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Successful implementation of bedaquiline for multidrug-resistant TB treatment in remote Papua New Guinea

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Setting: Bedaquiline (BDQ) was introduced in the multidrug-resistant tuberculosis (MDR-TB) programme in Daru in remote Papua New Guinea in 2015, along with a core package of active drug-safety monitoring (aDSM).

Objective: To assess interim results and safety of BDQ for the treatment of MDR-TB from 1 July 2015 to 31 December 2017.

Design: A retrospective cohort analysis of routine programme data.

Results: Of 277 MDR-TB patients, 77 (39%) received BDQ with a total of 8 serious adverse events including 5 (6.5%) deaths, of which 1 (1.3% QTcF prolongation, grade 3) was attributable to BDQ. Of 200 (61%) patients who did not receive BDQ, there were 17 (9%) deaths. Completeness of monitoring for the BDQ group was 90% for >5 electrocardiograms and 79% for ⩾2 cultures. In the interim result indicator analysis at month 6 in the BDQ and non-BDQ groups, there were respectively 0% and 1% lost to follow-up; 6.5% and 8.5% who died; 94% and 91% in care; and 92% and 96% with negative culture among those monitored.

Conclusion: Early experience in Daru shows BDQ is safe and feasible to implement with aDSM with good interim effectiveness supporting the rapid adoption and scale-up of the 2019 WHO MDR-TB treatment guidelines in the programme and in similar remote settings.

The United Nations' Sustainable Development Goal targets to end the global tuberculosis (TB) epidemic by 2030 have been threatened by the emergence of multidrug-resistant tuberculosis (MDR-TB). In 2017, an estimated 458 000 people developed MDR-TB, defined as resistance to isoniazid and rifampicin.[1] Among these, 8.5% had extensively drug-resistant TB (XDR-TB), characterised as MDR-TB with additional resistance to injectable agents and fluoroquinolones. Treatment success remains poor with only 55% of patients with MDR-TB and 34% of those with XDR-TB achieving a favourable outcome.[1] Treatment for MDR-TB is complex to deliver to patients due to the long duration, use of injectable agents, a high pill-burden and a high rate of adverse drug effects.[2]

Bedaquiline (BDQ) is the first new TB drug developed in almost 50 years. It was approved by the United States and European regulatory authorities based on efficacy and safety in 2 phase IIb trials.[2,3] There was initial concern about safety due to unexplained deaths in the BDQ arm (not attributed to the drug) and an increased frequency of QTc interval prolongation on the electrocardiogram (ECG). As a result, the World Health Organization (WHO) published interim policy guidance for the use of BDQ in 2013, which recommended that active drug-safety management and monitoring (aDSM) be used.[4] Despite this, the global scale-up of BDQ has been slow and not met the needs of patients with MDR-TB.[5] Barriers identified included limited awareness of procurement and WHO guidance (notably aDSM) and limited access to companion medications.[6] A recent and pivotal study reporting on implementation by the national programme in South Africa demonstrated a three times reduction in the risk of mortality in MDR-TB patients treated with BDQ compared to those without.[7] In 2019, the WHO issued major changes to MDR-TB guidelines, recommending BDQ as a core drug in the longer regimen.[8]

Papua New Guinea (PNG) is a high burden country for MDR-TB, TB and TB- human immunodeficiency virus (HIV) coinfection with an estimated TB incidence of 432 per 100 000 population.[1] An unprecedented outbreak of drug-resistant TB has been reported on Daru Island, South Fly District, in the Western Province of PNG.[9] This resulted in the establishment of the emergency response task force for MDR-TB by the National Department of Health in 2014 to provide stewardship and resource mobilisation in three 'hotspot' provinces, including Western Province.

BDQ was initially obtained through a compassionate access programme in October 2015 at Daru General Hospital (DGH) for patients with limited treatment options. In May 2016, the National TB Program (NTP) procured the drug through the Stop TB Partnership's Global Drug Facility and was initially supported by a global donation programme. We aimed to describe the implementation of BDQ and assess the safety and interim effectiveness for MDR-TB patients commenced on BDQ from July 2015 to December 2017 compared to those on regimens without BDQ.

