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Is 6 months of bedaquiline enough? Results from the compassionate use of bedaquiline in Armenia and Georgia

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SUMMARY

BACKGROUND AND SETTING: Bedaquiline (BDQ) was initially only available through compassionate use programmes.

OBJECTIVE: To assess the effectiveness and safety of multidrug-resistant tuberculosis (MDR-TB) treatment containing BDQ.

METHOD: Retrospective analysis of data from patients receiving BDQ through compassionate use in Armenia and Georgia from April 2013 to April 2015. Logistic regression was used to assess the risk factors associated with unsuccessful treatment outcomes.

RESULTS: Of 82 patients included, 84.2% (69/82) had fluoroquinolone-resistant MDR-TB and 43.4% (23/53) were seropositive for the hepatitis C virus (HCV). The culture conversion rate was 84.4% (54/64), and 18.5% (10/54) reverted back to positive. In total, 79.3% (65/82) of the patients reported at least one adverse event. Serious adverse events were reported in 14 patients, with 10/14 patients experiencing fatal outcomes—6/10 related to advanced TB and 2/10 assessed as possibly related to BDQ. Treatment outcomes were as follows: 58.5% treatment success, 12.2% deaths, 7.3% failures and 21.9% lost to follow-up. HCV coinfection was associated with unsuccessful outcomes (adjusted OR 4.45, 95%CI 1.23–16.13).

CONCLUSION: BDQ through compassionate use showed relatively good success rates and safety profiles in a cohort with difficult-to-treat MDR-TB. High rates of reversion may indicate that >24 weeks of BDQ is necessary in some cases. HCV coinfection should be diagnosed and treatment considered in MDR-TB patients.

KEY WORDS: MDR-TB; treatment; new anti-tuberculosis drugs; duration; hepatitis C

'COMPASSIONATE USE' PROGRAMMES are intended to provide potentially lifesaving experimental treatment for patients suffering from a disease for which no satisfactory authorised treatment exists and/or who cannot enter a clinical trial. For many patients, these programmes represent their last hope.[1]

Bedaquiline (BDQ), one of only two new drugs registered and recommended for tuberculosis (TB) in over 50 years,[2,3] was initially only available through a manufacturer-led compassionate use programme. Before the introduction of new drugs, the programmatic treatment outcomes for multidrug-resistant TB (MDR-TB, defined as TB strains resistant to rifampicin and isoniazid) were poor.[4] Although success rates of >80% have recently been reported for MDR-TB in clinical trials (Otsuka trial 213: preliminary results. 48th Union World Conference on Lung Health, Guadalajara, Mexico, 11–14 October 2017),[5] successful outcomes are much lower for extensively drug-resistant TB (XDR-TB, defined as MDR-TB with additional resistance to fluoroquinolones [FQs] and injectable drugs), ranging from 27% to 40% in published meta-analyses.[6,7]

Some countries with no previous experience of compassionate use have developed compassionate use frameworks to facilitate early access to BDQ.[8] Armenia and Georgia are two such countries who, with the support of Médecins Sans Frontières (MSF), introduced BDQ with repurposed drugs linezolid (LZD) and imipenem/cilastatin (IPM), also never used before in those countries, to provide the much needed possibility to treat highly resistant MDR- and XDR-TB patients.

We describe the treatment outcomes and factors associated with unfavourable outcomes in a cohort of patients treated under compassionate use with BDQ and repurposed drugs. We also discuss the effect of 24-week limited-duration BDQ use on treatment outcomes.

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METHODS

Setting and population

This was a retrospective cohort study of all patients who received MDR-TB regimens containing BDQ through an MSF-supported compassionate use programme in Armenia from April 2013 to April 2015, and in Georgia from July 2014 to April 2015. The National Centre for Tuberculosis and Lung Disease in Tbilisi, Georgia, had accessed the Janssen Compassionate Use programme independently without MSF support before this period. These patients were not included in the analysis.

National drug-resistant TB committees made up of physicians experienced in MDR-TB care identified eligible patients according to the guidance provided by the manufacturer for the global Compassionate Use programme.[9] Eligibility criteria were bacteriologically confirmed pulmonary MDR-TB with additional resistance to an FQ and/or injectable second-line drug, age > 18 years, inability to participate in a clinical trial, possibility of constructing a background regimen of at least three anti-tuberculosis drugs in addition to BDQ, and able to receive the appropriate patient follow-up in a medical institution.

