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

Gabriella Ferlazzo, Erika Mohr, Chinmay Laxmeshwar, Catherine Hewison, Jennifer Hughes, Sylvie Jonckheere, Naira Khachatryan, Virginia De Avezedo, Lusine Egazaryan, Amir Shroufi, Stobdan Kalon, Helen Cox, Jennifer Furin, Petros Isaakidis

Summary

Background **Bedaquiline and delamanid have been approved for treatment of multidrug-resistant (MDR) tuberculosis in the past 5 years. Because of theoretical safety concerns, patients have been unable to access the two drugs in combination. Médecins Sans Frontières has supported the use of combination bedaquiline and delamanid for people with few treatment options since 2016. We describe early safety and efficacy of regimens containing the bedaquiline and delamanid combination in patients with drug-resistant tuberculosis in Yerevan, Armenia; Mumbai, India; and Khayelitsha, South Africa.**

Methods **We retrospectively analysed a cohort of all patients who received 6–12 months of oral bedaquiline and delamanid in combination (400 mg bedaquiline once per day for 2 weeks, then 200 mg bedaquiline three times per week and 100 mg delamanid twice per day) in MSF-supported projects. We report serious adverse events, QTc corrected using the Fridericia formula (QTcF) interval data, and culture conversion data during the first 6 months of treatment.**

Findings **Between Jan 1, 2016, and Aug 31, 2016, 28 patients (median age 32·5 years [IQR 28·5–40·5], 17 men) were included in the analysis. 11 (39%) of 28 patients were HIV-positive. 24 patients (86%) had isolates resistant to fluoroquinolones; 14 patients (50%) had extensively drug-resistant tuberculosis. No patient had an increase of more than 500 ms in their QTcF interval. Four patients (14%) had six instances of QTcF increase of more than 60 ms from baseline but none permanently discontinued the drugs. 16 serious adverse events were reported in seven patients. Of 23 individuals with positive baseline cultures, 17 (74%) converted to negative by month 6 of treatment.**

Interpretation **Use of the bedaquiline and delamanid combination appears to reveal no additive or synergistic QTcF-prolonging effects. Access to bedaquiline and delamanid in combination should be expanded for people with few treatment options while awaiting the results of formal clinical trials.**

Funding **Médecins Sans Frontières (MSF).**

Lancet Infect Dis 2018

Published Online
February 13, 2018
http://dx.doi.org/10.1016/S1473-3099(18)30100-2

See Online/Comment
http://dx.doi.org/10.1016/S1473-3099(18)30106-3

Médecins Sans Frontières (MSF), Southern Africa Medical Unit (SAMU), Cape Town, South Africa (G Ferlazzo MD, P Isaakidis PhD); **MSF, Khayelitsha, Cape Town, South Africa** (E Mohr MPH, J Hughes MBBCh, A Shroufi MPhil); **MSF, Mumbai, India** (C Laxmeshwar MPH, S Jonckheere MD, S Kalon MPH); **MSF, Paris, France** (C Hewison MPH); **MSF, Yerevan, Armenia** (N Khachatryan MD); **City of Cape Town Health Department, Cape Town, South Africa** (V De Avezedo MD); **National Tuberculosis Programme, Yerevan, Armenia** (L Egazaryan MD); **University of Cape Town (UCT), Division of Medical Microbiology and Center for Infectious Disease Epidemiology and Research, Cape Town, South Africa** (H Cox PhD); **and Harvard Medical School, Department of Global Health & Social Medicine, Boston, MA, USA** (J Furin MD)

Correspondence to:
Dr Petros Isaakidis, Médecins Sans Frontières (MSF), Southern Africa Medical Unit (SAMU), Cape Town 7925, South Africa
petros.isaakidis@joburg.msf.org

Introduction

For almost half a century, the treatment landscape for tuberculosis has remained largely unchanged. For multidrug-resistant (MDR) tuberculosis, low-quality evidence has supported long, toxic, and poorly performing regimens for treatment. Approximately 50% of people with MDR tuberculosis worldwide are reported to be successfully treated, with success dropping to as low as 11–33% for those with fluoroquinolone-resistant or extensively drug-resistant (XDR) tuberculosis.[1–3]

In the past 5 years, two new drugs, bedaquiline (Janssen, Beerse, Belgium) and delamanid (Otsuka, Tokyo, Japan), have been shown to be effective in treating MDR tuberculosis both in randomised trials and in routine health-care settings.[4–6] Both medications are approved by stringent regulatory agencies—bedaquiline was approved in 2012 by the US Food and Drug Administration (FDA)[7] and the European Medicines Agency (EMA), and delamanid was approved in 2014 by the EMA[8] and Japan's Pharmaceuticals Medical Devices Agency. The approvals led to subsequent WHO recommendations for their individual use under specific conditions.[9,10]

As MDR tuberculosis needs to be treated with a combination of multiple effective drugs, the availability of two novel drugs has enormous potential to improve treatment outcomes, particularly for individuals with complex tuberculosis resistance profiles. However, concerns regarding the theoretical safety of combining bedaquiline and delamanid because of their common effects of prolonging the QT interval and an absence of studies on treatment regimens containing the combination have resulted in little or no WHO recommendations.[11–14]

