First case of extensively drug-resistant tuberculosis treated with both delamanid and bedaquiline

To the Editor:

The *European Respiratory Journal* has recently discussed delamanid and bedaquiline and their use in difficult-to-treat cases affected by multidrug-resistant tuberculosis (MDR-TB) or extensively drug-resistant (XDR-TB) [1–4]. The use of delamanid or bedaquiline is particularly important when four active drugs cannot be identified and included in a regimen, as per World Health Organization (WHO) guidelines [1–6]. Recently a debate has been initiated around the report of a severe, almost untreatable, XDR-TB case who could not access both new drugs simultaneously [7–10] due to concerns about possible additive toxicity (cardiotoxicity), as well as the lack of evidence and specific guidance on their combined use [10–13].

In the meantime some essential criteria have been proposed [10] which, if met, might allow for the co-administration of delamanid and bedaquiline to be appropriate and safe: an effective treatment cannot be designed by using only one new drug in addition to the optimised background regimen as per WHO guidelines; the clinical centre is qualified and equipped to monitor the patient during treatment; informed consent and pharmacovigilance are in place; and use of the new drugs is supported by expert opinion (*e.g.* the TB Consilium or similar bodies; www.tbconsilium.org) [5, 10]. This approach aims to increase the chance of treatment success, while minimising the patients' risk of adverse events and ensuring their timely management if they appear. Furthermore, it allows reduction of the risk of transmission of a potentially lethal strain [10] and prevents resistance to the new drugs.

This study reports the rationale for prescribing both delamanid and bedaquiline in an XDR-TB case and describes the difficulties encountered in the early phase of treatment.

The patient, a 39 year-old female Tibetan refugee living in India, who was HIV negative, had a TB relapse in 2011 after being declared cured twice, in 1997 and 2005, respectively. Based on drug susceptibility testing (DST), she was prescribed second-line drugs. Following 12 months of second-line drug treatment, her sputum culture was persistently positive; she was subsequently referred to Delek Hospital, Dharamshala, India. A new DST showed resistance to isoniazid, rifampicin, kanamycin, ethionamide, para-aminosalicylic acid (PAS), ofloxacin, moxifloxacin, amikacin and capreomycin (table 1). Despite different drug combinations, which included all five WHO classes of anti-TB drugs, the patient required a total of 38 months of anti-TB drugs to finally obtain culture conversion in the last year of treatment, which reverted 2 months after the suspension of the drugs.

At this stage the treating physician requested the inclusion of the patient in the delamanid compassionate use programme *via* the TB Consilium platform; based on DST, the patient had XDR-TB with a single certified active drug, clofazimine. DSTs for ethambutol, pyrazinamide, streptomycin, cycloserine/terizidone and meropenem/clavulanic acid were not available, while all other drugs tested showed resistance. The patient had bilateral upper zone fibrocavitary lesions on chest radiography and poor lung reserve ruling out the possible benefit of surgical resection.

In such a setting, the combination of clofazimine and delamanid without a third (and fourth) active drug may potentially have resulted in delamanid resistance. Given there were no other available drugs to design an effective regimen for this patient, the TB Consilium experts recommended the simultaneous introduction of delamanid and bedaquiline in combination with an optimised background regimen. Therefore, both new drugs were requested and made available to make an effective salvage regimen.

The regimen included delamanid and bedaquiline (at the recommended doses of 200 mg and 400 mg, respectively), clofazimine (200 mg) and terizidone (1 g) and meropenem (1 g three times daily) plus amoxicillin/clavulanate (1 g/200 mg three times daily, intravenous), all started on February 25, 2016 [6]. The patient's baseline ECG, serum albumin and potassium were normal, and there was no history of cardiac disease or comorbidities predisposing cardiac dysfunction. Moxifloxacin was not considered in the regimen as DST showed resistance to high-dose moxifloxacin, and adding this to regimen already containing three QT (ECG Q-T wave interval) prolonging drugs would have increased the risk of adverse events.

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TABLE 1 Clinical characteristics of the first case treated with both delamanid and bedaquiline

	Details	Comments
Country of birth	India	
Age	39 years	
Sex	Female	
Body weight at diagnosis[#]	65 kg	
Case category	Retreatment case	
Number of previous anti-TB treatments	4	
Drugs administered in previous anti-TB treatments	Kanamycin 750 mg *i.m.* (12 months) Levofloxacin 1 g, PAS 10 g, cycloserine 750 mg, ethionamide 750 mg, capreomycin 1 g *i.m.* (14 months) High-dose isoniazid 900 mg, rifabutin 300 mg, clofazimine 200 mg, clarithromycin 1 g, amoxicillin/clavulanate 625 mg, terizidone 1 g three times daily, imipenem 500 mg *i.v.* three times daily (12 months), linezolid 600 mg then 300 mg	
Previous outcome	Cured (twice)	
Body mass index at baseline	26.9 kg·m^{-2}	
Bacteriology at baseline	Sputum smear positive Culture positive Xpert positive	At Day 18: smear negative Culture taken after 28 days of treatment: ongoing (negative on the 14th day of MGIT culture)
Radiology	Bilateral upper zones fibrocavitary lesions	
Drug resistances	Resistant to 12 drugs: Isoniazid, rifampicin, kanamycin, amikacin, capreomycin, moxifloxacin, ofloxacin, ethionamide, PAS, linezolid, high-dose isoniazid, high-dose moxifloxacin Susceptible to: clofazimine	
Last treatment regimen	Delamanid, bedaquiline, clofazimine (200 mg), terizidone (1 g) and meropenem 1 g three times daily plus amoxicillin/clavulanate 1 g/200 mg three times daily *i.v.*, all started on February 25, 2016	Bedaquiline stopped on March 7, 2016, restarted March 12, 2016