METHODS

Study design and participants

We conducted a retrospective cohort analysis using routine programme data for all patients enrolled on MDR-TB treatment from 1 July 2015 to 31 December

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2017 in DGH. For the purpose of this assessment, MDR-TB includes rifampicin-resistant TB (RR-TB) that is either bacteriologically confirmed by Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) or culture, or is clinically diagnosed.

Setting

Western Province shares international borders with Indonesia and Australia and has three districts: North, Middle and South Fly districts. Daru Island, with a population of 15 142 is situated in South Fly District.[10] The DGH is a 100-bed provincial referral hospital providing inpatient and outpatient services including specialist care. It has a 40-bed inpatient TB unit and ambulatory TB services, as the only TB facility in the district. The provincial government leads the TB response in Western Province with support from the Australian Government through international partners and the PNG NTP. We have described the setting and TB programme interventions in South Fly District and Daru over this time period in detail elsewhere.[11]

Treatment model

TB diagnosis was centralised at the hospital in a dedicated outpatient clinic and laboratory. Presumptive TB cases were tested with Xpert as the initial test. This included Xpert for extrapulmonary TB (EPTB) when indicated, such as fine needle aspiration of lymph nodes and gastric aspiration for paediatric patients (aged <15 years). All samples with rifampicin resistance detected on Xpert were transported by air to the national TB reference laboratory in Port Moresby and to the supranational reference laboratory in Brisbane, Australia, for culture and/or drug susceptibility testing (DST). The PNG national TB reference laboratory commenced culture in late 2017 with validation in Australia. Culture and DST methods have been previously described.[12] All MDR-TB patients had baseline clinical assessment and laboratory investigations including blood tests, human immunodeficiency virus (HIV) testing, chest X-ray, audiometry, visual screening and education as per the national protocol. A community-based model of care was in place with treatment initiation on an outpatient basis, unless patients required hospital admission for medical or social reasons. Treatment was delivered by treatment supporters at community treatment sites and supervision was provided from community nurses. A patient-centred package of care was provided from January 2016, with patient education and counselling, transport support and daily meals. The standardised treatment regimen for MDR-TB in Daru included at least five drugs likely to be effective based on the known unique resistance pattern: kanamycin, levofloxacin, linezolid, clofazimine, cycloserine and pyrazinamide (prothionomide/ethionamide was not used).[13] Additional available second-line drugs for individualised regimens included capreomycin, moxifloxacin and para-aminosalicylic acid (PAS). The PNG protocol required monitoring cultures to be performed monthly in the intensive phase and every 2–3 months in the continuation phase due to resource (transport, human resources) and laboratory sample capacity constraints. It was known that culture monitoring, especially in the intensive phase was sub-optimal in the programme and multiple efforts were made to redress this in the study period.

Bedaquiline implementation

The conditions for BDQ use were implemented as per WHO recommendations and a core package of aDSM.[6,12] Adverse events that were classified as grade 3 (severe), grade 4 (life-threatening) or grade 5 (death) according to the national aDSM protocol (based on the Common Terminology Criteria for Adverse Events) were recorded by the treating clinicians.[14] Serious adverse events (SAEs) were defined as per WHO guidelines[15] and reported to the NTP and causality assessment committee in PNG and to the Global Drug Facility and Uppsala Monitoring Centre. All patients were monitored every 2 weeks for the first month and then monthly for the next 5 months with ECG, blood tests, sputum and clinical consultation. The QT interval was calculated by the treating physicians using the Fridericia formula (QTcF) as per guidelines.[16] The ECG was repeated if the QTcF was prolonged. The aDSM package including SAE reporting; routine ECG monitoring was not performed in the non-BDQ group.

Given the limited BDQ supply and high patient eligibility, the clinical team developed allocation criteria for BDQ use based on guidance from the NTP which prioritised those with resistance to fluoroquinolone and injectable agents and then patients with second-line drug intolerance. All patients identified as eligible for BDQ by the treating clinicians were discussed via telemedicine with the project clinical expert group comprised of international MDR-TB experts and reported to the NTP. Once there was consensus to initiate BDQ, the patient underwent counselling and was asked for informed consent.

