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SHORT COMMUNICATION

Experiences of introducing new drugs for drug-resistant TB at the ALERT Hospital, Addis Ababa, Ethiopia, 2017–2019

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BACKGROUND: Drug-resistant TB (DR-TB) remains a major public health concern. DR-TB patient data from ALERT (All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre) Hospital, Addis Ababa, Ethiopia, who received bedaquiline (BDQ) and/or delamanid (DLM) containing regimens were analysed.

RESULTS: From 2017 to 2019, 51 DR-TB patients were enrolled. Of 33 patients, 31 (93.9%) had culture converted at 6 months. Of those with final outcomes, 77% (n = 10) were cured. Thirty (58.8%) developed adverse events, the most frequent of which were gastrointestinal disorders (70%), haematological disorders (16.7%) and QTc prolongation (16.7%). Twenty patients discontinued the offending drug permanently.

CONCLUSION: With close monitoring, introduction of new DR-TB regimens brought good early results, which encouraged wider programmatic implementation in Ethiopia.

Ethiopia is included in the WHO list of 30 high multidrug-resistant TB (MDR-TB) burden countries.[1] In 2017, 680 laboratory-confirmed cases of rifampicin-resistant TB (RR-TB)/MDR-TB patients were put on second-line drug treatment. Adults with RR-/MDR-TB were previously recommended at least 18 months of treatment, including a second-line injectable (SLI) agent.[2] In recent years, WHO recommendations for drug-resistant TB (DR-TB) treatment have included regimens containing bedaquiline (BDQ) or delamanid (DLM).[3,4] In 2016, the Ethiopian National TB Programme (NTP) developed guidelines for the introduction of BDQ and DLM. In April 2016, the first eligible patients were started on BDQ- and DLM-based individualised treatment regimens (BDQ-/DLM-ITRs).*

The Challenge TB Project (CTB), a USAID-supported global flagship TB project, supported the NTP to introduce and scale-up new drug-containing DR-TB regimens in Ethiopia. The CTB project also supported laboratory work and DR-TB patient management. In addition, it helped in supplying BDQ from the USAID BDQ donation program, and procurement of DLM.

*Eligibility criteria for BDQ-/DLM-ITR: pre-XDR (extensively drug-resistant) and XDR-TB cases, patients with previous exposure to SLIs, contacts of XDR or pre-XDR cases, patients unable to tolerate MDR-TB drugs, MDR-/RR-TB treatment failures, extensive or advanced MDR-TB disease, those with comorbidities or other conditions with increased likelihood of acquisition of additional resistance or treatment failure.

The All-African Leprosy Rehabilitation and Training Centre (ALERT) Hospital in Addis Ababa, Ethiopia, has been a DR-TB treatment centre for many years. In April 2017, BDQ- and DLM-ITR were introduced. We report here on early results and drug toxicity patterns among DR-TB patients enrolled on BDQ-/DLM-ITRs at the hospital from April 2017 to March 2019 and the lessons learnt. Data on patients on BDQ-/DLM-ITR and analysis were collected retrospectively. Data were collected from the hospital's DR-TB Department Register and patient charts. Ethical clearance was obtained from the Armauer Hansen Research Institute (AHRI)/ALERT Ethics Committee, Addis Ababa, Ethiopia.

ASPECTS OF INTEREST

Demographic and clinical characteristics

Of the 51 patients enrolled on BDQ-/DLM-ITRs, 29 (56.9%) were men, with a mean age of 32.3 ± 13.7 years. Mean body mass index was 16.3 ± 2.4 kg/m^2. Fifteen (30%) were HIV-positive and on antiretroviral therapy.