After obtaining informed consent, individual case summaries with relevant test results, including human immunodeficiency virus testing results, were reviewed by the MSF-Partners in Health Compassionate Use Committee, now known as the endTB Medical Committee.[10] Once approved, the cases were sent to the Janssen Compassionate Use Advisory Committee.[11] If approval was received, 188 tablets of BDQ 100 mg (24 weeks) were provided by the manufacturer for use on a named-patient basis only, with no possibility of extension beyond the 24 weeks due to the restrictions imposed by the Compassionate Use programme.

LZD (600 mg/day) and IPM (2 g/day) given with amoxicillin clavulanate, which were previously unavailable in the National Tuberculosis Programmes (NTPs) in both countries, were supplied by MSF; other second-line MDR-TB drugs were supplied by the NTPs. Treatment regimens were individually constructed to include four or five effective drugs for a total duration of 20–24 months. All drugs were given under direct observation. There was close follow-up and management of adverse events (AEs) and comorbidities, and psychosocial support was provided by a dedicated medical team.

Patients were monitored according to the recommendations of the Compassionate Use programme and the 2013 World Health Organization interim policy recommendations on the use of BDQ.[2] This included standard monitoring of MDR-TB patients by monthly sputum microscopy, culture, drug sensitivity testing (DST), electrolytes, creatinine and audiometry, with additional monthly monitoring of QTcF, full blood count and liver function.

Definitions

Baseline resistance patterns were defined and classified according to the DST result: 1) MDR-TB only: isolate resistant in vitro to at least isoniazid and rifampicin and with susceptibility to an injectable (capreomycin, kanamycin or amikacin) and FQs; 2) pre-XDR-TB (injectable): MDR-TB with additional resistance to at least one injectable but susceptible to FQs; 3) pre-XDR-TB (FQs): MDR-TB with additional resistance to at least one FQ but susceptible to injectable drugs; 4) XDR-TB: MDR-TB plus resistance to any FQ and an injectable drug.

AEs, i.e., any untoward medical occurrence during treatment that does not necessarily have a causal relationship with this treatment, were reported irrespective of cause and severity if they resulted in the interruption of an individual drug or all treatment for >2 days, or if considered clinically important by the clinician. Serious adverse events (SAEs), i.e., any untoward medical occurrence irrespective of cause that resulted in death, was life-threatening, required hospitalisation, resulted in significant disability or congenital defect, or was considered otherwise medically important, and pregnancies were reported to the manufacturer using a standard reporting form.

A positive baseline culture was defined as any positive culture from 6 months before until 1 month after the start date of MDR-TB treatment. Culture conversion was defined as two consecutive culture-negative samples taken at least 28 days apart. Time to culture conversion was the time between the date of treatment initiation until the date of collection of the first of two negative cultures. Culture reversion was defined as two consecutive positive cultures on different occasions following initial culture conversion to negative. Time to culture reversion was defined as the time between the start date of treatment and the date of the collection of the first of two positive culture samples following conversion. Treatment outcomes were defined by clinicians based on World Health Organization definitions.[12] Favourable outcome was defined as a combination of cured and treatment completed. Unfavourable outcome was the combination of loss to follow-up, death and failure.

Management and analysis of data

Routine programme data and information on AEs were collected and entered into a standardised database (Koch 6, MSF, Paris, France) on site. SAEs and pregnancies were subsequently reported retrospectively to the MSF Central Pharmacovigilance Unit (operational from October 2015).

Patient characteristics were summarised using frequencies and percentages for categorical variables,

and median and interquartile ranges (IQRs) for continuous variables. Univariate and multivariate logistic regression was performed to identify risk factors for unfavourable outcomes. Covariates associated with $P < 0.4$ in the univariate analysis were included in the initial multivariate model, and missing values were imputed through multiple sequential imputation using chained equations. Statistical significance ($P < 0.05$) was assessed using the likelihood-ratio test. Kaplan-Meier analysis was used to evaluate the time to culture conversion. All data were anonymised before central analysis using Stata v 14.2 (Stata Corporation, College Station, TX, USA).

