des médicaments avec un protocole de tuberculose multirésistante (TB-MDR) standardisé de 9 mois parmi des patients encore jamais traités avec des médicaments de deuxième ligne.

SCHEMA : Etude prospective d'observation de patients TB-MDR traités par un protocole standardisé de 9 mois incluant la moxifloxacine, la clofazimine, l'éthambutol (EMB) et le pyrazinamide (PZA) tout au long du traitement, complétés par kanamycine, prothionamide et isoniazide à haute dose pendant une phase intensive d'un minimum de 4 mois à un maximum de 6 mois.

RESULTATS : Parmi les 1006 patients TB-MDR inclus dans l'étude, 200 (19,9%) étaient infectés par le virus de l'immunodéficience humaine (VIH). Les résultats ont été les suivants : 728 (72,4%) guéris, 93 (9,2%) traitements achevés (81,6% de succès), 59 (5,9%) échecs, 78 (7,8%) décès, 48 (4,8%) perdus de vue. La proportion de décès a été beaucoup plus élevée parmi les patients infectés par le VIH (19,0% contre 5,0%). Le succès du traitement n'a pas différé en fonction du statut VIH parmi les survivants. La résistance à la fluoroquinolone a été la cause principale d'échec, mais la résistance au PZA, à l'éthionamide ou à l'EMB n'a pas influencé le résultat bactériologique. L'effet secondaire le plus important a été l'atteinte auditive (11,4% de détérioration grave après 4 mois).

CONCLUSIONS : Les résultats de l'étude sont en faveur de l'utilisation du protocole court récemment recommandé par l'Organisation Mondiale de la Santé. Son taux élevé de succès même chez les patients VIH positifs promet d'améliorer de façon substantielle la lutte contre la TB.

RESUMEN

MARCO DE REFERENCIA: Nueve países en África Central y Occidental.

OBJETIVO: Evaluar el desenlace y los acontecimientos adversos por medicamentos, durante un esquema normalizado de 9 meses de tratamiento de la tuberculosis multirresistente (TB-MDR) en pacientes que nunca han recibido fármacos de segunda línea.

MÉTODO: Fue este un estudio observacional prospectivo de pacientes con diagnóstico de TB-MDR, tratados con un esquema normalizado de 9 meses, que comportaba moxifloxacino, clofazimina, etambutol (EMB) y pirazinamida (PZA) durante los 9 meses, complementados con kanamicina, protionamida e isoniazida en altas dosis durante una fase intensiva como mínimo de 4 semanas y hasta un máximo de 6 meses.

RESULTADOS: De los 1006 pacientes con TB-MDR incluidos en el estudio, 200 presentaban coinfección por el virus de la inmunodeficiencia humana (VIH; 19,9%). Los desenlaces fueron como sigue: 728 curados (72,4%), 93 tratamientos completos (9,2%; con 81,6% de éxito), 59 fracasos (5,9%), 78 muertes (7,8%) y 48 pérdidas durante el seguimiento (4,8%). La proporción de pacientes que fallecieron fue mucho más alta en el grupo que presentaba coinfección por el VIH (19,0% contra 5,0%). El éxito terapéutico no difirió con respecto a la situación frente al VIH en los sobrevivientes. La principal causa de fracaso fue la resistencia a fluoroquinolona, pero la resistencia a PZA, etionamida o EMB no influyó en el desenlace bacteriológico. El acontecimiento adverso a los medicamentos más importante fue el deterioro auditivo (11,4% de deterioro grave después de 4 meses).

CONCLUSIÓN: Los resultados del presente estudio respaldan la utilización del esquema corto recomendado recientemente por la Organización Mundial de la Salud. Su alta tasa de éxitos, incluso en los pacientes coinfectados por el VIH, ofrece buenas perspectivas de mejorar el control de la TB de manera apreciable.