Thirty-six (70.6%) cases were tested using Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), 10 (19.6%) using line-probe assays and 5 (9.8%) patients using conventional phenotypic drug susceptibility testing (DST). Respectively 26 (50.9 %) and 13 (25.4%) had been previously treated with first-line and second-line drugs. Respectively, 28 (54.9%), 10 (19.6%) and 13 (25.5%) patients were on BDQ-, DLM- and BDQ + DLM-ITR. By 6 months, 31/33 (93.9%) had culture converted; there were two deaths. Of 13 patients with final treatment outcomes, 10 (77%) patients were cured and 3 (23%) died.

Adverse drug events occurring during treatment

Thirty (58.8%) patients developed ⩾1 adverse event (AE) during treatment. Respectively 9.8%, 43.1% and 5.9% developed mild, moderate or severe AEs.[5] The most frequent AEs were as nausea, vomiting and gastritis (n = 21, 70%); haematological disorders (mainly anaemia, n = 5, 16.7%) and QTc prolongation (n = 5, 16.7%) (Figure). In respectively 40% and 14.3%, the offending drug(s) were either permanently removed or temporarily discontinued. Only one patient who received BDQ had electrocardiograph abnormalities resulting in permanent discontinuation of BDQ. At Week 5 of treatment, the patient developed QTcF > 450 ms but <500 ms, with premature ventricular complex bigeminy. This returned to normal after BDQ was discontinued.

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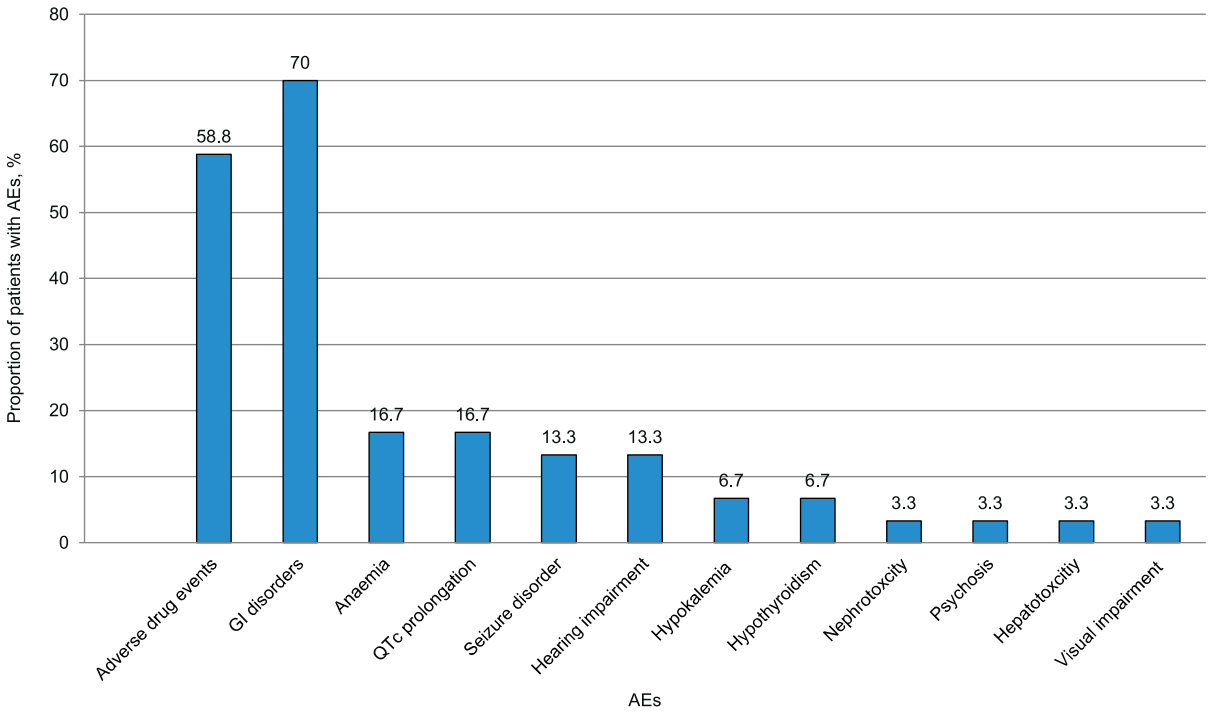

FIGURE Adverse events in patients on BDQ-/DLM-ITRs (*n* = 51). GI = gastro-intestinal; ITR = individualised treatment regimen.

