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Bedaquiline in MDR/XDR-TB cases: first experience on compassionate use

To the Editor:

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) are recognised as global emerging public health priorities [1, 2], with 310 000 MDR-TB cases notified to the World Health Organization (WHO) in 2011, 9% of them being XDR. MDR/XDR-TB testify to the failure of National TB Programmes to use available first- and second-line drugs correctly [3], and generate clinical dilemmas for clinicians managing these difficult-to-treat cases.

The chances of achieving treatment success, or even sputum smear and culture conversion, are largely suboptimal in these cases [1, 2]. In the largest MDR-TB cohort ever analysed [1, 2], the proportion of cases treated successfully was 54%, with 8% failing or relapsing, 15% dying and 23% defaulting. In the XDR-TB subgroup, 40% achieved treatment success, 22% failed treatment or relapsed, 15% died, and 16% defaulted.

The reason for this is simple: treatment of MDR/XDR-TB is expensive [4], more toxic [5, 6], and, as of today, takes up to 2 years of therapy according to current WHO guidelines [3]. The therapeutic armamentarium is limited in XDR-TB cases, where, by definition, the strains of *Mycobacterium tuberculosis* are resistant to the two most powerful anti-TB drugs (rifampicin and isoniazid, defining MDR-TB) plus any fluoroquinolones and to at least one second-line injectable (amikacin, capreomycin and kanamycin). The remaining treatment options available are the ''old'' bacteriostatic drugs and the not well-known WHO group 5 drugs [3, 5–7].

The real clinical dilemma clinicians face in managing these cases is how to ensure the fourth active drug during the intensive phase and/or the third active drug during the continuation phase of treatment, as recommended by WHO [3]. From this dark perspective, the present availability of new drugs in the development pipeline represents a possible solution. While delamanid is still completing the necessary registration procedures [5, 8], bedaquiline [5, 9] (a new diarylquinoline, formerly known as TMC207) has recently received US Food and Drug Administration approval and ''compassionate'' use in several European countries. While it is still undergoing phase III trials, phase I, II and IIb trials have shown the drug to be safe and effective, although an excess mortality has been identified in the treatment arm and will need further evidence [9].

In a multidrug treatment regimen, bedaquiline increased sputum culture conversion from 9% to 48% and reduced the time to sputum-negative conversion by 58%, suggesting its potential capacity to significantly reduce the treatment period as well as the debilitating and dangerous adverse effects associated with some of the existing second-line anti-TB drugs.

Compassionate use allows for potentially lifesaving investigational drugs or experimental treatments (with good efficacy and safety in trials, but which have not been registered for market use) to be made available for patients suffering from a disease for which no satisfactory authorised therapy exists and/or who cannot enter a clinical trial.

To our knowledge, no published evidence on the ''compassionate'' use of bedaquiline to treat MDR/XDR-TB cases is available; herein, we report the management of two patients with bedaquiline at the Italian TB Reference Centre ''Morelli Hospital'' in Sondalo, Italy (table 1).

Both cases, who were HIV negative, presented resistance to all first-line drugs, meeting the criteria for XDR-TB in the Ukraine-born patient, while the Italian case was pre-XDR-TB (resistance to a fluoroquinolone). Both patients had limited treatment options and suffered from different adverse events.

The Ukrainian patient had been poorly managed in two other centres where a single active drug was being added several times to a failing regimen for >12 months. She presented with an extensive ulcerated left confluent cavity in her upper left lung lobe and nodules in lower left and right lobes, and suffered from depression and poor appetite. Moxifloxacin and para-aminosalicylic acid (PAS) were not tolerated and were stopped. Due to the bilateral lung infiltrates, surgery was not indicated.

The Italian patient, who was recently retired, had received a standard TB regimen in March 2012. When drug susceptibility testing demonstrated resistance to isoniazid and pyrazinamide, he was treated with rifampicin, ethambutol, levofloxacin and streptomycin. Later, he was found to have MDR-TB with resistance to quinolones, was transferred to Sondalo, where, poorly tolerating treatment, he developed generalised anxiety (requiring diazepam) and improved on an antidepressant. PAS was stopped for generalised diarrhoea. He also developed severe hypoacusia with amikacin (stopped), becoming a ''functional'' XDR-TB patient. Surgery was not indicated as the lesions were bilateral.

