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Early View

Research letter

Compassionate Use of Delamanid in Combination with Bedaquiline for the Treatment of MDR-TB

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Title: Compassionate Use of Delamanid in Combination with Bedaquiline for the Treatment of MDR-TB

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Summary: Updated data from the Otsuka compassionate use program show that regimens combining delamanid and bedaquiline appear effective in MDR-TB cases with limited treatment options.

To the Editor:

Patients with multidrug-resistant tuberculosis (MDR-TB), in particular those with pre-extensively drug-resistant (Pre-XDR) and extensively drug-resistant (XDR)-TB, and those that fail standard second-line therapy, are difficult to treat and have poor long-term outcomes [1]. To address this unmet medical need, there is strong interest in exploring the combined use of delamanid and bedaquiline, the only two anti-TB drugs approved for the treatment of pulmonary MDR-TB in the last 40 years, as their novel mechanisms of action may offer treatment alternatives for patients who have developed resistance or non-tolerability to existing anti-TB drugs [2, 3]. Despite the initial regulatory approvals of bedaquiline and delamanid in 2012 and 2014, respectively, global usage of both drugs in combination with one another remains limited in part due to the uncertainty around the safety and efficacy of such a combination regimen. Hence, there is an urgent need for programmatic data to better understand the "real-world" use of these two medicines used together in MDR-TB patients.

As part of a global access initiative, Otsuka Pharmaceutical Co., Ltd. in coordination with the European Respiratory Society (ERS) / WHO TB Consilium, and Médecins Sans Frontières / Partners in Health (MSF-PIH) established its first Compassionate Use (CU) program in 2014 to provide access to delamanid, at no cost, for patients with limited treatment options [4]. In 2016, the program was modified to allow for the combined use of delamanid plus bedaquiline under specific conditions. We present here the early safety and efficacy outcomes of patients enrolled in this program receiving delamanid and bedaquiline concomitantly along with other anti-TB drugs for the treatment of MDR-TB.

Requests for CU were submitted to the ERS/WHO TB Consilium or MSF-PIH for review, followed by the final review and approval of the Otsuka CU committee as previously described [4]. Patients receiving combined delamanid plus bedaquiline were required to meet the following inclusion criteria: signed informed consent by patient (or by parent or legal guardian for minors); MDR-TB with limited

therapeutic options; unable to participate in a delamanid clinical trial; age ≥ 6 years and weight > 20 kg; able to receive treatment with a background regimen consistent with WHO guidelines at a centre experienced in MDR-TB management; and agreement to hospitalization for the initial 4 months of combination therapy. Exclusion criteria were: prior exposure to delamanid; albumin < 2.8 g/dL; electrolyte imbalances; baseline QT interval corrected for heart rate by Fridericia's method (QTcF) > 450ms; <two active or likely to be active drugs (not counting delamanid) to be included in the proposed background regimen based on recent drug susceptibility testing (DST) results and/or treatment history; concurrent use of strong cytochrome P450 3A4 (CYP3A4) inhibitors or other anti-TB agents in development; and hypersensitivity to delamanid.

Patients accepted for CU were treated with delamanid 100mg twice daily (or 50mg twice daily for patients with weight <35 kg) for 24 weeks in combination with a background regimen designed in accordance with WHO guidelines and local guidelines. Other drugs including bedaquiline were administered as per the treating physician's discretion with respect to dose and duration. Patient management, including length of and changes to the regimen, as well as frequency and duration of follow-up, were made by the treating physicians. (Note: weekly ECGs were recommended for all patients receiving delamanid combined with bedaquiline for the duration of co-administration). Pharmacovigilance (PV) training of treating physicians was performed prior to treatment initiation and safety data were collected throughout the delamanid treatment period. Culture negative status was defined as having one or more negative cultures within 24 weeks after starting delamanid without subsequent positive cultures within this period.

Data Capture and Analysis

Baseline data from all cases (e.g. demographic information, baseline culture status, DST results, disease type, presence of cavities, drug resistance category, history of prior treatment, and comorbidities) were

prospectively collected via standardized patient access forms (completed by the treating physician), and recorded into an Excel spreadsheet (Microsoft 2016, Redmond, WA) by the Otsuka CU team for further analyses. All adverse events (AEs) were prospectively captured and reported to the Otsuka PV team during the course of therapy and assessed for seriousness, severity, as well as association (i.e. causality) with delamanid. In addition, culture information during the 24-week period, confirmation of the regimen given at baseline, use of delamanid including temporary interruptions, permanent withdrawals from therapy, and completion of a treatment course were collected by Otsuka after the initiation of delamanid therapy. Descriptive statistics were performed for all patients who initiated treatment with delamanid (in combination with bedaquiline) prior to February 2018. Categorical data were reported as counts and proportions, and continuous data were reported as means and/or medians and ranges.

