Long-term safety and tolerability of delamanid-containing regimens in multidrug-resistant and extensively drug-resistant tuberculosis patients in a specialised treatment centre in Berlin, Germany

To the Editor:

Drug-resistant tuberculosis (DR-TB) is an ongoing challenge for patients and healthcare systems. The World Health Organization (WHO) estimated 484 000 (CI: 417 000–556 000) new multidrug-resistant/rifampicin-resistant tuberculosis (MDR-/RR-TB) cases for 2018 [1]. While new and repurposed drugs show promising results in studies, notified treatment outcomes are still below expectations. Germany, as a low incidence country, had 5429 newly diagnosed TB cases (incidence rate of 6.5 per 100 000), including 118 patients with MDR-TB and eight patients with extensively drug-resistant (XDR-) TB in 2018.

Delamanid (brand name: Deltyba; DLM) showed bactericidal antitubercular activity against drug-susceptible and drug-resistant strains of *Mycobacterium tuberculosis* in early studies [2]. It was conditionally approved in 2014 by the European Medicine Agency (EMA) for the treatment of MDR- and XDR-TB with daily administration over 6 months, where no sufficient treatment regimen could be composed with other second line drugs [3]. Discussions about efficacy and the role of DLM in the treatment of MDR-TB are ongoing after intensively discussed results of the phase III trial of DLM [4].

In this retrospective analysis, we evaluated safety and tolerability data of all patients who started treatment with DLM between 2014 and 2017 (n=29/112) in a specialised TB treatment centre in Berlin, Germany (Lungenklinik Heckeshorn, Helios Klinikum Emil von Behring). Data were extracted consecutively from hospital records. Sputum smear microscopy, molecular tests and culture, as well as molecular and phenotypic drug susceptibility testing (DST) was performed for all patients according to the Clinical and Laboratory Standard Institute 2011 as described previously [5, 6]. Treatment regimens were composed individually based on DST and according to current German treatment recommendations [7]. Electrocardiogram (ECG) controls were done at least weekly to monthly and more frequently during DLM–bedaquiline (BDQ) coadministration, in case of QT-prolongation, or when recommended by the treating physician. The QTc interval was corrected by the Fredericia method (QtcF). Blood tests (electrolytes, creatinine, liver enzymes, protein, C-reactive protein, full blood count) were performed at least monthly or more often when recommended by the treating physician.

All 29 patients included had pulmonary TB (100%), of which 13 (45%) had unilateral and one (3%) had bilateral cavities. One patient (3%) had concomitant extrapulmonary TB. Median age was 30 years (range 19–64 years) and 19 patients (65.5%) were male. 28 patients (96.5%) were born outside Germany and 19 (65%) reported previous TB treatment. One patient (3%) was HIV positive. Two patients (7%) had poly-resistant TB with limited treatment options due to side-effects, seven patients (24%) had MDR-TB, 15 (52%) had pre-XDR-TB and five (17%) had XDR-TB. Detailed patient characteristics are summarised in table 1.

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TABLE 1 Detailed demographic and clinical patient characteristics of all patients with a delamanid (DLM)-containing regimen (n=29)