Data variables, analysis and statistics

The data for the study cohort were recorded in the national drug resistant TB register and also entered into the programme electronic medical records system Bahmni v.0.86 (Thoughtworks, Chicago, IL, USA). The data variables collected included age, sex, date of TB treatment initiation, date of BDQ initiation, baseline height, baseline weight, TB site, registration category, TB diagnosis and monitoring results (smear, Xpert, culture), ECG results, grade 3–5 AEs, SAEs and interim outcomes at month 6. The data were extracted using automated scripts and imported into Stata v.15 (StataCorp, College Station, TX, USA) and R v.3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) with v.1.2.1 of the tidyverse package for validation and analysis. Categorical variables were described by frequency and proportion, and continuous variables by median and interquartile range [IQR]. Differences between categorical variables were tested using the $\chi 2$ test or the Fisher's exact test. Differences between continuous variables were tested using the Wilcoxon rank sum test. $P < 0.05$ was considered significant.

The current PNG and WHO definitions were used for MDR-TB enrolment categories.[17] For the purposes of this study we defined interim indicators (Table 1) that were relevant for evaluation of monitoring and

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TABLE 1 Study month 6 interim result indicators and definitions

6-month indicator	Definition or calculation of indicator
Lost to follow-up	Numerator: Number of RR-/MDR-TB patients registered whose treatment was interrupted for 2 consecutive months or more by the end of month 6 of their treatment Denominator: Number of RR-/MDR-TB patients who were registered and commenced on MDR-TB treatment
Died	Numerator: Number of RR-/MDR-TB patients registered who died of any cause by the end of month 6 of their treatment Denominator: Number of RR-/MDR-TB patients who were registered and commenced on MDR-TB treatment
In care	Numerator: Number of RR-/MDR-TB patients registered who were still on treatment by the end of month 6 of their treatment Denominator: Number of RR-/MDR-TB patients who were registered and commenced on MDR-TB treatment
Baseline or diagnostic culture definition	Any culture sent from 180 days prior to 7 days after RR/MDR-TB treatment initiation
Follow-up culture definition	Cultures sent within 6 months, specifically, from day 8 to 183 after RR/MDR-TB treatment initiation
Eligible for culture monitoring	Numerator: Number of patients with bacteriologically confirmed pulmonary RR-/MDR-TB and aged >15 years registered for treatment Denominator: Number of RR-/MDR-TB patients who were in care by the end of month 6 of their treatment Patients from whom collecting repeated culture specimens was clinically feasible children and extrapulmonary cases were excluded
Monitored by culture	Numerator: Number of RR-/MDR-TB patients who had at least 2 valid culture results by the end of month 6 of their treatment from specimens collected at least 30 days apart, one test of which was a follow-up culture Denominator: Number of RR-/MDR-TB patients who were eligible for culture monitoring
Culture negative / positive indicator	Numerator: Number of RR-/MDR-TB patients who had a negative or positive culture in their last result by the end of month 6 of their treatment Denominator: Number of RR-/MDR-TB patients who were monitored by culture

RR-TB rifampicin-resistant tuberculosis; MDR-TB multidrug-resistant TB.

programmatic effectiveness, based on the five WHO interim result indicators.[14] All patients started on treatment were classified as either lost to follow up (LTFU), died or in care at month 6. We assessed completeness of monitoring with ECG and culture only in patients who completed 6 months of treatment (in care), as those who were LTFU or died may not have had the opportunity to have tests performed.

Ethics

Ethics approval was obtained from the PNG Medical Research Advisory Council (MRAC), Port Moresby, PNG, and the Alfred Hospital Ethics Committee, Melbourne, VIC, Australia.

RESULTS

Of 277 MDR-TB patients enrolled on treatment from 1 July 2015 to 31 December 2017, 77 (28%) received BDQ in their regimen (BDQ group) and 200 (72%) did not (non-BDQ group). Figure 1 displays the scale-up of BDQ use over this period. Table 2 shows the baseline demographic and clinical characteristics of the patients in the study. Eligibility criteria for BDQ are presented in Table 3. Fifty-five patients (71.4%) were eligible for BDQ initiation based on drug intolerance, which was exclusively to injectable agent toxicity—19.9% of the entire cohort. There were 38 (49.4%) with ototoxicity, 40 (51.9%) with nephrotoxicity and 23 (29.9%) with both (Table 3). Of the 21 (27.3%) with resistance as an indication, 4 (5.2%) were clinically diagnosed and all were contacts of bacteriologically confirmed index cases with pre-XDR or XDR-TB. Table 4 displays the monitoring of patients in care with culture and ECG. Culture monitoring as per protocol (monthly) was poor. The median time from commencement of MDR-TB treatment to BDQ initiation was 50 days [IQR 15–105].