From February 2014 until February 2018, 238 CU requests for delamanid were received, 199 approved, 5 were pending review, 11 did not meet inclusion criteria, and 23 were withdrawn by the requestor prior to review. Of the 199 approved, 28 requests were withdrawn by the requestor prior to delamanid start, 2 were pending delamanid shipment, and 169 patients initiated delamanid treatment including 84 that initiated delamanid treatment with a bedaquiline-containing background regimen for at least 1 day. Of these 84 patients, 58 completed 24 weeks of treatment with delamanid, 12 were still on treatment, 1 permanently discontinued treatment (patient was non-cooperative with the clinic staff), 10 had died prior to completing delamanid (median of 39 days, range 3-113, after delamanid initiation), and 3 had unknown completion status. Of the 84 patients treated with delamanid and bedaquiline concurrently, 19.0% (16/84) started bedaquiline prior to starting delamanid (median of 110 days prior to the start of delamanid; range 25 – 331 days), 79.8% (67/84) were naïve to both drugs at the time of their initiation, and 1.2% (1/84) had unknown treatment history prior to receiving both drugs.

Demographic and clinical characteristics of the 84 patients who initiated treatment with delamanid in the context of a background regimen containing bedaquiline are provided in Table 1. The mean age and weight were 37 years and 55 kg, respectively. 7.1% (6/84) were <18 years and 67.0% (56/84) were male. 90.5% (76/84) of patients originated from sub-Saharan Africa, 3.6% (3/84) from Asia, 6.0% (5/84) from the Americas. 96.4% (81/84) had pulmonary disease alone, 2.4% (2/84) had extra-pulmonary disease plus pulmonary disease (one with central nervous system, lymph node disease plus pulmonary disease; and one with spinal disease plus pulmonary disease), one with 1.2% (1/84) extra-pulmonary disease alone (isolated lymph node disease) 88.1% (74/84) of patients were culture positive at referral. Of the 6 children enrolled in the CU project received both delamanid and bedaquiline, 5 had pulmonary TB and one had both pulmonary plus extrapulmonary involvement (lymphadenitis and cerebral disease). Their ages at the time of enrolment were 8, 11, 12, 13, 14, and 14 years.

88.1% (74/84) patients overall had received a previous course (or courses) of TB treatment (all with both first and second-line drugs), while only 11.3% (10/84) had delamanid added to their initial, current TB treatment course. In terms of baseline resistance status, 73.8% (62/84) had XDR-TB, 21.4% (18/84) had pre-XDR-TB (i.e. MDR-TB with additional resistance to either a fluoroquinolone or a second-line injectable agent), and 4.8% (4/84) had MDR-TB.

54.8% (46/84) of patients had concomitant HIV co-infection, and among the 34/46 (73.9%) those with available CD4+ T cell count at baseline, the mean value was 320 cells/mm^3, range 62 – 839. In addition, 44/46 (95.7%) were on ARV therapy, 1/46 (2.2%) was not on ARV, and ARV treatment status was unknown for 1/46 (2.2%).

In terms of other co-morbidities reported to have occurred in at least two or more individuals at baseline, 6/84 (7.1%) had diabetes, 4/84 (4.8%) had hearing impairment, 3/84 (3.6%) had renal

dysfunction, 3/84 (3.6%) had visual impairment, 3/84 (3.6%) had substance abuse, and 3/84 (3.6%) had hypertension.

The majority of patients received the following concomitant anti-TB agents (in addition to bedaquiline) during the six-month delamanid treatment period: linezolid 91.7% (77/84), pyrazinamide 81.0% (68/84), clofazimine 78.6% (66/84), PAS 75.0% (63/84), a fluoroquinolone 63.1% (53/84).

Of the 58 patients who completed 24 weeks of treatment with delamanid and bedaquiline plus a background regimen, 87.9% (51/58) achieved culture negative status at 24 weeks, 6.9% (4/58) remained culture positive at 24 weeks, and 5.2% (3/58) had results pending or unknown. Limiting the analysis to only the 40 patients with XDR-TB yielded similar results: 85.0% (34/40) achieved culture negative status at 24 weeks, 7.5% (3/40) remained culture positive at 24 weeks, and 7.5% (3/40) had unknown culture status.