Ethical approval

The study protocol was approved by the relevant health authorities and ethics committees in France (Comité de Protection des Personnes, Ile-de-France V, Hôpital Saint-Antoine, Paris), Armenia (National Centre for Tuberculosis Control, Yerevan) and Georgia (Ethics Committee of the National Centre for Tuberculosis and Lung Diseases, Tbilisi). Patients consented to the use of BDQ under compassionate use and the anonymised use of their data.

RESULTS

The patient and treatment characteristics of the 82 patients included are shown in Table 1. The majority were males (82.9%) with difficult-to-treat forms of MDR-TB: FQ resistance (84.2%), bilateral lung disease (64.6%), cavities on chest X-ray (86.6%) and previous treatment for MDR-TB (100%). Seropositivity for the hepatitis C virus (HCV) was common (43.4%). At treatment initiation, all patients received LZD, 82.9% received clofazimine (CFZ) and 75.6% IPM. The median duration of LZD use was 22 months (IQR 10.8–23.9); 10/82 (12.1%) patients stopped LZD before 6 months.

Of the 64 patients with a positive culture at treatment initiation, 54 (84.4%) culture converted in a median of 2.7 months (IQR 1.4–4.0). Of the 54 who culture converted, 10 (18.5%) subsequently reverted back to positive culture. No patients who were culture-negative at treatment start became culture-positive. The median time from culture conversion to subsequent reversion was 4.2 months (IQR 2.3–10.5), and the median time from treatment start to reversion was 7.9 months (IQR 6.2–12.7). Time to culture conversion is shown in the Figure.

End-of-treatment outcomes were as follows: 43.9% (36/82) cured, 14.6% (12/82) treatment completed (overall success rate 48/82, 58.5%), 12.2% (10/82) died, 7.3% (6/82) failed treatment and 21.9% (18/82) were lost to follow-up (LTFU). Among the latter, 77.8% (14/18) were LTFU after 9 months on treatment, the majority of whom were negative on final culture (11/14, 78.6%). The median time from BDQ start date to death was 6.9 months (IQR 4.6–14.0) and to LTFU it was 15.7 months (IQR 9.2–18.4). The results of the univariate and multivariate analyses on factors associated with unfavourable outcomes are shown in Table 2. The presence of cavities on chest X-ray, bilateral disease, HCV coinfection and smear positivity at treatment start were associated with unfavourable outcomes in the univariate analysis. After adjustment, the only factor that remained associated with an unfavourable outcome was HCV coinfection (adjusted odds ratio 4.45, 95% confidence interval [CI] 1.23–16.13). Unfavourable outcomes were not associated with previous exposure to CFZ, XDR-TB, coinfection with HIV, diabetes mellitus, sex or age.

Table 1 Characteristics of patients receiving bedaquiline at treatment start ($n = 82$)

Patient and treatment characteristics	*n* (%)
Country of origin	
Armenia	62 (75.6)
Georgia	20 (24.4)
Male sex	68 (82.9)
Age, years	
Median [IQR]	40.5 [31.0–51.0]
⩾35	52 (63.4)
Ex-prisoner	20 (24.4)
Health worker	2 (2.4)
Use of injecting drugs in the past	9 (11.0)
Data missing	43
Contact with a MDR-TB case	16 (19.5)
BMI, kg/m^2	
Median [IQR]	19.5 [17.8–22.1]
<18.5	28 (34.1)
Diabetes mellitus	6 (7.3)
HIV-positive	4 (5.0)
Data missing	2
Hepatitis C antibody-positive	23 (43.4)
Data missing	29
Cavities on CXR	71 (86.6)
Bilateral disease on CXR	53 (64.6)
Sputum culture-positive at treatment start	63 (76.8)
Smear result	
Negative	33 (40.2)
1+	16 (19.5)
2+	15 (18.3)
3+	17 (20.7)
Scanty	1 (1.2)
DST profile	
MDR-TB	6 (7.3)
Pre-XDR-TB resistant to injectables	7 (8.5)
Pre-XDR-TB resistant to FQs	29 (35.4)
XDR-TB	40 (48.8)
Previously treated with second-line drugs	82 (100)
Previously used drugs	
FQs	81 (98.8)
Injectables	81 (98.8)
CFZ	32 (39.0)
Repurposed drugs used at bedaquiline initiation	
CFZ	68 (82.9)
Linezolid	82 (100)
Imipenem	62 (75.6)

IQR = interquartile range; MDR-TB = multidrug-resistant tuberculosis; BMI = body mass index; HIV = human immunodeficiency virus; CXR = chest X-ray; DST = drug susceptibility testing; XDR-TB = extensively drug-resistant TB; FQ = fluoroquinolone; CFZ = clofazimine.