Patient	Age years	Sex	Previous treatment	HIV/Hepatitis B/C status	Lung cavities absent/ unilateral/ bilateral	Drug resistance	Resistance classification	Companion drugs to DLM[#]	Treatment duration, months[¶]	Duration of DLM months[¶]	Outcome	Observed adverse events
1	22	M	Yes	HIV – HBV + HCV (+)	Unilateral	H, R, Z, E, RFB, SM, MFX, PTH, CFZ, PAS	Pre-XDR	CM, TRD, LZD, PAS, CLR (0)	21	21	Cured	Increased liver enzymes
2	25	M	Yes	HIV – HBV – HCV –	Unilateral	H, R, E, SM, AM, CM, PTH	Pre-XDR	Z, E, MFX, TRD, LZD (3)	18	15	Cured	
3	39	F	Yes	HIV – HBV – HCV –	Unilateral	H, R, Z, E, RFB, SM, MFX[+], PTH	Pre-XDR	MFX, TRD, LZD, PAS, CLR (0)	24	24	Cured	Creatinine-increase
4	45	M	No	HIV – HBV – HCV –	Absent	H, R, Z, E, RFB, SM, MXF[+], PTH, PAS	Pre-XDR	MFX, TRD, CFZ, LZD, CLR (3)	23	21	Cured	Creatinine-increase
5	29	M	Yes	HIV – HBV – HCV –	Absent	H, R, Z, E, SM, AM, CM, PTH	Pre-XDR	MFX, TRD, CFZ, LZD, PAS (0)	8	8	Lost-to-follow up	Creatinine-increase
6	30	F	Yes	HIV – HBV – HCV –	Absent	[§]	Pre-XDR	TRD, CFZ, LZD, PAS, TMP/SMX (0)	5	5	Lost-to-follow-up	Creatinine-increase
7	46	M	Yes	HIV + HBV – HCV +	Absent	H, Z, E, SM, PTH	Polyresistant TB	MFX, TRD, CFZ, PAS (4)	24	20	Cured	QT-prolongation, increased liver enzymes, creatinine-increase
8	64	M	No	HIV – HBV – HCV –	Unilateral	H, R, Z, E, SM, PTH, TRD	MDR	RFB, MFX, CFZ, LZD (5)	24	19	Cured	
9	28	F	No	HIV – HBV – HCV –	Absent	H, R, Z, E, RFB, SM	MDR	E, TRD, LZD, PAS (0)	7	7	Transferred out	
10	51	F	No	HIV – HBV – HCV +	Unilateral	H, R, Z, E, RFB, SM, MFX, PTH	Pre-XDR	MFX, TRD, CFZ, LZD (1)	16	15	Treatment completed	Creatinine-increase
11	27	F	Yes	HIV – HBV – HCV –	Absent	H, R, Z, E, RFB, SM, MFX[+], AM, PTH	XDR	MFX, CM, TRD, LZD, PAS (0)	24	7	Cured	Sputum culture reversion, QT-prolongation, creatinine-increase

Continued

TABLE 1 Continued

Patient	Age years	Sex	Previous treatment	HIV/Hepatitis B/C status	Lung cavities absent/ unilateral/ bilateral	Drug resistance	Resistance classification	Companion drugs to DLM[#]	Treatment duration, months[¶]	Duration of DLM months[¶]	Outcome	Observed adverse events
12	31	F	Yes	HIV – HBV – HCV –	Absent	H, Z, E, SM, PTH	Polyresistant TB	R, MFX, CFZ, LZD (0)	18	18	Treatment completed	QT-prolongation
13	24	M	No	HIV – HBV – HCV –	Unilateral	H, R, Z, E, RFB, SM, MFX	Pre-XDR	E, MFX, TRD, LZD (3)	31	7	Cured	Sputum culture reversion, suicidal tendencies
14	29	M	Yes	HIV – HBV – HCV (+)	Unilateral	H, R, Z, E, RFB, LFX, MFX, PTH, CM, AM	XDR	TRD, CFZ, LZD, BDQ, TMP/ SMX (29)	33	4	Lost-to-follow up	
15	30	F	Yes	HIV – HBV – HCV –	Absent	H, R, Z, E, RFB, SM, MFX, AM, CM, PTH, PAS^{+}	XDR	CFZ, (AM, TRD, LZD, TMP/ SMX)[f] (1)	2	1	Lost-to-follow up	
16	36	M	Yes	HIV – HBV – HCV –	Absent	H, R, Z, E, RFB, SM, PTH, CLR	MDR	MFX, TRD, CFZ (14)	20	5	Cured	
17	33	M	Yes	HIV – HBV – HCV –	Absent	H, R, E, RFB, SM	MDR	Z, MFX, PTH, TRD, PAS (0)	24	13	Cured	QT-prolongation
18	26	F	Yes	HIV – HBV – HCV –	Absent	H, R, Z, E^{+}, RFB, SM, MFX, PTH, PAS	Pre-XDR	E, TRD, CFZ, LZD (1)	25	24	Treatment failure	Creatinine-increase
19	17	M	No	HIV – HBV – HCV –	Absent	H, R, Z, E, RFB, SM, MFX^{+}	Pre-XDR	MFX, TRD, CFZ, LZD, PAS (4)	23	1	Cured	Supraventricular tachycardia, creatinine-increase
20	20	M	Yes	HIV – HBV – HCV –	Bilateral	H, R, Z, E, RFB, SM	MDR	MFX, TRD, CFZ, LZD (7)	29	23	Treatment completed	Creatinine-increase
21	22	M	Yes	HIV – HBV – HCV +	Absent	H, R, RFB, SM, PTH, TRD	MDR	E, MFX, CFZ, LZD (0)	19	19	Treatment completed	Increased liver enzymes
22	30	M	No	HIV – HBV – HCV –	Unilateral	H, R, Z, E, RFB, SM, MFX^{+}, PTH, PAS	Pre-XDR	MFX, AM, TRD, LZD, MPM (0)	26	26	Treatment completed	