These results compare favourably to those seen in the population of patients who did not receive bedaquiline along with delamanid. Among these patients, 52/65 (80.0%) had negative culture status at 24 weeks, 11/65 (16.9%) had positive culture status, 2/65 (3.1%) had unknown culture status.

In terms of those patients who had prior exposure to either clofazimine or bedaquiline prior to starting combination delamanid plus bedaquiline, the 6 month culture responses were as follows: among the 5 patients who had prior bedaquiline exposure and completed 24 weeks of delamanid, 3/5 (60.0%) achieved negative cultures, 1/5 (20.0%) did not achieve negative cultures, and 1/5 (20.0%) had unknown culture status; among the 49 patients who completed 24 weeks of delamanid and had prior clofazimine exposure, 44/49 (89.8%) achieved negative cultures, 3/49 (6.1%) did not achieve negative cultures, 2/49 (4.1%) had unknown culture status. In terms of the patients who had no prior exposure to either clofazimine or bedaquiline the outcomes were as follows: among the 52 patients who had no prior bedaquiline exposure and completed 24 weeks of delamanid, 47/52 (90.4%) achieved negative cultures,

3/52 (5.8%) did not achieve negative cultures, 2/52 (3.8%) had unknown culture status; among the 8 patients who had no prior clofazimine exposure, 6/8 (75%) achieved negative cultures, 1/8 (12.5%) remained culture positive, and 1/8 (12.5%) had unknown culture status.

In terms of HIV status among the 6 month treatment completers, 35/58 (60.3%) were HIV positive, 21/58 (36.2%) were HIV negative, and 2/58 (3.4%) had unknown HIV status. Among the 35 HIV positive patients, 33/35 (94.3%) achieved culture negativity, 1/35 (2.9%) remained culture positive, 1/35 (2.9%) had an unknown culture status. Among the 21 HIV negative patients, 16/21 (76.2%) achieved culture negativity, 3/21 (14.3%) remained culture positive, and 2/21 (9.5%) had an unknown culture status.

Finally, among the 6 children enrolled in the CU project who received both delamanid and bedaquiline, the 5 with pulmonary disease were culture negative at the end of delamanid treatment, and the one child with additional extrapulmonary involvement was clinically doing well at the end of treatment.

QT prolongation of any duration was reported in five (6.0%) patients; however, only one (1.2%) patient was reported to have a corrected QT interval (QTc) of >500ms. In this case, the patient was receiving clofazimine in addition to delamanid and bedaquiline (i.e. all at the same time). Initial QT prolongation in this patient (i.e. QTc 486ms) led to temporary withdrawal of bedaquiline (days 12-16 of delamanid treatment), however, bedaquiline was successfully re-introduced (in combination with verapamil) in consultation with the ERS consillium. Subsequently, the treating physician chose to permanently discontinue clofazimine at week 6 due to QTc >500ms which eventually resolved (i.e. to levels below 500ms) without further regimen change [5, 6, 7]. Despite the QT elevation, the patient completed his course of delamanid without any associated clinical sequelae.

Amongst the 10 patients receiving both delamanid and bedaquiline who died prior to completing 24 weeks of treatment with delamanid, the causes of death were as follows: progressive TB (1 patient), pulmonary embolism (1 patient), myocardial infarction (1 patient), sepsis secondary to gangrene (1

patient), adrenal crisis and TB progression (1 patient), hemoptysis (2 patients), and unknown (3 patients). None of these deaths were described by the treating clinician as likely caused by delamanid, but rather due to other causes (i.e. predominantly underlying disease processes and/or progression). Of note, among the 10 patients who died, 5 were co-infected with HIV.

This analysis represents the largest published cohort of MDR-TB patients (n=84) treated with delamanid plus bedaquiline. Although the data remain preliminary, the majority (87.9%) of patients in the CU program who completed 24 weeks of delamanid treatment had encouraging outcomes (i.e. negative 24-week sputum culture status), which is consistent with results from other published reports on combined use of delamanid and bedaquiline [5, 6, 7, 8, 9, 10, 11].

Moreover, these results are comparable to a recent systematic review by Pontali et al which included 87 patients receiving delamanid and bedaquiline either concurrently or sequentially and reported culture conversion rates of 81.4% [11]. Similar to those patients included in the systematic review, the majority of patients in the present CU cohort had XDR-TB and were retreatment cases. Important differences, however, include the fact that the majority of patients in this CU cohort were co-infected with HIV, and that this analysis includes cases of combination delamanid plus bedaquiline use in children.

