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High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses

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SUMMARY

SETTING: Niger National Tuberculosis Programme. Regions supported by the Damien Foundation.

OBJECTIVE: To evaluate the effectiveness of a short-course standardised treatment regimen for patients with proven multidrug-resistant tuberculosis (MDR-TB) previously untreated with second-line drugs.

METHODS: Prospective study including all patients enrolled from 2008 to 2010. The 12-month standardised regimen comprised high doses of gatifloxacin, clofazimine, ethambutol and pyrazinamide throughout, supplemented by kanamycin, prothionamide and medium-high doses of isoniazid during the intensive phase of a minimum of 4 months. Patients were monitored using sputum smear and culture at start of treatment and every 2 months. Cured patients were followed up 6-monthly for 24 months.

RESULTS: Sixty-five patients with MDR-TB were included and analysed. One of 58 patients tested for human immunodeficiency virus (1.7%) infection was positive. Twenty-five patients (39.7%) were severely affected (body mass index ≤ 16 kg/m²). Cure was achieved in 58 patients (89.2%, 95%CI 81.7–96.7), 6 died and 1 defaulted. All 49 patients assessed at the 24-month follow-up after cure remained smear- and culture-negative. The main adverse events were vomiting (26.2%) and hearing impairment (20%), but no treatment had to be stopped.

CONCLUSION: Standardised 12-month treatment for MDR-TB was highly effective and well tolerated in patients not previously exposed to second-line drugs in Niger.

KEY WORDS: MDR-TB; fluoroquinolones; Niger

MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB) is a worldwide public health concern, with an estimated 450 000 new cases in 2012. Only 48% of patients were successfully treated in a cohort of 71 countries in 2010, with 28% of cases lost to follow-up or without outcome information.¹

Recent World Health Organization (WHO) guidelines for the management of MDR-TB strongly recommend using four effective second-line drugs, including a fluoroquinolone (FQ), a second-line injectable, ethionamide (ETH) or prothionamide (PTH) and cycloserine (or para-aminosalicylic acid), in addition to pyrazinamide (PZA), despite very low-quality evidence. Furthermore, a total treatment duration of 20 months, with an intensive phase of 8 months (including second-line injectables) are conditional recommendations.² A recent meta-analysis of individual patient data is at the basis of these recommendations, but serious limitations of the observational data are mentioned.³ In contrast, very good outcomes have been reported from one obser-

vatational study performed in Bangladesh and published in 2010, with relapse-free cure reaching 87.9% on a standardised regimen of only 9 months based on high-dose gatifloxacin (GFX), clofazimine (CFZ), ethambutol (EMB) and PZA throughout, supplemented by kanamycin (KM), PTH and medium-high dose INH during the intensive phase.⁴

The burden of MDR-TB in 2012 in Niger, a low-income sub-Saharan country, was estimated by the WHO at 1.8% among new notified pulmonary cases and 19% among retreatment cases.¹ Human immunodeficiency virus (HIV) prevalence among adults aged 15–49 years is 0.5%.⁵ In 2008, the Damien Foundation (DF), a non-governmental organisation, started supporting the National Tuberculosis Programme (NTP) and the MDR-TB programme in Niger with the construction of a National Tuberculosis Reference Laboratory and provision of technical assistance in three of the eight regions of the country (Tillabéri, Zinder and Maradi), covering more than 55% of the country's population. Before 2008, the

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NTP did not provide MDR-TB treatment per WHO recommendations, and second-line drugs had seldom been used. As all costs were borne by DF, the short-course Bangladesh regimen was chosen. However, as a precaution against relapses, the continuation phase of the regimen was extended to 8 months, for a total duration of 12 months. We report here the outcomes of the cohort enrolled from July 2008 to December 2010.

METHODS

Ethics committee approval

This study was approved by the National Ethics Committee, Niamey, Niger. Enrolled participants provided written informed consent.