Thus, very little documentation exists about the use of bedaquiline and delamanid treatment combinations. Two case reports of patients treated with bedaquiline and delamanid in combination have been published,[15,16] both of which described excellent early clinical outcomes. A case series of five patients treated with bedaquiline and

Research in context

Evidence before this study

We searched MEDLINE, Google Scholar, the Cochrane database of systematic reviews, and trial registries on Oct 25, 2017, to identify studies in which bedaquiline and delamanid were given in combination. We further screened abstracts of the International Union Against Tuberculosis and Lung Disease's 47th World Conference on Lung Health in 2016 to identify studies of people receiving both bedaquiline and delamanid that had been completed but not yet published. We used the following search terms alone and in combination: "antitubercular agents/therapeutic use", "tuberculosis, multidrug-resistant/therapy", "extensively drug-resistant tuberculosis/therapy", "diarylquinolines/therapeutic use", "nitroimidazoles/therapeutic use", "bedaquiline", "OPC-67683", "OPC-67683","and delamanid". Our search strategy was broad and no exclusion criteria were used. The searches were done by one of the study team members (PI), who then presented findings to all coauthors for discussion.

Three published studies were identified; two were research letters published in 2016 reporting one case each. The two patients described in case reports, one from the Democratic Republic of Congo treated in France and one Tibetan refugee treated in India, had extensively drug-resistant tuberculosis and complicated medical histories. Culture conversion was achieved by both patients over the study period, although one patient had QTc interval prolongation, which was managed with temporary discontinuation of bedaquiline and symptomatic treatment. A case-series of five patients treated with the bedaquiline and delamanid combination was published in October, 2017. Culture conversion was achieved by four of five patients and one patient died. QTc interval prolongation (but no arrhythmias) occurred in two patients. Our search identified one systematic review, which only included the two case reports; no relevant conference abstracts were found. Two registered clinical trials were identified, both of them currently recruiting participants, NCT02583048 and NCT02754765.

Added value of this study

Our data from three programmatic settings in Armenia, India, and South Africa, which have some of the major epidemic hotspots on three different continents, suggest that treatment regimens including the bedaquiline and delamanid combination are well tolerated and the early treatment response was highly satisfactory. By the end of the study period, two-thirds of patients had negative sputum culture and were clinically stable. In addition, regular electrocardiogram monitoring was sufficient to detect QTc prolongation and clinically significant cardiotoxicity was uncommon.

Implications of all the available evidence

Given the limited existing evidence on the coadministration of bedaquiline and delamanid in patients with complex drug-resistant tuberculosis, these study findings should inform clinical and programmatic practices and policies while definitive evidence is accumulating. Improved access to the new tuberculosis drugs as single agents and in combination is needed to improve the clinical management and survival of patients and to reduce community transmission of drug-resistant tuberculosis.

delamanid in combination was published in 2017,[17] which also reported promising early safety and efficacy results. Two clinical trials assessing the safety and efficacy of the combination have recently started enrolling: the US National Institutes of Health's AIDS Clinical Trials Group protocol (ACTG5343; NCT02583048), which will assess the safety, tolerability, and pharmacokinetics of bedaquiline and delamanid alone and in combination; and the endTB trial (NCT02754765), a randomised, open-label, phase 3 trial assessing the efficacy of several regimens for the treatment of MDR tuberculosis, including one combining bedaquiline and delamanid. Results of these trials are expected to be available in the next 3–5 years.[18]

Because of complex resistance profiles, previous exposure to second-line drugs, or drug intolerance, an effective treatment regimen cannot be constructed for a substantial proportion of patients worldwide when making use of only one of the two new drugs in the regimen.[19] Médecins Sans Frontières (MSF) has supported the use of treatment regimens combining bedaquiline and delamanid since 2016 in settings that are highly affected by MDR tuberculosis. The objective of this retrospective analysis was to assess early (up to 6 months) safety and efficacy of treatment regimens containing the combination of bedaquiline and delamanid in a cohort of patients treated in MSF-supported programmes in Armenia, India, and South Africa.

Methods

Study design and population

This was a retrospective cohort study of all consecutive patients with MDR tuberculosis who started on a treatment regimen containing the combination of bedaquiline and delamanid between Jan 1, 2016, and Aug 31, 2016. Patients were older than 18 years, except for one adolescent aged 14 years who was treated on the basis of the input of paediatric MDR tuberculosis experts and with parental permission and patient assent. All patients treated for at least 1 week were included to ensure they had sufficient exposure to both medications. Patients were managed under routine programmatic conditions at MSF-supported sites in Yerevan (and surrounding districts), Armenia; Mumbai, India; and Khayelitsha, South Africa.

The combination of bedaquiline and delamanid was used as part of an individualised, multidrug

anti-tuberculosis treatment regimen. Patients were eligible to receive the combination if a regimen with at least four other effective drugs could not be constructed because of confirmed drug resistance, suspected resistance in the setting of previous drug exposure, drug intolerance, or a combination of these three factors. All cases were reviewed and treatment regimens were approved by an international medical advisory committee (MSF/Partners in Health EndTB committee). Combination bedaquiline and delamanid was initiated in patients at a primary care level (ie, ambulatory patients) in South Africa and India, and in patients admitted to hospital as well as at a primary care level in Armenia.

