Early experience with delamanid-containing regimens in the treatment of complicated multidrug-resistant tuberculosis in Hong Kong

To the Editor:

Hong Kong is an intermediate tuberculosis (TB) burden region with a disease notification rate of 60.5 per 100 000 population in 2015. With the use of supervised treatment since 1970s and the use of drug susceptibility testing (DST) for guiding use of TB drugs for several decades [1], TB drug resistance rates in Hong Kong have declined and the multidrug-resistant (MDR)-TB rate has been kept at ∼1%. Successful control of MDR-TB was partly attributable to judicious use of ofloxacin and later levofloxacin in the 1990s [2, 3], the introduction of linezolid in the 2000s [4] among patients with fluoroquinolone-resistant MDR-TB or extensively drug-resistant (XDR)-TB, with intermittent dosing to enable its prolonged use [5], and selective use of delamanid among patients with complicated MDR-TB since 2012. To echo our support for using delamanid in the treatment of MDR-TB [6, 7], we would like to report our early experience in Hong Kong regarding the use of delamanid-containing regimens among patients with pre-XDR-TB (MDR-TB with bacillary resistance to either fluoroquinolone or second-line injectable agents) or XDR-TB.

Since 2012, we have used delamanid in a total of 11 patients with pre-XDR-TB or XDR-TB. Table 1 summarises their clinical profiles. There were seven females, aged from 29 to 59 years (median 48 years), and four males, aged from 44 to 59 years (median 52.5 years). Except for one Pakistani, all were Chinese. Comorbidity was common, with four having diabetes mellitus and one having dermatomyositis treated with chronic systemic corticosteroids. All patients had HIV status checked and none was infected by HIV. All received high-dose levofloxacin throughout, predominantly 750 mg daily. Except for two patients (patients 2 and 3) with discontinuation of linezolid after 5.5 months and 0.5 month, respectively, owing to adverse events, all received the oxazolidinone for a prolonged period. A total of eight patients (excluding patients 1–3) had delamanid and linezolid initiated concurrently. Patient 1 had delamanid and high-dose isoniazid added to a linezolid-containing regimen when treatment response was poor. Patients 2 and 3 were given delamanid to substitute for linezolid owing to linezolid intolerance, when treatment response was satisfactory.

Treatment outcomes regarding use of delamanid-containing regimens have been promising. Except for patient 1, all achieved early sputum culture conversion within 3 months dafter starting MDR-TB treatment. Nine were cured after a median treatment duration of 13.0 months (range 12.0–27.0 months) and not found to have relapse after a median follow-up period of 390 days (range 0–720 days). One with good progress is still receiving treatment. Treatment was prolonged beyond 20 months in three patients (patients 2, 3 and 11) owing to concerns about an increase in relapse risk due to poorly controlled diabetes mellitus. Treatment failure occurred in patient 1, who had fluoroquinolone-resistant MDR-TB with I572F mutation (located outside *rpoB* hotspot), low-level isoniazid resistance, bacillary resistance to ethionamide and dermatomyositis treated with chronic systemic corticosteroids. Patient 1 was initially treated using a linezolid-containing regimen that somehow omitted concurrent use of high-dose isoniazid. When treatment response to the linezolid-containing regimen was poor, high-dose isoniazid and delamanid were added, but treatment response was unsatisfactory. I572F mutation made it difficult to

Cite this article as: Chang K-C, Leung EC-C, Law W-S, *et al.* Early experience with delamanid-containing regimens in the treatment of complicated multidrug-resistant tuberculosis in Hong Kong. *Eur Respir J* 2018; 51: 1800159 [https://doi.org/10.1183/13993003.00159-2018].

TABLE 1 Clinical profiles of a cohort of 11 patients with complicated multidrug-resistant (MDR) tuberculosis (TB) who were given delamanid (Dlm)