Eight (10.4%) serious adverse events were reported in the BDQ group with only one (1.3%) attributable to BDQ: three hospitalisations (one with acute cholecystitis, unrelated to medications, grade 3); 1 status epilepticus (related to isoniazid, grade 4); 1 prolonged QTcF interval (related to BDQ, which was stopped, grade 3); and 5 (6.5%) deaths (grade 5). The five deaths had causality assessments performed, concluding they were not related to BDQ, but rather to severe disease and late presentation. Eleven patients received 'off-label' use of BDQ according to WHO guidelines:[18] 2 patients aged <18 years, 2 pregnant women and 7 patients who received an extended course for up to 48 months. All of the 7 patients on an extended course were bacteriologically confirmed with XDR-TB who had previous exposure to second-line drugs and insufficient effective drugs in their treatment regimens if BDQ was to be stopped. Among them, only 1 experienced an adverse event (prolonged QTcF) and all 7 were in care and clinically responding.

The interim result indicator analysis at month 6 is shown in Table 5. Ninety-one percent of all patients remained in care at 6 months. A similar proportion of patients in the BDQ group died compared with the non-BDQ group. Among the 15 patients with XDR-TB, there were 12 in the BDQ group (11 in care, 1 died) and 3 in the non-BDQ group (1 in care, 2 died). One XDR-TB patient in the non-BDQ group was identified as eligible but died prior to receiving BDQ. The other XDR and pre-XDR patients in the non-BDQ group (Table 3) were not considered eligible (2 children, 1

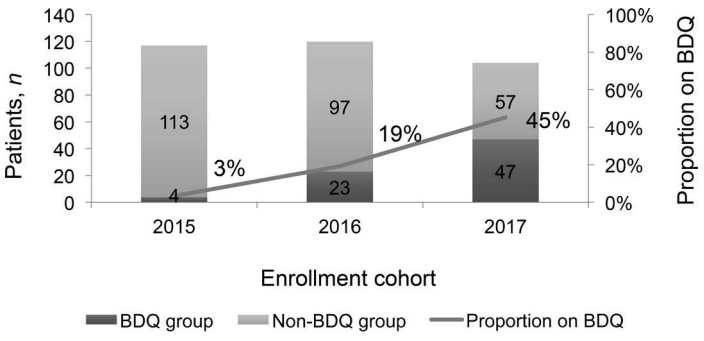

FIGURE 1 MDR-TB patients commenced on BDQ during MDR-TB treatment in Daru, Papua New Guinea, 2014–2017. BDQ = bedaquiline; MDR-TB = multidrug-resistant tuberculosis.

TABLE 2 Baseline demographic and clinical characteristics for patients with MDR-TB initiated on BDQ compared to those not initiated on BDQ, Daru, Papua New Guinea, between 1 July 2015 and 31 December 2017

	BDQ group (*n* = 77) *n* (%)	Non-BDQ group (*n* = 200) *n* (%)	Total (*n* = 277) *n* (%)
Demographic characteristics			
Sex			
Female	32 (41.6)	110 (55.0)	142 (51.3)
Male	45 (58.4)	90 (45.0)	135 (48.7)
Age, years, median [IQR]	39 [29–49]	27 [18–40]	30 [22–44]
Age, years			
<15	1 (1.3)	32 (16.0)	33 (11.9)
15–49	60 (77.9)	144 (72.0)	204 (73.6)
⩾50	16 (20.8)	24 (12.0)	40 (14.4)
Clinical characteristics			
BMI median [IQR]	17.3 [15.9–19.5]	16.4 [14.5–18.9]	17.0 [15.1–19.1]
HIV status			
Negative	76 (98.7)	182 (91.0)	258 (93.1)
Positive	1 (1.3)	6 (3.0)	7 (2.5)
Unknown	0 (0.0)	12 (6.0)	12 (4.3)
Case definition			
Clinical	8 (10)	47 (23.5)	55 (19.9)
Bac+	69 (89.6)	153 (76.5)	222 (80.1)
Registration category			
New	44 (57.1)	114 (57.0)	158 (57.0)
Previously treated*	33 (42.9)	86 (43.0)	119 (43.0)
Resistance profile†			
RR	10 (13.0)	58 (29.0)	68 (24.5)
MDR	45 (58.4)	131 (65.5)	176 (63.5)
Pre-XDR	10 (13.0)	3 (1.5)	13 (4.7)
XDR	12 (15.6)	3 (1.5)	15 (5.4)
Unknown	0 (0.0)	5 (2.5)	5 (1.8)
Disease site			
EPTB	8 (10.4)	44 (22.0)	52 (18.8)
Pulmonary	69 (89.7)	156 (78.0)	225 (81.2)
Pulmonary only	58 (75.3)	107 (53.5)	165 (59.6)
Pulmonary and EPTB	11 (14.3)	49 (24.5)	60 (21.6)