Ethical approval for this study was granted in South Africa by the University of Cape Town Human Research Ethics Committee (HREC 499/2011). The study has also fulfilled the exemption criteria set by the Médecins Sans Frontières Ethics Review Board (Geneva, Switzerland) for retrospective analyses of routinely collected clinical data and was done with permission from the Medical Director of Médecins Sans Frontières. All background treatment regimens were constructed according to WHO recommendations and patients were informed about the potential clinical benefits and potential adverse events of each drug in the treatment regimen, including bedaquiline and delamanid. Patients provided written informed consent to receive bedaquiline and delamanid.

Procedures

Treatment and hospital admission (when clinically indicated and regardless of cause) were offered free of charge to all patients in all three settings. Bedaquiline and delamanid were administered at the doses recommended by manufacturers: 400 mg of bedaquiline once a day for 2 weeks, followed by 200 mg three times a week and 100 mg of delamanid twice a day. All drugs were administered after a meal. Patients assessed as needing more than 24 weeks of bedaquiline and delamanid treatment were again reviewed by the expert advisory committee.

Treatment safety was regularly monitored. Serial laboratory tests were done systematically at least monthly, including haemoglobin measurement, electrolyte measurements, and renal and liver function tests. Other tests included baseline albumin measurements, thyroid function tests, and other investigations as indicated by clinical status.

An electrocardiogram was done at baseline at the start of treatment, every 2 weeks during the first 3 months of therapy, and monthly thereafter. QTc interval was calculated by the treating physicians and corrected for heart rate using the Fridericia formula (QTcF): observed QT interval divided by cube root of resting rate interval, in ms (QT/[resting rate]$^{0.33}$). The electrocardiogram was repeated only in the event of an abnormal QTcF. Treatment decisions were made on the basis of these results. The QTcF results used in this analysis to calculate the mean changes in QTcF have been recalculated independently by the study authors by use of the heart rate and QT from the electrocardiograms routinely done during the projects to control for potential calculation errors.

Active drug safety monitoring and management was done according to WHO recommendations.[20] Serious adverse events were reported, within 24 h of the clinical team becoming aware of the events, to the central MSF pharmacovigilance unit in Geneva, Switzerland. An assessment of causality associated with tuberculosis and non-tuberculosis drugs and other comorbidities was done by the treating physician and independently assessed by the MSF pharmacovigilance unit and reviewed by a medical adviser. Adverse events were graded according to the MSF pharmacovigilance unit severity scale based on the combined Division of Microbiology and Infectious Disease (DMID) adult toxicity table (November, 2007) and the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Severity of events was graded on a scale of 1 to 4 with 1 being mild and 4 being life threatening. Adverse events that were not considered as serious were reported and recorded in local data collection tools, then reported to the pharmacovigilance unit on a quarterly basis.

For the **DMID adult toxicity table** see https://www.niaid.nih.gov/sites/default/files/dmidadulttox.pdf

Bacteriological monitoring, consisting of monthly smear and culture (on solid or liquid media), plus additional drug susceptibility testing (DST) for first-line and second-line drugs when positive cultures were obtained, was done at the National Health Laboratory Service (NHLS), Cape Town, for the South African cohort, at PD Hinduja National Hospital and Medical Research Centre, Microbiology Laboratory, Mumbai, for the Indian cohort, and at the National Reference Microbiology Laboratory, Yerevan, for the Armenian cohort.

Outcomes

Efficacy was assessed in the cohort using sputum culture conversion measured at 6 months. Sputum culture conversion was defined as two consecutive negative results taken at least 2 weeks apart in a patient with a positive specimen at baseline.[21] Baseline was defined as the initiation of bedaquiline and delamanid in combination even if background MDR tuberculosis treatment was already ongoing. Culture status at 6 months was also assessed as an efficacy outcome and included all people in the study who had a documented negative culture at 6 months regardless of baseline culture status.

Safety was measured in two ways. The first measurement was the occurrence of serious adverse events in the first 6 months of combination therapy. Serious adverse events were defined as deaths irrespective of cause, hospital admissions, events leading to disability or congenital malformation, and events considered life threatening or otherwise medically significant.

	Patient cohort (n=28)
Site	
Armenia	7 (25%)
India	7 (25%)
South Africa	14 (50%)
Less than four effective drugs in the regimen	28 (100%)
Median age, years	32·5 (28·5–40·5)
Sex	
Men	17 (61%)
Women	11 (39%)
HIV-positive patients	11 (39%)
CD4 count, cells per μL*	111 (47–402)
Body-mass index, kg/m²†	18·7 (15·9–21·1)
Albumin, g/L‡	35 (32–38)
Baseline QTcF, ms§	401 (381–432)
Site of tuberculosis	
Pulmonary tuberculosis	26 (93%)
Extrapulmonary tuberculosis¶	1 (4%)
Both‖	1 (4%)
Previous treatment history	
No previous history of tuberculosis treatment	3 (11%)
First-line tuberculosis treatment history only	4 (14%)
Second-line tuberculosis treatment history	21 (75%)
Multidrug-resistant tuberculosis classification	
Multidrug-resistant	2 (7%)
Pre-extensively drug-resistant fluoroquinolone	10 (36%)
Pre-extensively drug-resistant injectable	2 (7%)
Extensively drug-resistant	14 (50%)
Number of drugs in the regimen (including bedaquiline and delamanid)	
5	1 (4%)
6	9 (32%)
7	9 (32%)
8	5 (18%)
9	2 (7%)
10	2 (7%)
Common accompanying drugs in the regimen	
Linezolid	23 (82%)
Clofazimine	19 (68%)
Moxifloxacin	6 (21%)
Carbapenem	15 (54%)
Other QT-prolonging drugs in the regimen	
Plus one QT-prolonging drug	21 (75%)
Plus two QT-prolonging drugs	2 (7%)
Culture status at baseline	
Positive	23 (82%)
Negative	5 (18%)