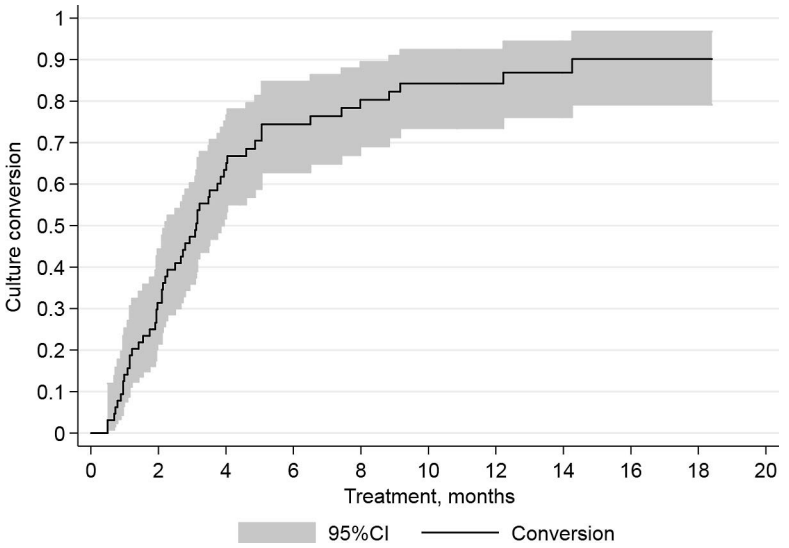

Figure Kaplan-Meier estimates of time to culture conversion in patients initially culture-positive who received bedaquiline at treatment start ($n = 63$). CI = confidence interval.

At least one non-SAE was reported in 79.3% (65/82) of patients. The median time to the first non-SAE was 1.9 months (IQR 0.6–3.6). A total of 237 non-SAEs were reported (Table 3). The most frequent non-SAEs were gastrointestinal symptoms (26.7%), hepatotoxicity (15.3%) and peripheral neuropathy (11%). A QTcF of >500 ms occurred in seven patients (8.5%), all of whom completed 24 weeks of BDQ.

A total of 19 SAEs were reported in 14 patients. Of these, 10/14 (71%) patients had fatal outcomes. The SAEs, possible relatedness to BDQ as reported by the treating physician and other reported causal factors are listed in Table 4 for patients with fatal outcomes and in Table 5 for patients with non-fatal outcomes. Of the 10 fatalities, six (60%) were reported as being related to advanced TB. A possible causal relationship to BDQ was reported in two cases, and to other anti-tuberculosis drugs in six cases.

DISCUSSION

MDR-TB treatment containing BDQ given through compassionate use programmes with LZD and/or IPM showed relatively good success rates in this cohort of previously treated patients with extensive and highly resistant TB. Only one patient is known to have had a relapse of XDR-TB and is now under a treatment regimen containing delamanid. Studies of the treatment outcomes of similar patients treated without BDQ and LZD have shown much lower rates of success.[6,13] BDQ and LZD combinations with the addition of other repurposed drugs, such as CFZ and IPM, have vastly improved outcomes in these patients.[14,15] However, despite having 6-month culture conversion rates comparable with other similar patient cohorts,[16,17] our cohort showed very high rates of culture reversion, and subsequent high failure and death outcomes. The median time to culture

Table 2 Risk factors for unfavourable treatment outcomes among patients receiving BDQ at treatment start ($n = 82$)