Setting and study design

Patients presumed to have MDR-TB were screened by the MDR-TB Unit of Niamey, managed by DF Niger, in an observational prospective study. Patients who had received second-line drugs in the past for >1 month and diabetic patients followed individualised treatment regimens; their results are not reported here. Pregnant women and patients with severe liver insufficiency were excluded from treatment. Retreatment failures and MDR-TB contacts were started on the study regimen without awaiting the results of drug susceptibility testing (DST), while relapses were not treated until confirmation of MDR-TB was obtained.

All subjects with proven MDR-TB started on the 12-month regimen were included in the analysis. Patients enrolled after 31 December 2010, when a shorter (9-month) regimen was adopted, patients who had previously received second-line drugs for at least 1 month, and those who proved not to have MDR-TB (culture-negative, other types of drug resistance or non-tuberculous mycobacteria), were excluded from the analysis.

Bacteriological investigations

Sputum microscopy for acid-fast bacilli was performed at the MDR-TB Unit. Two pre-treatment samples were shipped with cetylpyridinium chloride preservative to the Antwerp (Belgium) SupraNational TB Reference Laboratory for culture, species determination and DST on all isolates obtained at any time.

Sputum smear microscopy and solid culture were performed every 2 months during treatment; sputum smear microscopy was performed monthly during the intensive phase. Follow-up after cure continued for 2 years, with smear and culture every 6 months.

Treatment regimen and management

The regimen was essentially the same as that used in the Bangladesh programme,⁴ but was slightly longer.

The intensive phase regimen, consisting of high doses of KM, PTH, INH and GFX (Table 1), CFZ, EMB and PZA, lasted a minimum of 4 months. The intensive phase was extended up to a maximum of 6 months in the case of delayed sputum smear conversion at 4 or 5 months. The continuation phase regimen, comprising GFX, CFZ, EMB and PZA, was fixed at 8 months. The total duration of treatment was thus 12–14 months. No treatment was modified as a result of the initial drug resistance pattern.

Patients in poor clinical condition (body mass index [BMI] < 16 kg/m², inability to walk unaided) or with comorbidities were admitted to the National Hospital of Niamey during the intensive phase, and then followed the continuation phase as out-patients. With the exception of these patients, the entire treatment regimen was given on an out-patient basis. During the intensive phase, out-patients attended the Niamey MDR-TB facility daily for directly observed treatment performed by a nurse. Attendance at the MDR-TB Unit was weekly during the continuation phase, with daily home visits by a supervised health agent; patients who did not live in Niamey were supervised daily by trained regional agents and attended the Niamey MDR-TB Unit on a monthly basis.

Glycaemia and liver function were monitored on a monthly or bi-monthly basis throughout treatment. Renal function was checked monthly during the intensive phase; thyroid function and hearing were monitored at the start of treatment and at the end of the intensive phase. Chest radiography was performed at enrolment and at the end of treatment, while HIV and pregnancy tests were performed at enrolment only. Adverse events were promptly managed.

Patient support provided by DF included the costs of treatment monitoring, ancillary drugs and transport, food during hospitalisation and for out-patients, in addition to the management of adverse reactions such as hearing prostheses and social support for income-generating activities at the end of treatment.

Table 1 Drug dosages by weight group

Drug	Weight band, mg		
	<33 kg	33–50 kg	>50 kg
Kanamycin	500	750	1000
High-dose gatifloxacin	400	600	800
Prothionamide*	250	500	750
Medium-high dose isoniazid*	300	400	600
Clofazimine	50	100	100
Ethambutol	800	800	1200
Pyrazinamide	1000	1500	2000

* The highest dose given to patients weighing >55 kg (not 50 kg).