*Bacteriologically confirmed TB by smear microscopy, Xpert® MTB/RIF or culture.
†Includes relapse, treatment failure and treatment after loss to follow-up.
MDR-TB = multidrug-resistant tuberculosis; BDQ = bedaquiline; IQR = interquartile range; BMI = body mass index; HIV = human immunodeficiency virus; RR = rifampicin-resistant; XDR = extensively drug-resistant; EPTB = extrapulmonary TB.

EPTB clinically diagnosed case, 2 deaths prior to the drug being available in the programme). A high proportion (95%) of patients eligible and monitored were culture-negative by 6 months. This was based on a culture result in month 5 or 6 in a majority of patients: 54/77 (70.1%) for the non-BDQ group and 31/47 (66.0%) for the BDQ group. All of the 4 patients (1 pre-XDR, 3 drug intolerance) in the BDQ group with a positive culture by 6 months were clinically responding.

DISCUSSION

This operational research describes the initial implementation of BDQ for the treatment of MDR-TB in Daru, Papua New Guinea, and supports rapid adoption of the new WHO MDR-TB treatment guidelines[9] in the programme. BDQ was well tolerated and safe and it was feasible to implement a core package of aDSM. A high rate of toxicity from injectable agents necessitating initiation of BDQ was observed in this cohort. In the study period, the Daru MDR-TB programme demonstrated very good interim results at

TABLE 3 Eligibility of patients commenced on bedaquiline in Daru, Papua New Guinea, between 1 July 2015 and 31 December 2017

	Frequency (*n* = 77) *n*	(%)
Eligibility criteria		
Resistance	21	(27.3)
XDR	12	(15.6)
Pre-XDR	9	(11.7)
Drug intolerance*	55	(71.4)
Ototoxicity only	15	(19.5)
Nephrotoxicity only	17	(22.1)
Both	23	(29.9)
Unknown	1	(1.3)
Total	77	(100)

*Exclusively for injectable agents.
XDR = extensively drug-resistant.

TABLE 4 Monitoring with ECG and culture at month 6 for MDR-TB patients in care and commenced on BDQ compared to those not commenced on BDQ, Daru, Papua New Guinea, 1 July 2015–31 December 2017

	BDQ group *n* = 77 *n* (%)	Non-BDQ group *n* = 200 *n* (%)	Total *n* = 277 *n* (%)
Patients in care, total	72	181	253
Culture monitoring			
Eligible*	65 (84.4)	112 (56.0)	177 (63.9)
Baseline positive culture	42 (64.6)	56 (50.0)	98 (55.4)
Follow-up cultures, median [IQR]	2 [1.5–3]	2 [1–3]	2 [1–3]
Monitored†	51 (78.5)	80 (71.4)	132 (74.6)
⩾3 follow-up culture tests	16 (24.6)	24 (21.4)	40 (22.6)
⩾4 follow-up culture tests	6 (9.2)	3 (2.7)	9 (5.1)
ECG monitoring			
Completed (>5)	64 (89.9)	Not performed	
Partial (⩾3)	71 (98.6)		

*Patients in care; aged >15 years; pulmonary TB.
†Among eligible patients who had ⩾2 valid culture tests sent ⩾30 days apart (see Figure 2 for full definitions).
ECG = electrocardiogram; MDR-TB = multidrug-resistant tuberculosis; * BDQ = bedaquiline; IQR = interquartile range.