QTcF=QT interval calculated using the Fridericia formula. *CD4 cell count was done in ten patients. †Body-mass index was assessed in 24 patients. ‡Albumin was measured in 25 patients. §Baseline QTcF was measured in 27 patients. ¶Disseminated tuberculosis. ‖Both lymph node and pulmonary tuberculosis.

***Table 1*: Clinical and demographic characteristics of patients treated with combination bedaquiline and delamanid**

The second measurement was prolongation of the QT interval corrected using QTcF. QTcF prolongation was defined as any absolute QTcF interval of at least 500 ms or as any QTcF interval increase of more than 60 ms from baseline.

Tolerability was measured as retention in care, defined as a person still receiving treatment for drug-resistant tuberculosis 6 months after initiation of the combination of bedaquiline and delamanid.

Standard WHO definitions were used for MDR tuberculosis and XDR tuberculosis treatment outcomes, including treatment failure, loss to follow-up, and death.[22]

Statistical analysis

Data were compiled from prospective data information systems routinely used at the project level and, when necessary, retrospectively extracted from patient medical records. Analysis was done on all safety and early efficacy results available up to 6 months after initiation of the combination.

Continuous variables are presented as medians and IQR, while categorical variables are presented as frequencies and proportions. Changes in QTcF over time at the cohort level are reported as the median difference between each follow-up timepoint and the baseline value. Box plots were used to show the distribution of the QTcF values over time (from baseline up to 6 months) including median, IQR, range, and outliers. Life tables were used to report on culture status over time. All statistical analyses were done using Stata, version 14.1.

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or the writing of this report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Jan 1, 2016, to Aug 31, 2016, 28 patients were initiated on the combination of bedaquiline and delamanid. 14 patients (50%) were treated in Khayelitsha, South Africa, seven patients (25%) in Mumbai, India, and seven patients (25%) in Yerevan, Armenia (table 1). 17 (61%) patients were men and median age at combination initiation was 32·5 years (IQR 28·5–40·5). 11 patients (39%) were HIV positive. Of the 28 patients, 14 (50%) had MDR tuberculosis—ten of whom also had additional resistance to fluoroquinolones—and 14 (50%) had XDR tuberculosis. 21 patients (75%) had received previous treatment with second-line drugs, and 17 patients (61%) had a previous treatment failure.

All 28 patients received the bedaquiline and delamanid combination treatment because without the use of both drugs in combination, they had less than four effective core second-line drugs available to construct a regimen. 16 patients (57%) had bedaquiline

and delamanid initiated at the start of their MDR tuberculosis treatment and 12 patients (43%) had the drug combination added to their initial regimen at a later date. Of the 12 patients who initiated the bedaquiline and delamanid combination after their initial regimen was started, one patient (8%) started the combination of bedaquiline and delamanid at the same time, whereas ten patients (83%) had delamanid added to a regimen already containing bedaquiline, and one patient (8%) had bedaquiline added to a regimen already containing delamanid.

Patients were treated with a regimen containing a median of seven drugs (IQR 6–8), including the bedaquiline and delamanid combination. 23 patients (82%) were also treated with at least one other QTc interval-prolonging drug, 21 patients (75%) with either clofazimine or moxifloxacin, and two patients (7%) with both clofazimine and moxifloxacin (table 1).

23 (82%) of 28 patients were culture positive at baseline; eight (35%) of these had converted to culture negative by 2 months of treatment and 17 (74%) had converted by 6 months (figure 1). By 6 months, 22 patients (79%) were culture negative. Of the six patients who did not have confirmed culture conversion by 6 months, two (33%) were still culture positive at 6 months, two patients (33%) had only one negative culture available by 6 months, one patient (17%) was not able to produce sputum during the follow-up, and one patient (17%) was culture positive at 5 months and was lost to follow-up at week 24.

Of the five patients who were culture negative at the beginning of the combination, four patients (80%) remained culture negative during the first 6 months of treatment, and one patient (4%) died at week 6. Of the 26 patients (93%) alive and still receiving MDR tuberculosis treatment by 6 months, 22 patients (85%) were culture negative by 6 months. Overall, 19 patients (66%) were continued on the combination regimen beyond 6 months.