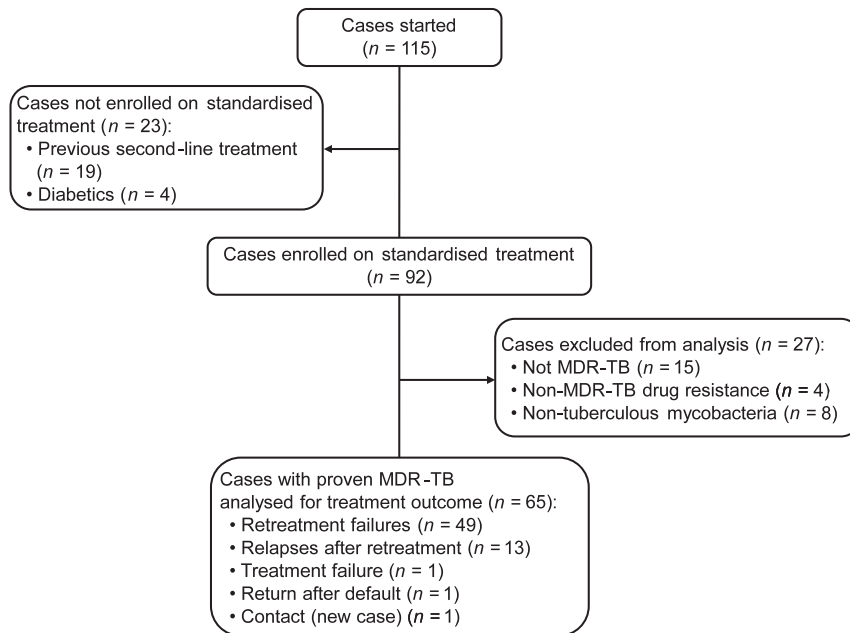


Figure 1 Patients started on second-line drugs with exclusions from enrolment, analysis of the study regimen and treatment antecedents of patients analysed.

Definitions of treatment outcome

Definitions of treatment outcomes were adapted from the WHO guidelines:⁶

- 1 Cured: treatment completed with at least five consecutive negative cultures from samples collected at least 30 days apart during the last 8 months of treatment; or one positive culture without concurrent clinical deterioration, followed by at least four consecutive negative cultures
- 2 Treatment completed: treatment completed with documented bacteriological conversion but not meeting the definition for cure
- 3 Died: death from any cause during the course of MDR-TB treatment
- 4 Failed: two or more of the five cultures positive in the final 8 months of treatment, or one of the final three, or treatment stopped definitively due to adverse drug reactions
- 5 Default: interruption of treatment for ≥ 2 consecutive months without medical approval
- 6 Relapse: cured or completed treatment with at least one positive culture during post-treatment follow-up.

Data collection and analysis

Baseline patient characteristics, previous history of TB, drug resistance profiles and HIV status were collected. Data were entered and analysed using Epi-Info version 7 (US Centres for Disease Control and Prevention, Atlanta, GA, USA; www.cdc.gov/epiinfo/7/index.htm).

RESULTS

Study population

MDR-TB treatment was started in 115 patients, of whom 23 received an individualised regimen, 19 due to previous use of second-line drugs and 4 due to diabetes. The remaining 92 patients were enrolled into the short-course treatment regimen (Figure 1). Twenty-seven patients were excluded from the analysis due to the lack of confirmed MDR-TB ($n = 15$), other drug resistance ($n = 4$) or non-tuberculous mycobacteria ($n = 8$).

Among the 65 patients analysed for treatment outcome, 64 were first-line retreatment cases and 1 was a new contact case. Retreatment cases included 49 retreatment failures, 13 relapses after retreatment, 1 failure of primo-treatment and 1 return after default. In addition to INH and RMP resistance, some of the MDR-TB isolates were also resistant to EMB ($n = 45$, 69.2%), ofloxacin (OFX) ($n = 1$, 1.5%) and ETH ($n = 7$, 10.8%). Sixty-four patients had strains with medium- to high-level INH resistance (1 mg/l). Except for one patient with resistance to OFX, all of the other subjects had strains susceptible to fluoroquinolones and KM. Excluding EMB, PZA and CFZ, the median number of drugs with in vitro activity was 4 (range 2–5).