TB: tuberculosis; PAS: para-aminosalicylic acid; *i.m.*: intramuscular; *i.v.*: intravenous; MGIT: mycobacteria growth indicator tube. [#]: August 31, 2015.

On March 4, 2016 the treating physician, concerned about QT corrected with heart rate (QTc) prolongation in his patient, consulted the TB Consilium again. The patient was asymptomatic, with a baseline QTc (prior to delamanid and bedaquiline administration) of <450 ms, thereafter increasing to 476 ms after five doses and to 486 ms on March 3, 2016 (after eight doses of the new drugs). Serum potassium was 3.5 mmol·L^{-1} on March 5, 2016 (day 10 of treatment) supplemented with oral potassium chloride, and been within the normal range on weekly follow-up.

Given the ongoing concerns and debate on QTc prolongation with the combination of delamanid, bedaquiline and clofazimine [11, 12], both the TB Consilium experts advised to stop bedaquiline (which was carried out on March 7, 2016) and to continue close patient monitoring.

The following management plan was recommended by the TB Consilium experts:

1) Repeat ECG biweekly and closely monitor the QTc interval.
2) Monitor urea and electrolytes weekly and rule out hypokalaemia, hypomagnesaemia, hypocalcaemia, *etc.* (which could potentially prolong QTc). Correct the electrolyte imbalance if necessary.
3) Repeat the thyroid function test to rule out hypothyroidism, which could potentially prolong QTc because of long-term exposure to ethionamide and PAS, and manage hypothyroidism accordingly.
4) If QTc increases to >500 msec, stop the whole regimen and then continue with biweekly ECG monitoring. It was unfortunately impossible to consider stopping clofazimine in absence of alternatives. Preliminary evidence in South Africa shows that the mean increase in QTc within a 2 month period using bedaquiline was ~8 msec (N. Ndjeka; National Dept of Health, Pretoria, South Africa; personal communication).
5) Once QTc is <500 msec, re-introduce the regimen and monitor ECG weekly/biweekly or monthly depending on the QTc levels.

In the same round of consultations, suggestions from the TB Consilium experts included:

1) Restart bedaquiline and continue the current regimen while observing QTc, and if above 500 msec, stop clofazimine.
2) Restart bedaquiline and continue the current regimen, monitor ECG and consider adding verapamil to control QTc. Verapamil is an agent that may negate the effect of bedaquiline and clofazimine on QTc; however, there is little evidence supporting this [14].
3) Should the patient become symptomatic (for example syncope or arrhythmias), consider a definitive stop of bedaquiline, unless implantation of a defibrillator device is possible.

Following the TB Consilium experts' recommendations, electrolytes were corrected, verapamil (40 mg three times daily) was added on March 12, 2016 and bedaquiline restarted, as QTc was still <500 ms (489 ms). After five additional days (day 21 of treatment), QTc was 479 ms and the patient remained asymptomatic. Bedaquiline was then reduced to 200 mg three times weekly. ECG repeated at day 27 reported a QTc of 491 msec. The patient remains asymptomatic. Electrolytes and serum albumin are in the normal range. As far as treatment response is concerned, the sputum smear was negative after 18 days of treatment, while the sputum culture taken after 28 days was still negative on the 14th day of mycobacteria growth indicator tube culture.

This experience emphasises the importance of conducting clinical trials on the combined use of delamanid and bedaquiline (e.g. those planned by the National Institute of Allergy and Infectious Diseases; https://clinicaltrials.gov/ct2/show/NCT02583048), whose results will, unfortunately, not be available for the next 2–3 years. In the meantime, in cases of extremely severe clinical conditions that may be life-threatening and when recourse to other second-line drugs is extremely limited, it is our opinion that associating the two drugs would be possible, provided that this is done in a properly qualified MDR-TB treatment centre with adequate facilities to closely monitor the patient's condition and drug safety, and that the patient is duly informed of the limited evidence available (i.e. signed informed consent) [10]. The support of the TB Consilium or similar platforms can help ensure appropriate use of the new drugs and close monitoring during their co-administration [10].

Furthermore, the experience of this first case treated with both drugs shows that if the safety criteria mentioned above are met as in this case [7], co-administration of delamanid and bedaquiline would be possible, although the clinical management of these cases can be demanding, expensive and complicated [15].

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Report of the first case, concerns and challenges of treatment of severe XDR-TB with both delamanid and bedaquiline http://ow.ly/WzeB3004Cmo

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