As noted previously, early sputum culture conversion (SCC) is a positive predictor of favourable long-term treatment outcomes. [12, 13]. The results are notable given that the majority of patients in this cohort had XDR-TB, extensive prior TB treatment history, cavitary disease, and HIV co-infection—all features known to be associated with poor treatment outcomes [14]. Despite the disease severity and presence of these co-morbidities, safety data amongst the patients initiating treatment with delamanid and bedaquiline concomitantly did not reveal any concerns not previously identified in the delamanid or bedaquiline clinical development programs.

An evaluation of the safety and/or efficacy of the combination of both medicines is underway in two ongoing, prospective, randomized clinical trials: AIDS Clinical Trials Group 5343 (NCT02583048) and EndTB (NCT02754765). However, data from these studies will likely not be available until 2019 and 2021, respectively.

The absence of a control arm, incomplete information on duration of and changes to the background regimen (following delamanid initiation), and the lack of long-term treatment outcomes (including relapse data) are important limitations of this analysis. Nevertheless, these results are important as they represent a large, diverse pool of patients who generally would not have qualified for enrolment in a clinical trial due to the severe nature of their disease. In summary, these results are encouraging, and provided that a treatment site is experienced in MDR-TB management and measures are in place for adequate treatment monitoring [15], the evidence appears to yield a favourable benefit-risk profile to support the combined use of delamanid and bedaquiline in MDR-TB (including XDR-TB) patients with limited treatment options.

Table 1: Demographic and Clinical Characteristics of Compassionate Use Patients Initiating Delamanid plus Bedaquiline Prior to February 2018		
Variable		**No. (%) or Mean (Range)**
Age (yrs) (N=84)		37 (8 – 63)
Weight (kg) (N=84)		55 (22 – 110)
Body Mass Index (kg/m^2) (N=79)		19.7 (12.0 – 31.5)
Sex (N=84)	Female	28 (33.0%)
	Male	56 (67.0%)
Region (N=84)	Europe	0 (0%)
	Asia	3 (3.6%) (All India)
	Sub-Saharan Africa	76 (90.5%) (1 Swaziland, 1 Namibia, 74 South Africa)
	Americas	5 (6.0%) (1 USA, 1 Chile, 1 Mexico, 2 Peru)
Disease Type (N=84)	Pulmonary Disease Alone	81 (96.4%)
	Pulmonary & Extrapulmonary Disease	2 (2.4%)
	Extrapulmonary Disease Alone	1 (1.2%)
Cavitary Disease (N=84)	No	6 (7.1%)
	Yes	53 (63.1%)
	Unknown	25 (29.8%)
Resistance Type (N=84)	MDR	4 (4.8%)
	Pre-XDR	18 (21.4%)
	XDR	62 (73.8%)
History of Prior TB Treatment (N=84)	Yes	74 (88.1%)
	No	10 (11.9%)
HIV Status (N=84)	Positive	46 (54.8%)
	Negative	36 (42.9%)
	Unknown	2 (2.4%)
Culture Status at Referral (N=84)	Positive	75 (89.3%)
	Negative	9 (10.7%)
Drugs Used in Optimized Background Regimens Among Patient Receiving Delamanid and Bedaquiline (N=84)	Linezolid	77 (91.7%)
	Pyrazinamide	68 (81.0%)
	Clofazimine	66 (78.6%)
	Para-aminosalicylic Acid	63 (75.0%)
	Fluoroquinolones	53 (63.1%)
	Ethionamide/Prothionamide	30 (35.7%)
	Carbapenems	30 (35.7%)
	Cycloserine/Terizadone	28 (33.3%)
	Ethambutol	15 (17.9%)
	Second-line Injectable	14 (16.7%)
	High Dose Isoniazid	11 (13.1%)
Culture Status at 24 Weeks Among Delamanid Treatment Completers* (N=58)	Culture Negative	51 (87.9%)
	Culture Positive	4 (6.9%)
	Unknown or Pending	3 (5.2%)

Abbreviations: MDR=multidrug-resistant; TB=tuberculosis; XDR=extensively drug-resistant

* **54/58 (93.1%) were culture positive at baseline**

Conflict of Interest: The authors of this manuscript are employed by Otsuka Pharmaceutical Co., Ltd., which discovered, developed, manufactures and distributes delamanid.

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