Fifty-three (81.5%) patients were male, and the median age of the whole cohort was 31 years (range 16–66) (Table 2). Of the 58 (89.2%) subjects who agreed to undergo HIV testing, one (1.7%) was positive. The median BMI determined at enrolment for 63 patients was 16.4 kg/m² (range 12.4–26.1); 25

Table 2 Baseline characteristics of the 65 cases analysed for outcome

Baseline patient characteristics	n (%)
Demographics	
Male	53 (81.5)
Female	12 (18.5)
Age, years, median [range]	31 [16–66]
HIV status	
Tested	58 (89.2)
HIV-positive	1 (1.7)
Previous anti-tuberculosis treatment	64
Number of episodes, median [range]	2 [0–6]
BMI, kg/m², median [range]*	16.4 [12.4–26.1]
<15 (very severely underweight)	15 (23.8)
15–16 (severely underweight)	10 (15.9)
16.1–18.5 (underweight)	18 (28.6)
18.6–25 (normal)	20 (31.7)
Radiographic extent	
Bilateral disease with cavitations	23 (35.4)
Bilateral disease without cavitations	39 (60)
Involvement of one lung	2 (3.1)
Involvement of one lobe	1 (1.5)

* Data missing for two patients.

HIV = human immunodeficiency virus; BMI = body mass index.

patients (39.7%) were severely or very severely underweight and 18 (28.6%) were underweight.

Sixty-two subjects (95.4%) had bilateral radiological disease, 23 (35.4%) with cavities, while 54 (83.1%) had 2+ or 3+ sputum smears. Apart from the single new case, the study patients had received 1–6 treatment regimens (median 2) (Table 2). No patients had pre-existing renal/hepatic impairment or hearing loss at the time of enrolment.

Treatment outcome and follow-up

Of the 65 cases analysed for outcome, none remained persistently culture-positive, and only one (1.5%) had late culture conversion, 2 months after the extension of the intensive phase. Three (4.6%) patients died before the end of the intensive phase, two of whom were culture-negative; 61 (93.8%, 95% confidence interval [CI] 87.9–99.7) experienced culture conversion by month 4 of the intensive phase. The patient

who did not convert died before the end of month 1. Smear conversion was obtained within 4 months in 57 cases (87.7%, 95%CI 79.7–95.7); 4 converted after 5 months and 1 after 6 months (Figure 2).

Fifty-eight patients were declared cured (89.2%, 95%CI 81.7–96.7) and six (9.2%) died, five of whom were culture-negative. One patient (1.6%) defaulted after 9 months of treatment, with culture conversion at month 2 and four consecutive negative cultures at month 9. Of the six deaths, four were caused by acute respiratory failure, one by haemoptysis and one by cerebral malaria.

Among the 58 cured patients, 49 (84.5%) remained culture-negative at 24 months' follow-up, 4 (6.9%) had left the country but were alive when contacted by phone, and 5 (8.6%) died within 2–8 months after cure, all due to respiratory failure. No relapse has been documented to date (Table 3).

A total of 11 deaths occurred, 6 under treatment and 5 during the 24 months of follow-up after cure; their characteristics are shown in Table 4. There were no comorbidities. We found a significant difference between surviving and deceased patients in terms of BMI (mean 17.8 kg/m² vs. 14.4 kg/m², $P < 0.002$), but not in terms of age, sex, initial resistance and disease extent/smear grading.

Adverse drug reactions

The majority of the patients (63%) had at least one adverse drug reaction, but none had to stop treatment definitively (Table 5). Seventeen (26.2%) had vomiting, mostly in the first months of treatment, which proved manageable with concomitant intake of food, ancillary anti-emetic drugs or divided intake of PTH.

Hearing loss was frequent (20%): among the 13 cases with impairment, six had taken two or more courses of streptomycin (SM) in the past. Nine patients had mild hearing loss, but in two it was moderate and in two others it was profound (40–70 and >90 decibels, respectively, at 2000 Hz). The dosing frequency of KM was reduced to three times a week for patients with ototoxicity. Nine of the 13