Continued

TABLE 1 Continued

Patient	Age years	Sex	Previous treatment	HIV/Hepatitis B/C status	Lung cavities absent/ unilateral/ bilateral	Drug resistance	Resistance classification	Companion drugs to DLM[#]	Treatment duration, months[¶]	Duration of DLM months[¶]	Outcome	Observed adverse events
23	50	M	Unknown	HIV – HBV – HCV –	Absent	H, R, Z, E, RFB, SM, MFX^{+}, CM, PTH, TRD	XDR	Z, AM, CFZ, LZD, PAS (0)	2	2	Death	
23	50	M	Unknown	HIV – HBV – HCV –	Absent	H, R, Z, E, RFB, SM, MFX^{+}, CM, PTH, TRD	XDR	Z, AM, CFZ, LZD, PAS (0)	2	2	Death	
24	29	M	Yes	HIV – HBV – HCV +	Unilateral	H, R, Z, E, RFB, SM, MFX^{+}, PTH	Pre-XDR	MFX, TRD, CFZ, LZD, PAS (0)	24	6	Cured	No sputum culture conversion, increased liver enzymes, creatinine-increase
25	19	M	No	HIV – HBV – HCV –	Unilateral	H, R, Z, E, SM, MFX^{+}	Pre-XDR	E, MFX, AM, TRD, LZD (1)	14	12	Still under treatment (culture negative)	Creatinine-increase
26	48	M	Yes	HIV – HBV – HCV +	Unilateral	H, R, Z, E, RFB, SM, AM,	Pre-XDR	MFX, TRD, CFZ, LZD, PAS (0)	14	14	Still under treatment (culture negative)	
27	32	M	Yes	HIV – HBV – HCV –	Unilateral	H, R, Z, RFB, SM, MFX^{+}, PTH	Pre-XDR	Z, MFX, TRD, LZD, PAS (0)	12	12	Still under treatment (culture conversion)	QT-prolongation
28	49	M	Yes	HIV – HBV – HCV +	Unilateral	H, R, E, SM, MFX, CM, PTH, TRD, LZD^{+}, PAS	XDR	TRD, CFZ, LZD, PAS (0)	24	24	Cured, pneumonectomy	QT-prolongation, creatinine-increase
29	23	F	No	HIV – HBV – HCV –	Absent	H, R, E, SM, PTH	MDR	Z, E, MFX, AM, LZD (1)	14	12	Still under treatment (culture conversion)	Creatinine-increase

M: male; F: female; MDR: multidrug-resistant; XDR: extensively drug-resistant; HIV –: HIV antibody-test negative; HIV +: HIV antibody-test and virus-PCR positive; HBV +: infection with hepatitis B virus (HBsAG^{+}); HBV –: no serological sign of hepatitis B virus infection (HBsAG^{-}); HCV +: active/chronic hepatitis C virus (Anti-HCV, HCV RNA^{+}); HCV (+): cleared hepatitis C infection (Anti-HCV IgG^{+}HCV RNA^{-}); H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; AM: amikacin; SM: streptomycin; BDQ: bedaquiline; CM: capreomycin; CLR: clarithromycin; CFZ: clofazimine; LZD: linezolid; MPM: meropenem; MFX: moxifloxacin; LFX: levofloxacin; PAS: para-aminosalicylic acid; PTH: protionamide; RFB: rifabutin; TMP/SMX: co-trimoxazole; TRD: terizidone; XDR: extensively drug-resistant; TB: tuberculosis; MDR: multidrug-resistant; DST: drug-susceptibility testing. [#]: companion drugs when DLM was started. If DLM was started with the initial treatment "0" is put in brackets. If DLM was added later to the regimen the month of treatment is put in brackets and number is rounded to full month. [¶]: months rounded to full month. $^{+}$: phenotypical DST showed intermediate result or low-level resistance.[§]: only molecular DST available, mutations found in InhA-, KatG-, rpoB-, gyrA-genes. [f]: drugs in brackets were paused due to side-effects and reintroduced one by one.

We included all patients, who received at least one dose of DLM (n=29). Mean treatment duration was 18.3 months (range 2–33 months). 22 patients (76%) received DLM for longer than the recommended duration of 6 months, with a median time of 13.3 months (range 1–26 months). The mean number of drugs in the individualised treatment regimens including DLM was 5.5 (range 4–6). The background regimen at the start of DLM included linezolid 300 mg (n=25, 86%), terizidone (n=23, 79%), moxifloxacin (MFX) (n=21, 72%), clofazimine (CFZ) (n=18, 62%), para-aminosalicylic acid (n=14, 48%), ethambutol (n=7, 24%), pyrazinamide (n=5, 17%), amikacin (n=4, 14%), clarithromycin (n=3, 10%), capreomycin (n=2, 7%), co-trimoxazole (n=3, 10%), meropenem/clavulanic acid (n=1, 3%), BDQ (n=1, 3%), prothionamide (n=1, 3%), rifampicin (n=1, 3%), rifabutin (n=1, 3%).