Characteristics	OR (95%CI)	*P* value	aOR (95%CI)	*P* value
Male sex	1.34 (0.40–4.42)	0.632		
Age ⩾ 35 years	2.16 (0.83–5.60)	0.113		
Former prison inmate	2.73 (0.97–7.68)	0.057		
Contact of an MDR-TB case	1.12 (0.37–3.38)	0.836		
BMI < 18.5 kg/m^2	2.13 (0.84–5.56)	0.112		
Cavities on CXR	8.68 (1.05–71.48)	0.044		
Bilateral disease on CXR	3.26 (1.19–8.93)	0.021		
HIV-positive	1.37 (0.18–10.28)	0.756		
Hepatitis C antibody-positive	4.27 (1.31–19.92)	0.016	4.45 (1.23–16.13)	0.023
Smear positive at treatment start	3.53 (1.33–9.36)	0.011	2.59 (0.88–7.57)	0.083
XDR-TB strain at treatment start	0.89 (0.37–2.14)	0.793		
Previous use of CFZ	0.95 (0.38–2.33)	0.902		
CFZ at BDQ initiation	1.34 (0.41–4.42)	0.632		
Imipenem at BDQ initiation	1.43 (0.50–4.08)	0.501		

BDQ = bedaquiline; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; MDR-TB = multidrug-resistant tuberculosis; BMI = body mass index; HIV = human immunodeficiency virus; CXR = chest X-ray; XDR-TB = extensively drug-resistant TB; CFZ = clofazimine.

Table 3 Frequency of non-SAE grouped by body system in 82 patients starting a bedaquiline-containing treatment

Reported AE by body system	AE* *n* (%)	Patients† *n* (%)
Gastrointestinal	63 (26.6)	34 (41.5)
Hepatotoxicity	36 (15.2)	27 (32.9)
Peripheral neuropathy	26 (11.0)	21 (25.6)
QT prolongation	17 (7.2)	12 (14.6)
Neurological disorder/headache	17 (7.2)	14 (17.1)
Cardiac event (includes hypotension)	15 (6.3)	13 (15.9)
Allergy	13 (5.5)	8 (9.8)
Ototoxicity	11 (4.6)	9 (11.0)
Other (low magnesium, intolerance, raised lipase, respiratory)	10 (4.2)	10 (12.2)
Dermatological	6 (2.5)	6 (7.3)
Nephrotoxicity	9 (3.8)	5 (6.1)
Haematological	8 (3.4)	3 (3.7)
Musculoskeletal	5 (2.1)	4 (4.9)
Ophthalmologic	1 (0.4)	1 (1.2)
Total	237 (100.0)	

* Number of times the event was reported (% of total events reported).
† Number of patients who experienced this event at least once (% of patients who experienced the event at least once).
SAE = serious adverse event.

reversion from treatment start suggests that stopping an effective drug such as BDQ at 24 weeks, combined with the fact that this patient cohort had been previously treated with second-line drugs, may have contributed to the lack of sustained culture conversion. Since 2013, when WHO BDQ guidelines recommended a maximum duration of 24 weeks of BDQ (the same duration as used in the clinical trial C208[18]), more than 10 000 patients have benefited from BDQ in an MDR-TB regimen,[19] many for more than 24 weeks (Seung K. end TB symposium: accelerating TB elimination through access to bedaquiline and delamanid. 48th Union World Conference on Lung Health, Guadalajara, Mexico, 11–14 October 2017), and evidence has been published on the safety of >24 weeks of BDQ.[15] In addition, a 2017 WHO review found that MDR-TB patients who received BDQ were more likely to survive than those who did not, leading to a downgrading of the anticipated undesirable effects of BDQ.[20] Our study may further support the need for more than 24 weeks of BDQ in patients who do not have sufficient effective drugs in their treatment regimen.

The high proportion of patients co-infected with the HCV, which was associated with a higher risk of unfavourable outcomes, may be explained by risk factors for HCV infection found commonly in MDR-TB patients (such as incarceration and drug use), prolonged contact with the health system and high HCV prevalence in the region.[21] HCV infection has been associated with higher levels of drug-induced liver injury in MDR-TB patients,[22,23] often leading to treatment interruption, itself a risk factor for unfavourable outcomes.[24] Previously active TB was a contraindication to treatment for HCV infection with interferon, frequently leading to a vicious circle of MDR-TB treatment interruptions due to drug-induced hepatotoxicity and subsequent MDR-TB treatment failure. As this is no longer the case with new treatments for HCV infection with direct-acting antivirals, treatment of HCV infection may reduce mortality and hepatotoxicity in co-infected MDR-TB patients, although no published data are currently available.