month 6, with <1% LTFU, 91% in care and 95% culture-negative among those monitored. This was delivered through a community-based model of care, in a rural setting in a resource-limited country. There was a similar proportion of patients with a negative culture by month 6 in the BDQ and non-BDQ groups, despite patients eligible for BDQ having a higher risk for poor outcome.[19]

There was successful implementation of a core package of aDSM and ECG monitoring in the programme. Our cohort had sub-optimal culture monitoring, which was related to multiple factors including human resource shortages and interruption to transportation systems. The programme has since taken steps to address this. BDQ was safe, including in those with 'off-label' use, with only one serious adverse event attributable to BDQ among eight cases (including 5 deaths). This is consistent with the safety data from studies that informed the latest WHO guidance.[9] The high rates of injectable agent toxicity support the rapid adoption of the new WHO guidance in the programme.[11]

The standardised MDR-TB regimen used in the Daru programme comprised 5 effective agents and included linezolid and clofazimine during the study period. This demonstrated good interim results in the non-BDQ group. The 6-month culture-negative rate of 92.2% for the BDQ group in this study compares favourably with the published literature, notwithstanding the differences in definitions used. Previous interim cohort analyses of BDQ-containing regimens have reported culture conversion rates between 64–97%.[20,21] These studies have largely been conducted at higher level facilities in metropolitan centres or in programmes that are not resource-constrained. The high proportion of patients in care could be attributed to high quality care and treatment. This involved training medical staff with field-based mentoring and remote technical support, dedicated nursing, counselling and education staff for TB, patient monitoring systems for follow-up and an ambulatory patient-centred care model.

The strengths of our study were that it was conducted under routine programme conditions with the implementation of a core aDSM package and therefore the findings are relevant to scale-up plans in PNG. Enhanced and high-quality data collection from the electronic medical record system in the TB programme in Daru enabled this operational research and there were little missing data.

The limitations were that the comparison of BDQ effectiveness was difficult in a small retrospective cohort due to confounders and the suboptimal culture monitoring in the programme. Implementation conditions changed over time (monitoring, staffing, quality of care, patient counselling) and patient selection criteria were applied for BDQ. In the culture-negative analysis by month 6, there was a potential bias toward a favourable outcome in the non-BDQ group as BDQ was received for <6 months at analysis. This would be more pronounced in the 21 (27.3%) patients who received BDQ due to resistance, as their regimens may have been less effective. There was a bias toward a lower proportion of death

TABLE 5 Interim result indicator analysis at month 6 for MDR-TB patients commenced on BDQ compared to those not commenced on BDQ, Daru, Papua New Guinea, 1 July 2015–31 December June 2017

	BDQ group *n* = 77 *n* (%)	Non-BDQ group *n* = 200 *n* (%)	Total *n* = 277 *n* (%)
Interim result indicators			
Lost to follow-up	0	2 (1.0)	2 (0.7)
Died	5 (6.5)	17 (8.5)	22 (8.0)
In care	72 (93.5)	181 (90.5)	253 (91.3)
Culture status by 6 months among those in care and monitored*	51	80	131
Culture-negative	47 (92.2)	77 (96.2)	124 (94.7)
Culture-positive	4 (7.8)	3 (3.8)	7 (5.3)

*Among eligible patients who had ⩾2 valid culture tests sent ⩾30 days apart (see Figure 2 for full definitions).
MDR-TB = multidrug-resistant tuberculosis; BDQ = bedaquiline.

in the BDQ group as data on time from BDQ eligibility (determined by clinicians) to initiation were not available, although there were known delays in procurement and supply, particularly in the initial 12 months of the study. Our operational definition of culture-negative has potential problems, noting our denominator is restricted to those who were monitored, rather than all enrolled patients. Monthly cultures were not performed in the majority of patients, however 66% of valid culture results were from months 5 or 6 in the BDQ group, meaning reversion at month 6 is less likely. However, the study objective was not to assess the efficacy of BDQ, as this is established,[9,21] but rather to assess the indicators to reflect the programmatic effectiveness. Furthermore, there is debate around the utility of culture as a surrogate marker of cure or relapse-free survival.[22] It will be important to conduct further operational research to report on final treatment outcomes and relapse-free survival in this cohort.