In total, seven (25%) of 28 patients had at least one serious adverse event, with a total of 16 serious adverse events being reported (9·8 events per 100 person-months; table 2). The median number of serious adverse events per patient was 1·0 (IQR 1·0–3·5). Gastrointestinal disorders (four [25%] of 16 events) and nervous system disorders (four [25%] of 16 events) were the most common serious adverse events, followed by psychiatric disorders (two events [12%]). Of the seven patients who had serious adverse events, one (14%) died. This was a patient with disseminated tuberculosis and advanced HIV (CD4 count of ten cells per µL at the time of tuberculosis diagnosis and 55 cells per µL at 1 month after), and was not receiving antiretroviral therapy at the time of treatment initiation with the combination of bedaquiline and delamanid. The patient was started on antiretroviral therapy 2 weeks after MDR tuberculosis treatment initiation and, after 4 weeks, had developed acute renal failure, severe hypoglycaemia, and other systemic signs and symptoms with a fatal outcome, which was assessed as likely to be related to immune reconstitution inflammatory syndrome. None of the other events led to permanent discontinuation of bedaquiline and delamanid combination; however, one serious adverse event led to the temporary withdrawal of bedaquiline. Four serious adverse events were classified as grade 4 in severity, one (angio-oedema) was not graded, and the remaining 11 events were classified as grade 3 or less. Four serious adverse events were assessed as potentially related to both bedaquiline and delamanid, one event to delamanid, and one event to bedaquiline. 11 (69%) of the 16 serious adverse events were resolved. Assessment of the causal association between serious adverse events and other coadministered drugs is presented in table 2.

The median QTcF values were 401 ms (IQR 381–432) at baseline, 430 ms (408–439) at 2 months, and 434 ms (408–446) at 6 months (figure 2). One patient was missing the baseline QTcF value and was therefore excluded from the analysis of QTcF change from baseline. The median changes from baseline at 2 months were 8 ms (–1 to 26) and 16 ms (–13 to 31) at 6 months (figure 3). No clinically significant cardiovascular events or cardiac arrhythmias were detected in our cohort. No patients had QTcF values greater than 500 ms. QTcF interval prolongation of more than 60 ms from baseline occurred in six instances in four patients; none of these patients were symptomatic and none led to permanent discontinuation of bedaquiline and delamanid. One instance was reported as medically significant and led to the temporary withdrawal of bedaquiline and delamanid for 1 week. One of the patients who had prolongation was receiving bedaquiline, delamanid, clofazimine, and moxifloxacin. The remaining

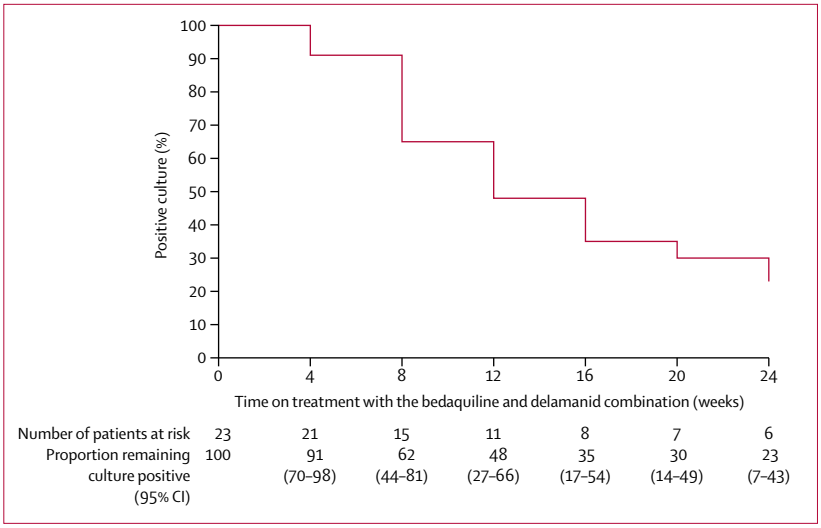

Figure 1: **Effect of combination bedaquiline and delamanid treatment on sputum cultures positive for tuberculosis**

Proportion of patients with positive sputum culture over time in patients enrolled and treated with combination bedaquiline and delamanid from January, 2016, to August, 2016, in Yerevan, Armenia; Mumbai, India; and Khayelitsha, South Africa. This figure includes only patients who had a positive culture at the time the bedaquiline and delamanid combination was initiated