The high percentage of patients in this cohort who were LTFU remains a matter of concern and, although consistent with the published results of other cohorts of MDR-TB,[4,7,13] some countries and recent clinical trials have achieved much lower LTFU rates.[5,25] The majority of the patients in our cohort were LTFU after 9 months of treatment and were culture-negative at the time, suggesting that a shorter treatment regimen would improve outcomes. However, other factors associated with loss to follow-up, such as AE management as well as social- and patient-related factors, should also be addressed more comprehensively.[26]

BDQ was safe in our cohort of patients, with no unexpected AEs reported; patients were carefully monitored and AEs were managed in a timely fashion. The majority of the deaths were due to progression of extensive and longstanding TB disease. Non-SAEs were common and as expected in patients receiving combinations of anti-tuberculosis drugs. It

Table 4 Reported association between BDQ, other anti-tuberculosis drugs and SAEs with fatal outcomes

Patient no	SAEs with non-fatal outcomes	Possibly related to BDQ	Related to other anti-tuberculosis drugs?	Other reported causal factors
1	Respiratory failure	No	No	Bilateral extensive XDR-TB
1	Peripheral oedema	No	Yes	Bilateral extensive XDR-TB
2	Respiratory failure	No	Yes	Extensive TB, cor pulmonale
3	Nephrotic syndrome	No	Yes	Amyloidosis of kidneys due to TB
4	Tuberculosis	No	Unknown	
5	Cardiopulmonary failure	No	Yes	
6	Committed suicide	No	Yes	Disease duration (TB for 6 years)
7	Acute respiratory failure	No	No	Aspiration pneumonia, overdose
8	TB disease progression	No	No	Extensive TB disease, anaemia
9	Myocardial infarction	Yes	Yes	
10	Cardiopulmonary failure	Yes	Unknown	Extensive TB, cor pulmonale

BDQ = bedaquiline; SAE = serious adverse event; XDR-TB = extensively drug-resistant tuberculosis.

Table 5 Reported association between BDQ, other anti-tuberculosis drugs and SAEs with non-fatal outcomes

Patient no	SAEs with non-fatal outcomes	Possibly related to BDQ	Related to other anti-tuberculosis drugs?	Other reported causal factors
8	Cardiac failure	No	No	Extensive TB disease, anaemia
8	Myocardial infarction	No	No	Extensive TB disease, anaemia
11	COPD	No	Yes	
10	Myocardial infarction	Yes	Unknown	
12	Bronchospasm	Yes	Yes	
12	Cough	Yes	Yes	
13	Hepatotoxicity	Yes	Yes	
14	Gastrointestinal carcinoma	Yes	Yes	

BDQ = bedaquiline; SAE = serious adverse event; TB = tuberculosis; COPD = chronic obstructive pulmonary disease.

should be noted that while QTcF prolongation was detected through routine monitoring with regular electrocardiography, it did not result in the discontinuation of BDQ. This is important because most patients received at least one other QT-prolonging drug (CFZ in 82.9%). The majority of the patients were able to continue to use LZD throughout treatment, despite 25.6% reporting symptoms of peripheral neuropathy, which, although similar to rates seen in other cohorts,[27,28] may indicate that peripheral neuropathy was not confirmed on further specialist testing.

Limitations

Our study had two principal limitations. First, the limited number of patients restricted the analysis of associated factors. Once BDQ became available through regular channels, compassionate use of BDQ was stopped. Additional studies are underway for patients started on BDQ under programmatic conditions.[29] Second, this was an observational study conducted under programmatic conditions and, although extensive data collection had been done by MSF-supported programmes in Armenia and Georgia for many years, this may have led to incomplete or non-standardised data. The patients in this cohort represent patients with no other treatment options, and in general the most severe cases. Extrapolation to other MDR-TB patients without extensive disease, previous treatment and complex resistance patterns is therefore of limited value.

CONCLUSION

The compassionate use of BDQ in combination with LZD and other repurposed drugs showed relatively good success rates and safety profiles. However, high rates of reversion may indicate that more than 24 weeks of BDQ is necessary for some patients, and this finding deserves further investigation. HCV coinfection should be diagnosed and treatment considered in MDR-TB patients. Further studies are necessary to explore the impact of HCV coinfection on MDR-TB treatment completion and treatment success.