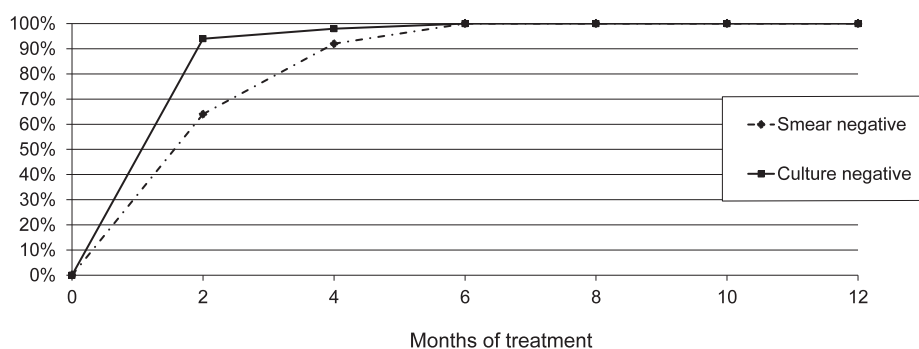


Figure 2 Cumulative conversion on smear and culture, percentage of cases on MDR-TB treatment. MDR-TB = multidrug-resistant tuberculosis.

Table 3 Status of 58 cured patients at follow-up

	Follow-up: 6 months after cure <i>n</i> (%)	12 months after cure <i>n</i> (%)	18 months after cure <i>n</i> (%)	24 months after cure <i>n</i> (%)
Culture-negative	53 (91.4)	51 (87.9)	51 (87.9)	49 (84.5)
Relapse	0	0	0	0
Moved to another jurisdiction	3 (5.2)	4 (6.9)	4 (6.9)	4 (6.9)
Death	2 (3.4)	3 (5.2)	3 (5.2)	5 (8.6)
Total	58 (100)	58 (100)	58 (100)	58 (100)

Table 4 Characteristics of 11 deceased cases (6 under treatment and 5 after cure)

Patient (MDR-TB registration number)	Age years	Sex	Month of culture conversion	Month of death	Body mass index (kg/m ²)	Smear status	Resistance profile	Radiological extent
5/08	48	Male	No conversion	Month 1	Unknown	3+	HRES	Bilateral with cavitation
7/08	41	Male	Month 2	Month 3	Unknown	3+	HRES	Bilateral without cavitation
59/10	45	Male	Month 2	Month 3	13.4	3+	HRS	Bilateral without cavitation
23/09	28	Female	Month 2	Month 5	14.9	3+	HRES	Bilateral without cavitation
29/09	18	Male	Month 2	Month 5	13	1+	HRES	Bilateral without cavitation
51/10	30	Male	Month 2	Month 7	15.2	3+	HRES	Bilateral without cavitation
58/10	32	Male	Month 2	Month 14	16.4	3+	HRES	Bilateral without cavitation
06/08	30	Male	Month 2	Month 17	14	3+	HRES	Bilateral with cavitation
65/10	26	Male	Month 2	Month 20	14	3+	HR	Bilateral without cavitation
08/08	32	Male	Month 2	Month 32	14.5	2+	HRS	Bilateral with cavitation
13/08	28	Male	Month 2	Month 32	14.5	2+	HRS	Bilateral with cavitation

MDR-TB = multidrug-resistant tuberculosis; H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin.

Table 5 Adverse drugs reactions reported during treatment*

Adverse drug reactions	Incidence <i>n</i> (%)	Most/least probable cause	Drug stopped (<i>n</i>)	Month of treatment median [range]
Vomiting	17 (26.2)	PTH, CFZ, H, E, Z	None	1 [1–3]
Hearing loss	13 (20)	KM	None	3 [1–4]
Hyperglycaemia	6 (9.2)	GFX	None	3 [1–6]
Gastritis	5 (7.7)	PTH, CFZ, H, E, Z	None	2 [1–4]
Arthralgia	4 (6.2)	Z, GFX	None	5.5 [1–9]
Depression	3 (4.6)	MDR-TB, GFX, PTH, H	None	4 [2–4]
Peripheral neuropathy	3 (4.6)	H, PTH, GFX, KM	None	7 [3–9]
Skin pigmentation	2 (3.1)	CFZ	None	9 [8–10]
Optic neuritis	2 (3.1)	E	E (2)	5.5 [1–10]

* Some patients had multiple reactions.