Both patients received psychiatric assessments, where it was deemed safe to continue terizidone. Following ethics committee approval, a request for compassionate use of bedaquiline was made to Janssen

TABLE 1 Clinical and demographic characteristics of the first two multidrug-resistant (MDR)/extensively drug-resistant (XDR) tuberculosis (TB) patients treated with bedaquiline under ''compassionate'' conditions in Sondalo, Italy

Country of birth	Ukraine	Italy
Age years	35	65
Sex	Female	Male
Weight kg	55	60
Height m	1.75	1.65
BMI kg·m^{-2}	17.95	24.28
HIV	Negative	Negative
Radiology at MDR/XDR-TB diagnosis	Bilateral cavity lesions	Bilateral cavity lesions
Surgery	No	No
Previous treatment >30 days n	2	1
Drugs received during previous treatments	Am, Clr, Cs, E, Eto, H, Ipm, Lzd, Mfx, PAS, R, S, Z	E, H, Lfx, R, S, Z
Drug-resistance at MDR/XDR diagnosis	Am, Cm, E, Eto, FQ, H, Km, R, S, Z	E, Eto, FQ, H, R, S, Z
Drugs used in treatment	Amx/Clv, Bd, Cfz, Lzd, Mp, Trd	Amx/Clv, Bd, Cfz, Lzd, Mp, Trd
Hospital admission days	91	101
Smear conversion days	63	58
Culture conversion days	75	58
Bedaquiline exposure days	180 (September 10, 2012 to March 8, 2013)	180 (November 23, 2012 to May 21, 2013)
Adverse events	Anorexia, depression	Generalised anxiety, deafness, diarrhoea
***Ad interim* outcome**	Clinically and radiologically improved, consistently bacteriologically negative, at the last clinical examination at 15 months (July 3, 2013)	Clinically and radiologically improved, consistently bacteriologically negative, at the last clinical examination at 13 months (July 12, 2013)
Treatment duration	On 15th month of treatment with Amx/Clv, Cfz, Lzd, Trd (439 days)	On 13th month of treatment with Amx/Clv, Lzd, Trd (387 days)
Directly observed treatment performed	Yes	Yes

BMI: body mass index; Am: amikacin; Clr: clarithromycin; Cs: cycloserine; E: ethambutol; Eto: ethionamide; H: isoniazid; Ipm: imipenem; Lzd: linezolid; Mfx: moxifloxacin; PAS: para-aminosalycilic acid; R: rifampicin; S: streptomycin; Z: pyrazinamide; Lfx: levofloxacin; Cm: capreomycin; FQ: fluoroquinolone; Km: kanamycin; Amx: amoxicillin; Clv: clavulanate; Bd: bedaquiline; Cfz: clofazimine; Mp: meropenem; Trd: terizidone.

Pharmaceuticals (Beerse, Belgium), which responded quickly and provided us with consent forms and drug information in Italian. We were able to obtain the new drug in 2 months from the initial request, the first time round, and after only 1 month the second time. Patients were provided with formal written informed consent.

The patients received bedaquiline for the first 2 weeks under highly monitored conditions as in-patients with frequent ECG testing (initially daily, then weekly) and blood tests as standard, with additional amylase and creatine kinase being monitored.

Both cases achieved sputum smear and culture conversion after ~2 months (58 and 63 days) on meropenem and amoxicillin/clavulanate, and linezolid, and were exposed after conversion to bedaquiline for a total of 180 days at the dose of 400 mg once daily for 2 weeks followed by 200 mg three times per week with food [9], without major adverse events. The main side-effects of nausea, joint pain or headache previously noted with bedaquiline were not noted here [9]. The reason for stopping at 180 days is that Janssen Pharmaceuticals only provides 6 months of the drug as there are no trial data supporting continuation after this period; however, a phase III trial starting this year will evaluate 9-month use of the drug [9]. It should be noted that bedaquiline has a very large apparent volume of distribution and has a markedly prolonged terminal half-life (~5.5 months), which reflects the slow release of the compound from peripheral tissue compartments [9].

Both patients achieved consistent bacteriological conversion (table 1) and radiological improvements, being currently in the continuation phase of treatment (15th and 13th month of well-tolerated treatment), with a plan to continue for 24 months.

Compassionate use with bedaquiline provided the extra drug needed to comply with the WHO recommendations [3].

Although we were concerned that our patients, both taking clofazimine, would fall victim to side-effects (mainly the potential QT elongation), no additional adverse events or QT elongation were noted.