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Conflicts of interest: none declared.

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RÉSUMÉ

CONTEXTE : Initialement, la bedaquiline (BDQ) n'était disponible qu'à travers les programmes d'usage compassionnel.

OBJECTIF : Evaluer l'efficacité et l'innocuité du traitement de la tuberculose multirésistante (TB-MDR) contenant la BDQ.

MÉTHODE : Analyse rétrospective des données des patients traités avec la BDQ par usage compassionnel en Arménie et en Géorgie, d'avril 2013 à avril 2015. Une régression logistique a été utilisée pour évaluer les facteurs de risque associés aux résultats de traitement défavorables.

RESULTATS : Parmi 82 patients inclus, 84,2% (69/82) présentaient une TB-MDR résistante aux fluoroquinolones et 43,4% (23/53) étaient co-infectés avec l'hépatite C. Le taux de conversion des cultures était de 84,4% (54/64) et 18,5% (10/54) des patients ont présenté des cultures positives ultérieurement (réversion). Au total, pour 79,3% (65/82) des patients au moins un évènement indésirable a été rapporté. Des évènements indésirables sérieux ont été rapportés parmi 14 patients, parmi lequels 10/14 furent fatals : 6/10 liés avec une TB avancée et 2/10 possiblement liés avec la BDQ. Les résultats de traitement étaient comme suit : 58,5% succès du traitement, 12,2% décès, 7,3% échecs et 21,9% perdus de vu. L'hépatite C était associée à des résultats défavorables de traitement (OR ajusté 4,45 ; IC95% 1,23–16,13).

CONCLUSION : La BDQ en usage compassionnel montre un taux de succès et une innocuité relativement bonne dans cette cohorte de patients ayant une forme de TB-MDR difficile à traiter. Le fort taux de réversion peut indiquer que plus de 24 semaines de BDQ sont nécessaires pour certains cas. L'hépatite C devrait être diagnostiquée et un traitement envisagé pour les patients présentant une TB-MDR.

RESUMEN

MARCO DE REFERENCIA: La bedaquilina (BDQ) en un comienzo solo era accesible por intermedio de programas de uso compasivo.

OBJETIVO: Evaluar la eficacia y la seguridad toxicológica de un tratamiento de la tuberculosis multirresistente (TB-MDR) que contiene BDQ.

MÉTODO: Fue este un análisis retrospectivo de los datos de pacientes que recibieron BDQ en el marco de programas de uso compasivo en Armenia y Georgia de abril del 2013 a abril del 2015. Mediante una regresión logística se evaluaron los factores de riesgo asociados con los desenlaces desfavorables del tratamiento.

RESULTADOS: De los 82 pacientes incluidos en el estudio, el 84,2% (69/82) presentó TB-MDR con resistencia a las fluoroquinolonas y el 43,4% (23/53) fue seropositivo frente a la hepatitis C. La tasa de conversión del cultivo fue 84,4% (54/64) y en el 18,5% de los casos (10/54) el cultivo volvió a ser positivo. En total, el 79,3% de los pacientes (65/82) refirió por lo menos una reacción adversa. Se notificaron reacciones adversas graves en 14 pacientes y en 10 de ellos el desenlace fue mortal, a saber: seis relacionados con una TB avanzada y en dos casos se consideró que podrían estar relacionados con la BDQ. Los desenlaces terapéuticos fueron como sigue: 58,5% de éxitos, 12,2% de defunciones, 7,3% de fracasos y 21,9% de pérdidas durante el seguimiento. La hepatitis C se asoció con desenlaces desfavorables (OR ajustado 4,45; IC95% 1,23–16,13).

CONCLUSIÓN: La utilización de la BDQ en los programas de uso compasivo exhibe tasas de éxito y un perfil de toxicidad relativamente buenos, en una cohorte con TB-MDR de tratamiento difícil. Las altas tasas de reversión de los cultivos pueden indicar que algunos casos requieren más de 24 semanas de BDQ. Es importante diagnosticar la coinfección por el virus de la hepatitis C en los pacientes con TB-MDR y considerar la posibilidad de tratarla.