Patient	Starting MDR-TB treatment	Sex/ age[#] years	Comorbidity	Drugs with bacillary resistance	Past TB treatment	Total treatment duration months	Dlm treatment duration months	Lzd treatment duration months	Other drugs ⩾1 month	QTc range ms	Time to culture conversion after starting MDR-TB treatment days	Outcome (follow-up duration after completing MDR-TB treatment[¶] days)
1	December 2012	M/57	DMS on CS	S, H^r, E, Z, Ofx, Eto	Yes	35.0	12.5	29.5	Lfx^+,Km^+,H^{h+} Pto, E, PAS, Cs	408–443	NA	Failure
2	June 2014	F/48	DM	H^r, R, Z, Lfx, Eto	Yes	27.0	6.0	5.5	Lfx^+,Km^+,H^{h+} Pto, Z, E, PAS, Cs	453–467	91	Cured (390)
3	September 2014	F/57	DM	S, H, R, E, Lfx, Mfx	No	21.0	9.0	0.5	Lfx^+,Am^+,Pto^+ Z, PAS, Cs	435–452	17	Cured (461)
4[§]	November 2014	F/54		S, H^r, R, E, Z, Lfx, Am, Km, Cm, PAS	Yes	12.0	12.0	12.0	Lfx^+, H^{h+}	410–436	0	Cured (720)
5[§]	March 2015	F/48		S, H, R, Z, Am, Km, Cm	Yes	13.0	6.0	13.0	Lfx^+, E	429–440	14	Cured (672)
6[§]	April 2015	M/44	Alcoholic liver disease	H, E, Z, Lfx	Yes	13.0	12.5	13.0	Lfx^+, Am^+, PAS	432–459	28	Cured (454)
7[§]	September 2015	M/48		S, H^r, R, E, Z, Am, Km, Cm, Lfx	No	13.0	12.0	11.5	Lfx^+, H^{h+}, PAS	389–415	67	Cured (338)
8[§]	June 2016	F/29		S, H, R, E, Z, Am, Km, Cm, Lfx, Mfx, Eto, PAS, Cs	No	14.5	12.0	14.5	Lfx^+, Pto, Z, PAS, Cs	401–471	79	Cured (174)
9[§]	December 2016	F/59	DM	S, H, R, E, Z, Lfx, Eto, Am, Km, Cm	Yes	>14.5	>14.5	>14.5	Lfx^+, PAS, Cs	423–446	58	Treatment in progress
10[§]	December 2016	F/29		S, H, R, E, Z, Am, Km, Cm	No	13.0	6.5	13.0	Lfx^+, PAS, Cs	418–486	35	Cured (0)
11[§]	April 2016	M/59	DM	S, H, R, E, Ofx, Mfx, Eto, Km, PAS, Cs	No	22.0	22.0	22.0	Lfx^+, Km, E, Cs	404–447	76	Cured (0)

Lzd: linezolid; QTc: corrected QT interval; M: male; F: female; DMS: dermatomyositis; CS: corticosteroids; S: streptomycin; H^r: low-level isoniazid resistance; E: ethambutol; Z: pyrazinamide; Ofx: ofloxacin; Eto: ethionamide; Lfx: levofloxacin; Km: kanamycin; H^h: high-dose isoniazid; Pto: prothionamide; PAS: para-aminosalicylic acid; Cs: cycloserine; NA: not applicable; DM: diabetes mellitus; R: rifampicin; Mfx: moxifloxacin; Am: amikacin; Cm: capreomycin. [#]: age upon starting MDR-TB treatment. [¶]: follow-up duration after completing treatment was estimated from the duration between the last follow-up date and the treatment completion date. [+]: drugs with likely *in vitro* activity refer to those to which drug susceptibility testing suggests bacillary susceptibility; however, in the case of fluoroquinolone resistance and H^r, high-dose later-generation fluoroquinolone and H^h are considered to have likely *in vitro* activity, respectively, and in the context of pre-extensively drug resistant (XDR)-TB and XDR-TB, owing to poor test reliability, E, PAS and Cs were not considered to have likely *in vitro* activity even if drug susceptibility testing suggested bacillary susceptibility. [§]: Dlm was concurrently initiated with Lzd in these eight patients; in the other patients, Dlm was given later (please refer to the main text).

monitor drug resistance pattern during treatment as a result of excessively slow growth observed in the culture isolates. Despite the lack of evidence from phenotypic or molecular DST, the probability of sequentially acquired bacillary resistance, first to linezolid and then delamanid, was high. The patient was kept in the hospital throughout MDR-TB treatment until death, which occurred ∼6 months after termination of MDR-TB treatment. Our experience with patient 1 corroborated the relatively frequent (10^{-5} to 10^{-6}) spontaneous mutations that confer resistance to nitroimidazoles such as delamanid and pretomanid. When a delamanid-containing regimen is used to treat fluoroquinolone-resistant MDR-TB, it would probably be better to include drugs with a lower propensity to develop drug resistance, such as linezolid or bedaquiline. The combined use of bedaquiline and delamanid has been reported by at least three case studies [8–10]. Trial 213 suggested that delamanid could help prevent amplification of drug resistance among companion drugs [11]. However, this property should not be confused with the propensity of *Mycobacterium tuberculosis* to develop resistance against delamanid, which is related to bacillary load, frequency of spontaneous resistance-associated mutations and potency of the treatment regimen.