A clear limitation in our study is that observations refer to only two individuals, so findings cannot be generalised yet.

This first experience suggests that bedaquiline can be used for compassionate use, given that the recommended criteria and the recent WHO bedaquiline recommendations are satisfied [9, 10]: 1) national guidelines are followed; 2) XDR-TB and pre-XDR-TB cases are targeted; 3) the case is managed in a reference centre, which is able to offer the best possible background regimen; 4) the centre is supported by a quality-controlled laboratory; and 5) treatment history, including outcomes and adverse events, are recorded and made available for international use, thereby contributing to providing additional evidence on the safety and effectiveness of the drug.

A careful introduction of the new drugs, while providing life-saving support, will hopefully protect them from the development of drug resistance (or reducing its development over time) and add quality data for their further evaluation.

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Bedaquiline added to a background regimen for compassionate use achieved bacteriological conversion in MDR/XDR-TB cases http://ow.ly/pQ5SI

Simon Tiberi[1], Saverio De Lorenzo[2], Rosella Centis[3], Pietro Viggiani[2], Lia D'Ambrosio[3] and Giovanni Battista Migliori[3]
[1]Imperial College Healthcare NHS Trust, London, UK. [2]AOVV E. Morelli Hospital, Reference Hospital for MDR and HIV-TB, Sondalo, and [3]World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy.

Correspondence: G.B. Migliori, World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Via Roncaccio 16, 21049, Tradate, Italy. E-mail: giovannibattista.migliori@fsm.it

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Extensively drug-resistant tuberculosis: early access to bedaquiline for a UK patient

To the Editor:

The prevalence of drug resistance among tuberculosis (TB) cases is increasing in the UK [1] and worldwide [2], with increasing proportions of cases with multidrug- and extensively drug-resistant TB (MDR-/XDR-TB) being reported [1, 2]. Toxicity and poor efficacy of treatment are major problems and long durations with culture-positive disease increase the risk of transmission. This report describes difficulties in managing XDR-TB and the pre-license use of bedaquiline outside of clinical trials.

Bedaquiline is an anti-tuberculous drug of the diarylquinoline class, which inhibits bacterial adenosine triphosphate synthase, and represents the first new class of anti-tuberculous agents for at least four decades. Its unique mechanism means that there is no cross-resistance with other drugs in current use. In phase II clinical trials, in combination with background MDR-TB regimens, bedaquiline resulted in reduced time to sputum culture conversion, reduced emergence of resistance to companion drugs and little additional toxicity compared with background regimens alone [3]. At present it is not yet licensed in Europe and the World Health Organization (WHO) has recently issued interim policy guidance for its use as part of combination therapy for adults with MDR-TB under specific conditions, based on currently available evidence [3].

A 28-year-old, HIV-negative Indian female with no prior history of TB treatment or contact was diagnosed with TB through screening on arrival in the UK. A pre-departure chest radiograph 3 months before assessment in the UK was reported to be normal. A bacille Calmette–Guérin scar was seen on examination. A tuberculin skin test and interferon-γ release assay were positive and she was asymptomatic. Chest radiograph revealed mediastinal lymphadenopathy and 1 month later she developed cough and fever. Sputum specimens were sent for microscopy and culture, and further imaging was requested.

Computed tomography (CT) imaging confirmed thoracic lymphadenopathy, and showed small pericardial and pleural effusions and a small pulmonary nodule. *Mycobacterium tuberculosis* was isolated on culture from smear-negative sputum specimens. The identification of the organisms was confirmed by GenoType DNA strip (Hain Lifescience, Nehren, Germany), but no molecular tests for resistance were requested by the referring centre. Standard quadruple therapy (rifampicin, isoniazid, pyrazinamide and ethambutol) was commenced in May 2011 (week 1) (fig. 1), while drug susceptibility testing (DST) was in progress and the appropriate contact tracing procedure was initiated.

After 3 weeks of quadruple therapy, first-line DST showed resistance to rifampicin, isoniazid and ethambutol. The patient was transferred to the regional infectious diseases unit (Dept of Infectious Diseases and Tropical Medicine (Monsall Unit), North Manchester General Hospital, Manchester, UK) and hospitalised to commence treatment for MDR-TB with pyrazinamide, moxifloxacin, amikacin, prothionamide, cycloserine and azithromycin (fig. 1). Pericardial involvement was confirmed by