PTH = prothionamide; CFZ = clofazimine; H = isoniazid; E = ethambutol; Z = pyrazinamide; KM = kanamycin; GFX = gatifloxacin; MDR-TB = multidrug-resistant tuberculosis.

subjects were provided with hearing aids, while the four patients with bilateral mild impairment did not require them. Hyperglycaemia was recorded in six patients (9.2%), but this proved manageable with oral anti-diabetic drugs and subsided after the end of treatment. None of the patients suffered from hypoglycaemia.

EMB was stopped in two patients suffering from optic neuritis, after month 1 and month 10, respectively. Both had received several first-line treatment regimens with EMB, for a total of 32 months. Other minor side effects, such as gastritis (7.7%), arthralgia (6.2%), peripheral neuropathy (4.6%) and skin pigmentation (3.1%), were easily managed and reversible. No patient developed renal or hepatic impairment during treatment.

DISCUSSION

The rationale used for the 'Bangladesh' regimen was also applied to our study.⁴ GFX was used as the central drug due to evidence that the last-generation FQs have a bactericidal activity that is better than or at least as good as that of INH,^{7,8} and enhanced sterilising activity, allowing for shorter treatment duration.⁹ The dosage of GFX was increased because of reports about rapid acquisition of resistance to fluoroquinolones.^{10,11} GFX was chosen also due to its greater affordability.

PZA was added for its sterilising activity, which was recently shown to be important for the effectiveness of FQ-based treatments.¹² Apart from being shorter, the regimen also deviates from current WHO guidelines in its composition.² The poorly tolerated

PTH was omitted in the continuation phase to reduce defaulting.⁴ CFZ was given throughout treatment as a well-tolerated companion drug. Developed for TB in the late 1950s,¹³ it was prematurely abandoned despite its promise and its low frequency of resistance development.¹⁴ Interest in this drug for the treatment of MDR-TB is growing again, mainly because of its excellent sterilising activity in murine models.^{15,16}

EMB and INH were used despite laboratory-defined resistance. The action of EMB remains unclear, and severe overdiagnosis of resistance is likely,¹⁷ while high-dose INH may help to reduce time to culture conversion.¹⁸ Moreover, strains with low-level INH resistance (0.2 mg/l) show cross-resistance to thioamides. High-dose INH may thus kill strains resistant to PTH, while strains with high-level INH resistance may be PTH-susceptible.¹⁹ Levels of INH resistance below the peak serum level with standard dosing have been reported for a considerable proportion of strains; these may respond to higher doses,^{20,21} and the 7–12 mg/kg dosage was not expected to increase adverse events.²² Sputum culture conversion occurred remarkably early in our study, probably due to the combination of a fourth generation fluoroquinolone with CFZ.^{16,23}

Not a single treatment failure was recorded, and there was no amplification of resistance. With over 92% of patients assessed, the high relapse-free cure rate at 24 months shows that the Bangladesh results⁴ can be replicated in Africa. This is a clear improvement on the results typically reported from resource-limited settings.^{24,25} The absence of relapse is even more remarkable in view of the low BMI, high bacillary sputum load and radiographically extensive disease in the vast majority of our patients. These factors also explain the relatively high frequency of death, despite the low prevalence of HIV.^{26,27} However, mortality during treatment reached only half the rate notified for Africa in the last WHO report.¹ Adverse drug reactions occurred among 63% of our cohort, but were easily managed, comparing favourably with the conventional longer regimens.^{28,29} Only EMB had to be stopped in two cases who had used the drug previously for years. The higher frequency of hearing loss compared to that reported from Bangladesh may be explained by more careful monitoring, but also by the high proportion of our patients who had had repeated courses of SM.^{30,31}

Limitations of our study mainly concern its observational type and small cohort size. However, the protocol was strictly followed by trained personnel. The close-to-routine conditions with very few exclusions might offer greater guarantees for its wide applicability in the field than those reported from randomised clinical trials. Finally, confirmation from other settings with higher levels of HIV coinfection or second-line drug resistance is still required.

CONCLUSIONS

A short-course treatment regimen for MDR-TB based on a fourth generation fluoroquinolone, a second-line injectable and CFZ is as successful as first-line treatment in Niger. Intensive follow-up, including regular cultures, did not show any failures or relapses up to 24 months after cure. Adverse drug effects were few and could be managed without stopping more than one drug.