Twelve (23.5%) patients developed serious adverse events (SAEs).[6] Six (11.7%) died, 1 (2%) developed severe pneumonia which treatment improved, and 5 (9.8%) developed medically significant conditions (seizure disorder in 4 patients and 1 patient had a psychotic episode – all improved with treatment). Of the 6 deaths, 4 were on BDQ-ITR and 2 on DLM-ITR; none were attributed to any specific drug (Table).

DISCUSSION

The management of DR-TB is challenging and needs thorough clinical evaluation of the patient, DST and meticulous patient monitoring. Six-month culture conversion was found to be >90% in the cohort – much better than a cohort study done in three countries in which 28 patients put on BDQ- and DLM-ITR showed a culture conversion rate of 74% by 6 months.[7]

TABLE Eligibility criteria, BDQ-/DLM-ITR, and possible cause of death (*n* = 51)

	n (%)
Indication for individualised treatment	
Hearing impairment	12 (23.5)
Pre-XDR-TB to SLI	3 (5.9)
Pre-XDR to FQ	7 (13.7)
Advanced and multiple cavitary lung lesions	16 (31.4)
Failed by standard MDR-TB treatment	5 (9.8)
Acute kidney injury	8 (15.7)
Chronic kidney disease	3 (5.9)
Treatment regimens	
Regimen containing BDQ	28 (54.9)
Regimen containing DLM	10 (19.6)
Regimen containing BDQ and DLM	13 (25.5)
Possible cause of death	
Severe respiratory failure secondary to severe pneumonia	1 (20 years old, male, HIV co-infected, C+)
Sudden death of unknown cause after overnight excess alcohol intake	1 (33 years old, male, HIV-infected, C–)
End-stage renal disease with uremic encephalopathy	1 (31 years old, male, chronic renal disease, C–)
Severe peripheral arterial disease with wet gangrene and severe sepsis	1 (42 years old, male, HIV co-infected, C–)
Respiratory failure secondary to severe pulmonary hypertension	1 (62 years old, male, Cardiac illness, C–)
Multi-organ failure secondary to disseminated TB	1 (19 years old, female, HIV co-infected, C+)

BDQ = bedaquiline; DLM = delamanid; ITR = individualised treatment regimen; XDR-TB = extensively drug-resistant TB; SLI = second-line injectable; FQ = fluoroquinolone; MDR-TB = multidrug-resistant TB; C = culture; + = positive; – = negative.

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Adverse events are an almost inevitable occurrence during DR-TB treatment. Almost 60% in the cohort had ⩾1 AE, most commonly gastrointestinal disorders, QTcF prolongation and haematological disorders. Nausea, vomiting and dyspepsia were more prevalent, similar to an MDR-TB cohort treated in two other hospitals in Ethiopia.[8] In a large study conducted in 15 countries with patients receiving BDQ-ITR, including various other SLIs, 24/247 (9.7%) patients experienced a QTcF prolongation of >500 ms.[9] Haematological disorders were another important AE in patients on regimens containing linezolid, well known to potentially cause bone marrow suppression with severe anaemia.

Thirteen (25.5%) patients were on both BDQ and DLM because of the extremely limited drug options available to construct an effective regimen. However, just five (16.7%) developed moderate QTc prolongation (<500 msec) and of these, only two were on combined BDQ + DLM-ITR. This re-confirms the finding of others which show that the combined use of BDQ and DLM is a relatively safe therapeutic option.[10]

To manage the AEs in the study cohort, either the offending drug was permanently removed and replaced with a new drug (40%) or it was temporarily interrupted and additional ancillary drugs used (14.3%). The same practice has been implemented in different countries. SAEs occurred in 12 patients (6 deaths, 1 life threatening and 5 medically significant conditions), which is consistent with the findings of other studies. However, none of the deaths were attributed to any specific drug.