	Severity	Related to bedaquiline	Related to delamanid	Other related drugs	Action for bedaquiline and delamanid	Outcome
Patient 1, female, aged 35 years						
Chest pain	Grade 1	Yes	Yes	High-dose isoniazid, levofloxacin, linezolid, pyrazinamide, terizidone	Dose unchanged	Recovered or resolved
Generalised tonic–clonic seizure	Grade 2	No	No	High-dose isoniazid, levofloxacin, linezolid, terizidone	Dose unchanged	Recovered or resolved
Haematemesis	Grade 2	Yes	Yes	High-dose isoniazid, levofloxacin, linezolid, pyrazinamide, terizidone	Dose unchanged	Recovered or resolved
Psychotic disorder	Grade 4	No	No	High-dose isoniazid, levofloxacin, terizidone	Dose unchanged	Recovered or resolved
Central nervous system lesion	Grade 4	No	No	None	Dose unchanged	Recovering or resolving
Patient 2, male, aged 39 years						
Psychotic disorder	Grade 4	Yes	No	High-dose isoniazid, levofloxacin, para-aminosalicylic acid, terizidone	Bedaquiline temporarily withdrawn; delamanid dose unchanged	Recovered or resolved with sequelae
Patient 3, male, aged 37 years						
Angio-oedema	Unknown	No	No	None	Dose unchanged	Recovered or resolved
Patient 4, male, aged 54 years						
Diarrhoea	Grade 3	No	No	None	Dose unchanged	Recovered or resolved
Nausea	Grade 3	No	No	None	Dose unchanged	Recovered or resolved
Vomiting	Grade 3	No	No	None	Dose unchanged	Recovered or resolved
Peripheral neuropathy	Grade 2	No	Yes	Capreomycin, cycloserine, linezolid	Dose unchanged	Not recovered or not resolved
Patient 5, female, aged 14 years						
Fungal sepsis	Grade 3	No	No	Imipenem	Dose unchanged	Recovered or resolved
Patient 6, male, aged 44 years						
Increased transaminases	Grade 3	Yes	Yes	Amoxocilin–clavulanate, capreomycin, cycloserine, imipenem, linezolid, moxifloxacin, para-aminosalicylic acid, pyrazinamide	Dose unchanged	Recovered or resolved
Patient 7, male, aged 36 years						
Acute kidney injury	Grade 2	Yes	Yes	Clofazimine, ethambutol, ethionamid, high-dose isoniazid, levofloxacin, linezolid, moxifloxacin, rifampicin, terizidone	Dose unchanged	Fatal
Seizures	Grade 2	No	No	High-dose isoniazid, levofloxacin, linezolid, terizidone	Dose unchanged	Recovered or resolved with sequelae
Hypoglycaemia	Grade 4	No	No	Ethambutol, high-dose isoniazid, levofloxacin, rifampicin	Dose unchanged	Fatal

Table 2: **Description of serious adverse events reported in patients enrolled on combination treatment with bedaquiline and delamanid**

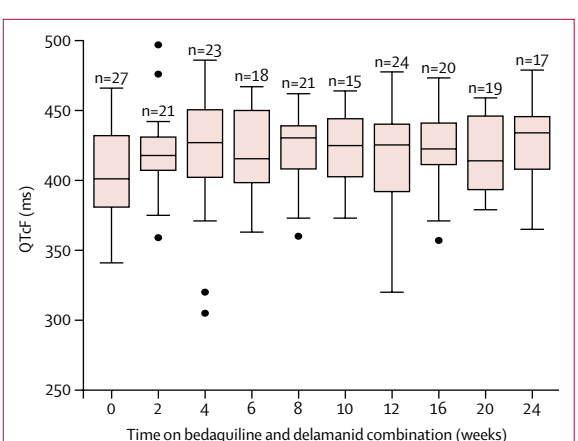

Figure 2: **QTcF in patients treated with bedaquiline and delamanid**
Distribution of median QTcF values at each timepoint. Boxes show median and IQR, bars show the range, and dots show outliers. QTcF=QTc interval calculated using the Fridericia formula.

three patients were on bedaquiline, delamanid, and clofazimine. These six instances of prolongation occurred at week 4 (n=1), week 6 (n=1), week 12 (n=1), week 16 (n=2), and week 24 (n=1).

Discussion

This is the largest reported cohort of patients with MDR tuberculosis treated with a regimen that included the combination of both new antituberculosis drugs, bedaquiline and delamanid, under routine programmatic conditions in three epidemic hotspots in eastern Europe, south Asia, and South Africa. Although the number of patients treated in the cohort was quite small, our preliminary results show that the use of the combination of bedaquiline and delamanid appears to be safe and can lead to high rates of culture conversion in patients who have historically had very little treatment success. Although our findings need to be extended to full treatment outcomes and confirmed in other settings and

populations, these data support the use of combination bedaquiline and delamanid as part of multidrug treatment regimens for people with drug-resistant tuberculosis while definitive evidence is accumulating.

These data challenge the theoretical risk of combining bedaquiline and delamanid because of concerns with regard to QTc prolongation.[19] In our cohort of closely monitored patients, no cardiac arrhythmias or unexplained deaths occurred and no patients had an absolute QTcF interval greater than 500 ms. Four patients in the cohort had a change in QTcF interval of more than 60 ms from baseline; however, these events were managed without permanent discontinuation of the bedaquiline and delamanid combination. In the two previously published case reports of patients taking the combination of bedaquiline and delamanid, one patient had a transient QT interval increase from week 5 to week 17, which was managed by temporary discontinuation of bedaquiline, and reintroduction after verapamil was administered.[7,23] Of note, in patients on bedaquiline only in a study by Guglielmetti and colleagues,[23] 9% of patients had experienced QTcF of more than 500 ms, which led to bedaquiline discontinuation in two (6%) of 35 patients.[23] However, in our cohort, permanent discontinuation of the bedaquiline and delamanid combination or of either drugs individually was not required, which is of particular interest given that other potentially cardiotoxic drugs were commonly coadministered in this cohort; 21 patients received either clofazimine or moxifloxacin and two patients received both.

The only death recorded in our cohort was in a patient with HIV infection with severe immunosuppression who died 6 weeks after the combination treatment initiation. The death was probably a result of immune reconstitution inflammatory syndrome; however, the exact cause of death could not be ascertained without an autopsy. The death was not associated with QTcF prolongation or other bedaquiline-associated or delamanid-associated serious adverse events.