QTcF-prolongation was recorded in six patients (20%) with an increase of more than 60 ms compared to the QTcF at the beginning of DLM-containing treatment. All received at least one additional QT-prolonging drug (MFX or CFZ). Three of these six patients had an increase in QTcF of more than 500 ms, all had two additional QT-prolonging drugs (MFX and CFZ) at this time. Treatment was continued under intensified ECG-monitoring in all cases and QT-time returned to normal without treatment interruption. 10 patients (34%) had asymptomatic bradycardia; none of them had to discontinue treatment. One patient (3%) developed palpitations, his long-term ECG showed a supraventricular tachycardia, but no other ECG abnormalities were detected. DLM was stopped and the palpitations stopped.

Throughout treatment DLM was co-administered with BDQ in four patients (14%) for a median duration of 7.4 months (range 3.2–13.8 months). One of these four had two additional QT-prolonging drugs (CFZ and MFX). In all patients coadministration was safe and well tolerated, no QT-prolongation was observed.

14 patients (48%) had a mild, asymptomatic increase in creatinine during their MDR-TB therapy. At baseline, median creatinine level of all patients was 0.78 $mg{\cdot}dL^{-1}$, and throughout treatment, median maximum creatinine level was 1.02 $mg{\cdot}dL^{-1}$. The maximum creatinine value of a single patient was 1.84 $mg{\cdot}dL^{-1}$ at month 5 of treatment, while baseline level was within normal range. Treatment was continued under intensified laboratory controls without interruption of treatment.

Four patients (14%) had an increase of liver enzymes, three of them had chronic hepatitis C.

DLM treatment was stopped in one patient (3%) due to a suicide attempt, although it was most likely linked to an acute stress disorder.

No other clinically relevant adverse events could be attributed to DLM treatment. DLM was well tolerated, even in patients with drug exposure for longer than 6 months. Most side-effects were related to other drugs of the regimen.

Treatment outcomes were available for 25 patients (86%), while four patients (14%) were still under treatment. 18 patients (18 out of 25; 72%) showed treatment success (cure and treatment completion). Four patients (4/25; 16%) were lost to follow-up, one (1/25; 4%) was transferred to another hospital and one (1/25; 4%) had treatment failure after more than 2 years of treatment. One patient (1/25; 4%) died, post-mortem autopsy showed a heart failure not related to TB treatment. In three patients (3/25; 12%) sputum conversion could not be achieved after 6 months of DLM or sputum culture reversed after conversion to negative. In these latter 3 patients, DLM was stopped, treatment regimens were changed, and all patients reached treatment success. DST for DLM was not available at the time of study and acquired DLM-resistance could not be investigated. Among the 14 patients (14/25; 56%) under follow-up (4 months to 2 years), no relapse has been registered to date.

Although there are some data for safety and treatment outcomes of DLM-containing regimens, there is little evidence from high-income countries and for extended treatment durations. Our real-life data indicate a good tolerability and safety of DLM, even when administered for a longer duration than the recommended 6 months.

QT-prolongation is described in several studies with similar frequencies [8–10]. Although a review found QT-prolongation in DLM–BDQ coadministration, we could not observe this effect [11]. In a study by Mohr *et al.* [12] this effect was also not observed, but they found a lower rate of QT-prolongation in total.

To our knowledge no other study described increased creatinine levels under DLM-containing regimens. To evaluate the impact of this observation and the relationship to a regimen or a single drug, it would be helpful to analyse a bigger set of data such as the active drug safety monitoring project by WHO and global TB network.

In studies from South Korea and Latvia high treatment success rates were observed (81.6% and 84.2%) with DLM-containing regimens in patients with MDR-/XDR-TB [13, 14]. Treatment was successful in 72% of our patients even though some of the final results are still pending and we had a higher proportion

of patients lost to follow-up. Limitations of our study include the retrospective design and the small patient number. This retrospective study was intended to investigate the safety of DLM in a high income, low incidence setting with treatment durations longer than 6 months. Nevertheless, our real-life data support the effectiveness of an individualised treatment regimen using all available drugs, including new and repurposed drugs. Currently DLM is recommended as a Group C drug by WHO and further studies are necessary to analyse the efficacy of different treatment regimens including DLM [15].

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