In Hong Kong, an ambulatory treatment policy is adopted regardless of the drug resistance pattern. To facilitate treatment supervision in the community after initial treatment in the hospital, we gave delamanid 200 mg once daily instead of 100 mg twice daily after the first 1–2 months. We did not check serum drug levels. Although delamanid exposure for at least the first 2 months may be optimally achieved with 100 mg twice daily [12], delamanid 200 mg once daily is probably efficacious with reference to the published literature regarding the pharmacokinetics and early bactericidal activity [13, 14]. Delamanid has a long plasma half-life of 30–38 h, with a steady-state concentration reached after 10–14 days [13], maximum exposure at the 300 mg dosage (oral administration) [14], and substantial and similar early bactericidal activity over 14 days for 200 mg once daily and 300 mg once daily [14]. Although efficacy findings from Trial 213 suggested small benefit from adding delamanid to an optimised background regimen when 200 mg once daily was used after the first 2 months, this might be related more to an unexpectedly good treatment outcome in the control group than inadequate delamanid exposure, which would be internally inconsistent with another Trial 213 finding that suggested delamanid could help prevent amplification of drug resistance [11]. Our early experience echoes findings from Trial 213 that it would probably be safe and efficacious to give delamanid 200 mg once daily after the first 2 months.

In none of our patients did we find it necessary to stop delamanid owing to prolongation of corrected QT interval, which was periodically monitored throughout treatment. Delamanid was initiated in the hospital to enable close monitoring for about 6–9 weeks. ECG was monitored once weekly in the hospital and once monthly in the chest clinic after hospital discharge. Further delineation of the optimal way to monitor the corrected QT interval under programmatic settings is required.

In the absence of adverse events, use of delamanid was substantially extended beyond 6 months by ⩾3 months in eight patients (9 months in one, ∼12 months in five and >12 months in two), with the longest duration of use being 22 months. Extending use of delamanid beyond 6 months, alongside use of linezolid, was found to be well tolerated.

Restricting analysis to eight patients with linezolid and delamanid concurrently initiated in the regimen (excluding patients 1–3), seven patients (patients 4–8, 10 and 11) have been cured after receiving treatment for 12.0–22.0 months (median 13.0 months), and followed up after completing treatment for a median of 338 days (range 0–720 days). Patient 9 is still receiving treatment with good progress. Patient 11 received treatment for 22 months despite sputum culture conversion within 3 months after starting MDR-TB treatment owing to concerns about a higher relapse risk due to poorly controlled diabetes mellitus. We have been successfully treating the majority of fluoroquinolone-susceptible MDR-TB patients with regimens that lasted for only 12–15 months (1 year after culture conversion) [15], except for those with comorbidity that may substantially increase the relapse risk. Our early experience with delamanid-containing regimens suggests that treatment could be stopped 1 year after sputum culture conversion among difficult MDR-TB patients with delamanid and linezolid concurrently initiated in the treatment regimen, except for those with comorbidity that may substantially increase the relapse risk.

In summary, our early experience suggests that: 1) fluoroquinolone-resistant MDR-TB or XDR-TB may be successfully treated with shorter (about 12–15 months) regimens comprising both delamanid and linezolid, except for those with comorbidity that may substantially increase the relapse risk; 2) it would probably be better to initiate delamanid alongside linezolid; 3) longer courses of delamanid are well tolerated and safe; and 4) delamanid could be given once daily instead of twice daily after the first 1–2 months. Further evaluation in a larger patient database is required to substantiate these preliminary observations.

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Received: Jan 24 2018 | Accepted after revision: March 24 2018

Conflict of interest: W.W. Yew was a consultant to Otsuka, with an honorarium, until July 2016.

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