CONCLUSION

This hospital-based intervention showed that BDQ and/or DLM introduction is feasible and resulted in satisfactory 6-month culture conversion rates and final treatment outcomes. High levels of AEs led to drug discontinuation either permanently or temporarily. However with good monitoring and management practices, these were identified and managed appropriately in a timely manner. BDQ- and DLM-containing DR-TB regimens should be followed by rapid country-wide introduction in national policies of all-oral treatment regimens for a wide group of DR-TB patients to improve treatment outcomes and quality of life among DR-TB patients.

References

1 World Health Organization. Global tuberculosis report, 2018. Geneva, Switzerland: WHO, 2019. https://www.who.int/tb/publications/global_report/en/
2 Falzon D, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Eur Respir J 2011; 38(3): 516–528.
3 World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva, Switzerland: WHO, 2013. http://www.ncbi.nlm.nih.gov/books/NBK154134/.
4 World Health Organization. The use of delamanid in the treatment of multidrug-resistant tuberculosis. Geneva, Switzerland: WHO, 2019. https://www.who.int/tb/publications/delamanid-in-mdr-tb-treatment/en/
5 Division of AIDS Regulatory Support Center, National Institutes of Health. Table for grading the severity of adult and pediatric adverse events corrected, Version 2.1. Bethesda, MD, USA: DAIDS, 2017. https://rsc.niaid.nih.gov/clinical-research-sites/grading-severity-adult-pediatric-adverse-events-corrected-version-two-one
6 World Health Organization. Active tuberculosis drug-safety monitoring and management (aDSM): framework for implementation. Geneva, Switzerland: WHO, 2016. http: //www.who.int/tb/publications/aDSM/en/
7 Ferlazzo G, et al. Early safety and efficacy of the combination of bedaquiline and delamanid for the treatment of patients with drug-resistant tuberculosis in Armenia, India, and South Africa: a retrospective cohort study. Lancet Infect Dis 2018; 18(5): 536–544.
8 Meressa D, et al. Achieving high treatment success for multidrug-resistant TB in Africa: initiation and scale-up of MDR TB care in Ethiopia—an observational cohort study. Thorax 2015; 70(12): 1181–1188.
9 Borisov SE, et al. Effectiveness and safety of bedaquiline-containing regimens in the treatment of MDR- and XDR-TB: a multicentre study. Eur Respir J 2017; 49(5): 1700387.
10 Maryandyshev A, et al. Bedaquiline and delamanid combination treatment of 5 patients with pulmonary extensively drug-resistant tuberculosis. Emerg Infect Dis 2017; 23(10): 1718–1721.

CONTEXTE : La TB pharmacorésistante (DR-TB) reste une préoccupation de santé publique majeure. Les données des patients DR-TB de l'hôpital ALERT (All Africa Leprosy, Tuberculosis and Rehabilitation Training Centre, Addis Ababa, Ethiopie) qui ont reçu des protocoles contenant de la bédaquiline et/ou du délamanide ont été analysées.

RÉSULTATS : Des 51 patients DR-TB ont été enrôlés de 2017 à 2019, 90 ont eu une conversion de culture à 6 mois, 77% ont été guéris, 30 ont eu des effets secondaires, les plus fréquents étant des troubles gastro-intestinaux (70%), des troubles hématologique (16,7%) et un allongement de QTc (16,7%). Vingt patients ont définitivement arrêté le médicament incriminé.

CONCLUSION : Moyennant une surveillance étroite, l'introduction de nouveaux protocoles DR-TB a eu de bons résultats précoces qui encouragent une mise en œuvre programmatique plus large en Ethiopie.

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