Early experience in Daru shows BDQ is safe and feasible to implement in a remote, community-based setting with aDSM with good interim effectiveness. This has led to the adoption and plan for national scale-up of a BDQ-containing longer regimen, as per the 2019 WHO consolidated MDR-TB treatment guidelines.[8] Off-label use of BDQ will be further explored for patients in need, according to WHO best practices.[17] Steps have been taken by the programme to strengthen culture monitoring in the programme. Our experience serves as an example for similar programmes in remote settings that may be hesitating to scale up newer TB drugs or regimens. It is feasible to implement aDSM and embed operational research into programmes in resource-limited settings to enable innovations in the delivery of MDR-TB care and improve patient outcomes.

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Contexte : La bédaquiline (BDQ) a été introduite dans le programme de la tuberculose multirésistante (MDR-TB) de Daru, région isolée de Papouasie Nouvelle Guinée, en 2015, en parallèle à un ensemble de mesures de suivi actif de la sécurité des médicaments (aDSM).

Objectif : Evaluer les résultats d'intérim et la sécurité de la BDQ pour le traitement de la MDR-TB du 1 juillet 2015 au 31 décembre 2017.

Schema : Analyse rétrospective de cohorte des données de routine du programme.

Resultats : Sur 277 patients MDR-TB, 77 (39%) patients ont reçu de la BDQ avec un total de 8 effets secondaires graves dont 5 (6,5%) décès ; l'un d'eux (1,3%, allongement de QTcF, grade 3) a été attribuable à la BDQ. Sur 200 (61%) patients qui n'ont pas reçu de BDQ, il y a eu 17 (9%) décès. L'exhaustivité du suivi du groupe BDQ a été de 90% pour plus de 5 électrocardiogrammes et de 79% pour au moins 2 cultures. Dans l'analyse des indicateurs de résultats d'intérim au 6e mois dans les groupes BDQ et non-BDQ, il y a eu respectivement 0% et 1% de perdus de vue ; 6,5% et 8,5% de décès ; 94% et 91% de patients en traitement; 92% et 96% de culture négative parmi les patients suivis.

Conclusion : Une expérience précoce à Daru montre que la BDQ est sûre, que sa mise en œuvre est faisable avec aDSM avec une bonne efficacité d'intérim en faveur de l'adoption et de l'expansion rapides des directives OMS 2018 du traitement de la MDR-TB dans le programme et dans des contextes isolés similaires.

Marco de Referencia: En el 2015 se introdujo la bedaquilina (BDQ) en el programa de tratamiento de la tuberculosis multirresistente (MDR-TB), al mismo tiempo que un conjunto básico de medidas de vigilancia activa de la toxicidad de los medicamentos en Daru, que es una región remota de Papua Nueva Guinea.
Objetivo: Evaluar los resultados intermedios y la seguridad toxicológica de la BDQ en el tratamiento de la MDR-TB del 1 de julio del 2015 al 31 de diciembre del 2017.
Metodo: Fue este un análisis retrospectivo de cohortes, a partir de los datos corrientes del programa.
Resultados: De los 277 pacientes con diagnóstico de MDR-TB, 77 recibieron BDQ (39%) y se presentaron ocho episodios adversos graves que incluyeron cinco defunciones (6,5%), una de las cuales atribuible a la BDQ (1,3%, por prolongación del intervalo QTcF de grado 3). En los 200 pacientes que no recibieron BDQ (61%), se presentaron 17 defunciones (9%). La exhaustividad de la vigilancia en el grupo que recibió BDQ fue de 90%, con más de cinco electrocardiogramas y 79%, con dos o más cultivos. Según los resultados intermedios del análisis de indicadores a los 6 meses del grupo que recibió BDQ y el grupo sin BDQ, se observaron respectivamente pérdidas durante el seguimiento en 0% y 1%; una mortalidad de 6,5% y 8,5%; permanencia en el servicio de atención de 94% y 91%; y negatividad del cultivo en los pacientes supervisados de 92% y 96%.
Conclusion: La experiencia inicial en Daru pone de manifiesto la seguridad toxicológica de la BDQ y la factibilidad de su introducción con medidas de vigilancia activa de la toxicidad; los resultados intermedios de efectividad respaldan una adopción programática rápida con ampliación de escala de las directrices de la Organización Mundial de la Salud sobre el tratamiento de la MDR-TB del 2018, en otros entornos remotos semejantes.

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