ERJ Express. Published on August 29, 2013 as doi: 10.1183/09031936.00122313

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

Simon Tiberi[1], Saverio De Lorenzo[2], Rosella Centis[3], Pietro Viggiani[2], Lia D'Ambrosio[3], Giovanni Battista Migliori[3]

1 Imperial College Healthcare NHS Trust, London, United Kingdom

2 AOVV E. Morelli Hospital, Reference Hospital for MDR and HIV-TB, Sondalo, Italy

3 World Health Organization Collaborating Centre for Tuberculosis and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy

Key words: MDR-TB, XDR-TB, bedaquiline, compassionate use, prevention of drug resistance

Short sentence (max 120 characters): bedaquiline added to a background regimen for compassionate use achieved bacteriological conversion in M/XDR-TB cases

Running head: bedaquiline for compassionate use

Address for 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

Text:1205 words

Multidrug- and extensively drug-resistant tuberculosis (MDR- and XDR-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- and XDR-TB testify the failure of National TB Programmes to use available first- and second-line drugs correctly (3), and generate clinical dilemmas to clinicians managing these difficult-to-treat cases.

The chances to achieve treatment success, or even sputum smear and culture conversion are largely sub-optimal in these cases (1,2). In the largest MDR-TB cohort ever analyzed (1,2) the proportion of cases treated successfully was 54%, with 8% failing or relapsing, 15% dying and 23% defaulting.

In XDR-TB subgroup, 40% achieved treatment success, 22% failed treatment or relapsed, whereas 15% died and 16% defaulted.

The reason why is very easy to explain: treatment of M/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 *M. 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, kanamycin). The remaining treatment options available are the "old" bacteriostatic drugs and the not well known WHO Group V 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 one during the continuation phase of treatment, as recommended by WHO (3).

Under 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 still undergoing Phase III trials, Phase I, Phase 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 multi-drug 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 haven't 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 in the literature on the “compassionate” use of bedaquiline to treat M/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, 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 (resistance to a fluroquinolone). 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 over12 months. She presented with an extensive ulcerated left confluent cavity in her upper left lung lobe and nodules in lower left and right lobes, suffered from depression and poor appetite. Moxifloxacin and para-aminosalycilic acid (PAS) were not tolerated and were stopped. Due to the bilateral lung infiltrates, surgery was not indicated. The Italian case, 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 be MDR with resistance to quinolones, was transferred to Sondalo, where poorly tolerating treatment, developed generalized anxiety (requiring diazepam) and improved on an antidepressant. PAS was stopped for generalized diarrhea. 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 was made to Janssen 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 initial request first time round and after only a month the second time. Patients were provided with formal written informed consent.

The patients received bedaquiline for the first two weeks under highly monitored conditions as in-patients with frequent electrocardiogram (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 about 2 months (58 and 63 days) on meropenem and amoxicilin/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 two weeks followed by 200mg three times per week with food (9), without major adverse events. The main side effects of nausea, joint pain or headache noted with bedaquiline were not noted here (9). The reason for stopping at 180 days is that Janssen only provides 6 months of the drug as there is 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 (about 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 on continuation phase of treatment, (15^{th} and 13^{th} month of well tolerated treatment, respectively) with plan to continue for 24 months.

Compassionate use with bedaquiline provided the extra drug needed to comply with 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 two individuals only, so that findings cannot be generalized yet.

This first experience suggests that bedaquiline can be used for ‘’compassionate’’ use given the recommended criteria and the recent WHO bedaquiline recommendations are satisfied (9,10):

- National guidelines are followed;
- XDR and pre-XDR-TB cases are targeted;
- The case is managed in a reference centre, able to offer the best possible background regimen;
- The centre is supported by a quality-controlled laboratory
- Treatment history including outcomes and adverse events are recorded and made available for international use, contributing to provide additional evidence on the drug safety and effectiveness.

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

References

1. Migliori GB, Sotgiu G, Gandhi NR, Falzon D, Deriemer K, Centis R, et al. Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. Eur Respir J. luglio 2013;42(1):169–79.

2. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox HS, Holtz TH, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on multidrug-resistant TB outcomes. Eur Respir J. luglio 2013;42(1):156–68.

3. Falzon D, Jaramillo E, Schünemann HJ, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Eur Respir J. settembre 2011;38(3):516–28.

4. Diel R, Rutz S, Castell S, Schaberg T. Tuberculosis: cost of illness in Germany. Eur Respir J. luglio 2012;40(1):143–51.

5. Sotgiu G, Centis R, D'Ambrosio L, Alffenaar J-WC, Anger HA, Caminero JA, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. Eur Respir J. dicembre 2012;40(6):1430–42.

6. Migliori GB, Sotgiu G. Treatment of tuberculosis: have we turned the corner? Lancet. 15 settembre 2012;380(9846):955–7.

7. De Lorenzo S, Alffenaar JW, Sotgiu G, Centis R, D'Ambrosio L, Tiberi S, et al. Efficacy and safety of meropenem/clavunate added to linezolid containing regimens in the treatment of M/XDR-TB. Eur Respir J. 20 settembre 2012;doi: 10.1183/09031936.00124312.

8. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, et al. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur Respir J. giugno 2013;41(6):1393–400.

9. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Document WHO/HTM/TB/2013.6. Geneva, World Health Organization. 2013.

10. Horsburgh CR Jr, Haxaire-Theeuwes M, Lienhardt C, Wingfield C, McNeeley D, Pyne-Mercier L, et al. Compassionate use of and expanded access to new drugs for drug-resistant tuberculosis. Int J Tuberc Lung Dis. febbraio 2013;17(2):146–52.

Table 1 . Clinical and demographic characteristics of the first two MDR/XDR tuberculosis patients treated with bedaquiline under ''compassionate'' conditions in Sondalo, Italy

Country of birth	Ukraine	Italy
Age	35	65
Gender	F	M
Weight	55	60
Height	1.75	1.65
BMI	17.95	24.28
HIV	Neg	Neg
Radiology at M/XDR diagnosis	Bilateral cavity lesions	Bilateral cavity lesions
Surgery	No	No
Previous treatment (>30 days)	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 M/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 (10.9.2012 to 08.3.2013)	180 (23.11.12 to 21.05.13)
Adverse events	Anorexia, depression	Generalized anxiety, deafness, diarrhoea
Ad interim outcome (as of 18.07.2013)	Clinically and radiologically improved, consistently bacteriologically negative, at the last clinical examination at 15 months (03/07/2013)	Clinically and radiologically improved, consistently bacteriologically negative, at the last clinical examination at 13 months (12/07/2013)
Treatment duration (days)	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)
DOT performed	Yes	Yes

MDR: Multidrug-resistant tuberculosis; XDR-TB: Extensively drug-resistant tuberculosis
BMI: Body Mass Index
HIV: Human Immunodeficiency Virus
DOT: Directly Observed Treatment

First line drugs: E: Ethambutol; H: Isoniazid; R: Rifampin; S: Streptomycin; Z: Pyrazinamide
Second-line and new drugs: Am: Amikacin; Cm: Capreomycin; Cs: Cycloserine; Eto: Ethionamide; FQ: Fluoroquinolone, Km: Kanamycin; Lfx: Levofloxacin; Mfx: Moxifloxacin; PAS: Para-aminosalycilic acid; Trd: Terizidone; Amx/Clv: Amoxicilin/Clavulanate; Bq: Bedaquiline; Clr: Claritromycin; Cfz: Clofazimine; Ipm: Imipenem; Lzd: Linezolid; Mp: meropenem