Although our data are preliminary, they also support the efficacy of combinations of bedaquiline and delamanid in the treatment of highly resistant forms of tuberculosis. In our cohort of patients with complex resistance profiles (86% fluoroquinolone resistant and 50% XDR), and an HIV co-infection rate of 36%, we report a 6 month culture conversion rate of 74%. Even though final outcome data are not yet available, this is a notable finding. The proportion of patients with culture conversion in our study (74%) was considerably higher than those previously reported in patients with XDR tuberculosis in South Africa (55–58%).[3,24] However, notably, linezolid was also used in most patients in our cohort (82%) as was clofazimine (68%), and these drugs have been shown to be associated with improved culture conversion and final outcomes in randomised trials.[25,26]

MSF began using the combination of bedaquiline and delamanid in patients for several reasons. Clinical trials formally assessing bedaquiline and delamanid only started enrolling patients in August, 2016. Furthermore, most of the patients treated in our observational cohort might not have qualified for participation in any of the ongoing or planned studies given the high proportion of second-line drug resistance, the substantial histories of previous treatment, and poor clinical conditions. Waiting 3–5 years until the studies are complete and formal results are available could result in excess morbidity and mortality in people with MDR tuberculosis while also contributing to ongoing community transmission.[27] Furthermore, although multiple ongoing trials are assessing shorter-duration combination regimens of new and repurposed tuberculosis drugs for MDR tuberculosis, careful assessments of novel therapies in populations outside of the controlled trial setting will always be needed, and MSF remains committed not only to providing this therapy but also to carefully analysing and reporting the data.

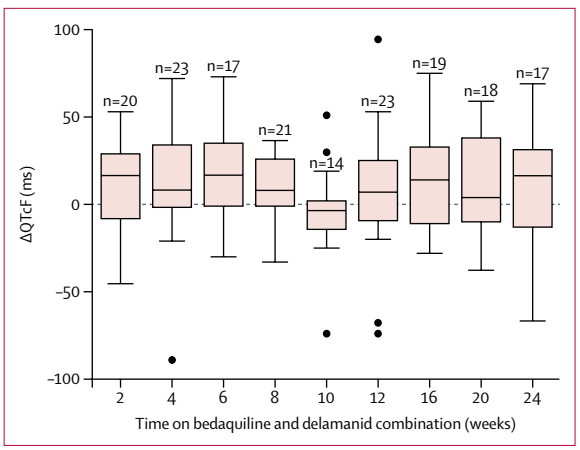

Figure 3: **Change in QTcF from baseline**
Distribution of median difference of QTcF (ΔQTcF) from baseline. Boxes show median and IQR, bars show the range, and dots show outliers. QTcF=QTc interval calculated using the Fridericia formula.

This interim analysis has several limitations. First, some QTcF data were missing, especially during the first 12 weeks of treatment. The missing data might be explained by the nature of the treatment administration and monitoring under programmatic conditions. Given the small size of the cohort, missing data, especially on one of the main safety outcomes of interest, might have led to an underestimation of QTcF interval prolongation in this cohort. The fact that monthly data were available for most individuals in the study and that these data were most robust during the first 2 months of treatment—and that such data did not show a prolonged effect on the absolute value of the QTcF interval—shows that if transient QTcF interval prolongation occurred during the periods of missing data, then such prolongation was likely to be temporary and self-correcting. Although MSF continues to strive to document QTcF data every 2 weeks in its patients on combination therapy, these data show

that such intensive monitoring might have only a partial effect on patient care decisions, rendering it potentially unnecessary in the future. A similar phenomenon has been reported with HIV monitoring leading to more cost-effective mechanisms being put into place.[28]

Other limitations derive from the small size of the cohort, the short follow-up time, and the observational, non-controlled study design. We report on surrogate markers of early treatment response, since final outcome data are not yet available; therefore, the results should be interpreted with caution. Some important follow-up data, mainly sputum culture, were also missing, which reflects the programmatic nature of this multisite study. Our excellent retention in care might indirectly indicate a selection bias in enrolling patients who were less likely to be lost to follow-up, which would have had a partial effect on safety outcomes. The potential efficacy risk bias is likely to be balanced by the fact that the patients more likely to be offered the combination were in fact those with the fewest treatment options.

The small cohort size also precluded us from looking at a number of important clinical topics, including the effect of HIV status and the effect of serial drug introduction (*vs* simultaneous drug introduction) on efficacy and safety outcomes. Such variables could be assessed in future observational cohorts in larger populations. Our study also did not assess baseline or acquired bedaquiline or delamanid resistance, since no standard microbiological definitions of resistance exist as yet. Measuring baseline and acquired resistance during therapy in future cohorts will be important to understand factors associated with the resistance to these two new drugs.

In conclusion, the treatment of 28 individuals with combination bedaquiline and delamanid appears to show both a reassuring safety profile and encouraging culture conversion results by 6 months when used as part of a multidrug regimen. Our results are especially important given the high proportion of patients with resistance to second-line drugs, previous treatment histories, and poor clinical status and comorbidities in people with MDR tuberculosis worldwide. While awaiting evidence from randomised trials on the efficacy and safety of bedaquiline and delamanid given in combination, we believe our results support continued simultaneous use of both drugs in patients with few treatment options in the setting of correct patient assessment and monitoring. Providing access to such therapy while formal clinical trials are being completed is essential, given the current landscape for successfully treating individuals with highly resistant strains of tuberculosis.[19] Our data suggest that broadly withholding such access over theoretical safety concerns is no longer justifiable.