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Conflict of interest: none declared.

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R E S U M E

CONTEXTE : Programme national de lutte contre la tuberculose du Niger et régions soutenues par la Fondation Damien.

OBJECTIF : Evaluer l'efficacité d'un protocole de traitement court standardisé pour les patients qui ont une tuberculose multirésistante (TB-MDR) qui n'a pas encore été traitée par des médicaments de deuxième ligne.

MÉTHODES : Une étude prospective incluant tous les patients enrôlés de 2008 à 2010. Le protocole standardisé de 12 mois était basé sur des doses élevées de gatifloxacine, de clofazimine, d'éthambutol et de pyrazinamide pendant tout le traitement, avec un supplément de kanamycine, de prothionamide et d'une dose moyennement élevée d'isoniazide pendant la phase intensive d'au moins 4 mois. Les patients ont été suivis grâce à un frottis de crachats et une culture au démarrage

puis tous les 2 mois. Les patients guéris ont été suivis tous les 6 mois pendant 24 mois.

RÉSULTATS : On a inclus et analysé 65 patients porteurs d'une TB-MDR. Un des 58 patients testés pour le virus de l'immunodéficience humaine (1,7%) était positif ; 25 patients (39,7%) avaient une atteinte grave (indice de masse corporelle ≤ 16 kg/m²) ; 58 patients (89,2% ; IC95% 81,7–96,7) sont guéris, 6 sont décédés et 1 a abandonné. Les 49 patients évalués lors du suivi de 24 mois après la guérison sont restés négatifs pour le frottis et la culture. Les effets secondaires les plus fréquents étaient les vomissements (26,2%) et l'atteinte auditive (20%), mais aucun traitement n'a dû être arrêté.

CONCLUSION : Le traitement standardisé de 12 mois de la TB-MDR s'est montré très efficace et bien toléré chez des patients non encore exposés aux médicaments de deuxième intention au Niger.

R E S U M E N

MARCO DE REFERENCIA: Las regiones donde se aplica el Programa Nacional contra la Tuberculosis del Níger apoyado por la Fundación Damien.

OBJETIVO: Valuar la eficacia de un tratamiento breve normalizado, dirigido a los pacientes con diagnóstico confirmado de tuberculosis multidrogorresistente (TB-MDR) sin antecedente de tratamiento antituberculoso con medicamentos de segunda línea.

MÉTODOS: Fue este un estudio prospectivo de todos los pacientes registrados en tratamiento del 2008 al 2010. En el régimen normalizado de tratamiento de 12 meses se usaron altas dosis de gatifloxacino, clofazimina, etambutol y pirazinamida durante toda su duración, complementados con kanamicina, protionamida y dosis medias-altas de isoniazida durante una fase intensiva como mínimo de 4 meses. La supervisión de los pacientes comportó la baciloscopia y el cultivo del esputo al comienzo del tratamiento y cada 2 meses. Los pacientes curados se siguieron con intervalos de 6 meses durante 24 meses.

RESULTADOS: Se incluyeron en el estudio y el análisis 65 pacientes con diagnóstico de TB-MDR. Uno de los 58 pacientes con prueba diagnóstica del virus de la inmunodeficiencia humana obtuvo un resultado positivo (1,7%). Veinticinco pacientes (39,7%) presentaron inicialmente una deficiencia ponderal grave (índice de masa corporal ≤ 16 kg/m²). Cincuenta y ocho pacientes alcanzaron la curación (89,2%; IC95% 81,7–96,7), 6 pacientes fallecieron y se presentó 1 abandono. En todos los 49 pacientes que se evaluaron durante los 24 meses del seguimiento tras la curación, la baciloscopia y el cultivo permanecieron negativos. Las principales reacciones adversas fueron vómito (26,2%) y trastornos auditivos (20%), pero no fue necesario suspender ningún tratamiento.

CONCLUSIÓN: En el Níger, el tratamiento normalizado de la TB-MDR durante 12 meses fue muy eficaz y bien tolerado por los pacientes sin exposición anterior a los medicamentos de segunda línea.