Contributors

GF, EM, CH, and PI conceived and designed the study. CL, JH, SJ, NK, VDA, LE, and JF provided clinical services and collected study data. AS and SK supervised the study. GF, EM, HC, and PI analysed the data. GF, EM, CH, HC, JF, and PI interpreted the results and drafted the manuscript. All authors contributed to the writing of the manuscript. GF, EM, CH, HC, JF, and PI undertook the manuscript revisions. All the authors have read and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

This was a retrospective cohort analysis of patients receiving care for MDR tuberculosis in MSF projects, and funding for their care and for the collection and analysis of the data presented was provided by MSF. In Armenia the MSF project received support for programmatic activities through the EndTB grant from Unitaid from April, 2015. MSF also received a donation of delamanid from Otsuka, manufacturer of delamanid.

References

1 WHO. Global tuberculosis report 2017. Geneva: World Health Organization, 2017.

2 Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9153 patients. *PLoS Med* 2012; **9:** e1001300.

3 Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: a cohort study. *Lancet* 2014; **383:** 1230–39.

4 Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012; **366:** 2151–60.

5 Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; **371:** 723–32.

6 Borisov SE, Dheda K, Enwerem M, 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:** 1700387.

7 Janssen. Sirturo (bedaquiline) product insert. Food and Drug Administration, 2014. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/204384s000lbl.pdf (accessed July 11, 2015).

8 European Medicines Agency. Deltyba. 2017. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002552/human_med_001699.jsp&mid=WC0b01ac058001d124 (accessed May 8, 2017).

9 WHO. A 2016 review of available evidence on the use of bedaquiline in the treatment of multidrug-resistant tuberculosis. 2017. http://www.who.int/tb/publications/2017/GDGreport_Bedaquiline/en/(accessed May 8, 2017).

10 The use of delamanid in the treatment of multidrug-resistant tuberculosis. http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014·23_eng.pdf (accessed May 8, 2017).

11 Pontali E, Sotgiu G, D'Ambrosio L, Centis R, Migliori GB. Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence. *Eur Respir J* 2016; **47:** 394–402.

12 Pontali E, D'Ambrosio L, Centis R, Sotgiu G, Migliori GB. Multidrug-resistant tuberculosis and beyond: an updated analysis of the current evidence on bedaquiline. *Eur Respir J* 2017; **49:** 1700146.

13 Pontali E, Sotgiu G, Ambrosio LD, Centis R, Migliori GB. Cardiac safety of bedaquiline: a systematic and critical anlaysis of the evidence. *Eur J Respir* 2017; **50:** 394–402.

14 Skripconoka V, Danilovits M, Pehme L, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. *Eur Respir J* 2013; **41:** 1393–400.

15 Lachâtre M, Rioux C, Le Dû D, et al. Bedaquiline plus delamanid for XDR tuberculosis. *Lancet Infect Dis* 2016; **16:** 294.

16 Tadolini M, Lingtsang RD, Tiberi S, et al. First case of extensively drug-resistant tuberculosis treated with both delamanid and bedaquiline. *Eur Respir J* 2016; **48:** 935–38.

17 Maryandyshev A, Pontali E, Tiberi S, et al. Bedaquiline and delamanid combination treatment of 5 patients with pulmonary extensively drug-resistant tuberculosis. *Emerg Infect Dis* 2017; **23:** 1718–21.

18 Cox HS, Furin JJ, Mitnick CD, Daniels C, Cox V, Goemaere E. The need to accelerate access to new drugs for multidrug-resistant tuberculosis. *Bull World Health Organ* 2015; **93:** 491–97.

19 Dheda K, Gumbo T, Maartens G, et al. The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis. *Lancet Respir Med* 2017; **5:** 291–360.

20 WHO. Active tuberculosis drug-safety monitoring and management. Geneva: World Health Organization, 2015.

21 Furin J, Alirol E, Allen E, et al. Drug-resistant tuberculosis clinical trials: proposed core research definitions in adults. *Int J Tuberc Lung Dis* 2016; **20:** 290–94.

22 WHO. Definitions and reporting framework for tuberculosis—2013 revision. Geneva: World Health Organization, 2013.

23 Guglielmetti L, Le Du D, Jachym M, et al. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. *Clin Infect Dis* 2015; **60:** 188–94.

24 O'Donnell MR, Padayatchi N, Kvasnovsky C, Werner L, Master I, Horsburgh CR Jr. Treatment outcomes for extensively drug-resistant tuberculosis and HIV co-infection. *Emerg Infect Dis* 2013; **19:** 416–24.

25 Tang S, Yao L, Hu, et al. Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, multicenter, randomized controlled study in China. *Clin Infect Dis* 2015; **60:** 1361–67.

26 Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis *Int J Tuberc Lung Dis* 2012; **16:** 447–54.

27 Shah NS, Auld SC, Brust JCM, et al. Transmission of extensively drug-resistant tuberculosis in South Africa. *N Engl J Med* 2017; **376:** 243–53.

28 Koenig SP, Schackman BR, Riviere C, et al. Clinical impact and cost of monitoring for asymptomatic laboratory abnormalities among patients receiving antiretroviral therapy in a resource-poor setting. *Clin Infect Dis* 2010; **51:** 600–08.