

New developments in the treatment of drug-resistant tuberculosis: clinical utility of bedaquiline and delamanid

Grania Brigden¹
Cathy Hewison²
Francis Varaine²

¹Access Campaign, Médecins Sans Frontières, Geneva, Switzerland;

²Medical Department, Médecins Sans Frontières, Paris, France

Abstract: The current treatment for drug-resistant tuberculosis (TB) is long, complex, and associated with severe and life-threatening side effects and poor outcomes. For the first time in nearly 50 years, there have been two new drugs registered for use in multidrug-resistant TB (MDR-TB). Bedaquiline, a diarylquinoline, and delamanid, a nitromidoxazole, have received conditional stringent regulatory approval and have World Health Organization interim policy guidance for their use. As countries improve and scale up their diagnostic services, increasing number of patients with MDR-TB and extensively drug-resistant TB are identified. These two new drugs offer a real opportunity to improve the outcomes of these patients. This article reviews the evidence for these two new drugs and discusses the clinical questions raised as they are used outside clinical trial settings. It also reviews the importance of the accompanying drugs used with these new drugs. It is important that barriers hindering the use of these two new drugs are addressed and that the existing clinical experience in using these drugs is shared, such that their routine-use programmatic conditions is scaled up, ensuring maximum benefit for patients and countries battling the MDR-TB crisis.

Keywords: MDR-TB, XDR-TB, tuberculosis drugs, group 5 drugs

Introduction

Tuberculosis (TB) is one of the leading causes of death worldwide: an estimated 9 million people developed active TB in 2013, of which approximately 1.5 million died. In 2013, the World Health Organization (WHO) estimated that there were 480,000 new multidrug-resistant TB (MDR-TB) cases (defined as resistance to isoniazid and rifampicin) and 210,000 deaths. Up to 30% of MDR-TB patients have further resistance to either fluoroquinolones (FQ) or injectable anti-TB agents; approximately 9% of MDR-TB cases have both, which is defined as extensively drug-resistant TB (XDR-TB). In 2013, cases of XDR-TB were reported in 100 countries.¹ In some regions, MDR-TB appears to be an epidemic in its own right, with evidence of direct transmission of drug-resistant forms of TB.^{2,3}

The emergence of MDR-TB hampers efforts to effectively prevent and treat TB, and threatens the prospects for success of the new END TB strategy ratified by the World Health Assembly in 2014.⁴ This is because current treatments for MDR-TB are inadequate: they require patients to undergo lengthy courses of treatment, subject them to severe side effects, are programmatically expensive to implement – and despite all these drawbacks, still show poor success rates, ranging from 48% for MDR-TB to 22% for XDR-TB.¹

Correspondence: Grania Brigden
Access Campaign, Médecins Sans Frontières, 78 Rue de Lausanne, Geneva, Switzerland
Tel +41 78 742 4025
Email grania.brigden@geneva.msf.org

Therefore, it is of enormous significance that, for the first time in nearly 50 years, two new compounds bedaquiline and delamanid have been approved for the treatment of MDR-TB when an effective treatment regimen is not otherwise available.⁵⁻⁷ Bedaquiline (Janssen, Beerse, Belgium), the first new drug, received accelerated approval from the US Food and Drug Administration in December 2012.⁷ The second drug, delamanid (Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan), received approval from the European Medicines Agency and Japan's Pharmaceuticals Medical Devices Agency in 2014.⁵ Alongside these completely new drugs, there is growing evidence for the potential role of repurposed medicines, including clofazimine and linezolid, which are showing effectiveness against drug-resistant forms of TB.⁸⁻¹⁰

It is hoped that the new drugs and the repurposed drugs that accompany them offer promise for improving the treatment of drug-resistant forms of TB, in terms of both better outcomes and quality of life for patients. This article reviews current clinical data and guidance on the use of these new drugs, discusses how they might be used to change MDR-TB treatment outcomes, and raises the challenges seen by clinicians and patients with experience using the drugs.

Efficacy and safety evidence from clinical trials of the new drugs

Delamanid, previously OPC-67863, is a drug of the dihydro-nitroimidazole class and has potent anti-TB activity. Delamanid is thought to primarily inhibit synthesis of methoxy-mycolic and keto-mycolic acid, components of the mycobacterial cell wall. As a prodrug, it requires metabolic activation to exert its anti-TB activity.¹¹

Clinical trial data come from three related Phase IIb studies on the same cohort of MDR-TB patients (trial 204, trial 208, and observational study 116).^{11,12} The key data are from trial 204, which investigated the effect of delamanid, taken with a WHO-recommended MDR-TB optimized background treatment regimen (OBR), on 2-month sputum culture conversion rates in patients with pulmonary MDR-TB (Table 1). Patients were randomized into three arms: delamanid 100 mg or 200 mg twice daily, or placebo, all administered with an OBR.

The number of patients withdrawing from trial 204 due to adverse effects was small and was evenly distributed across the three treatment groups. Rates of hepatotoxicity were low across all groups.¹¹

To assess longer term safety and efficacy, trial 208 followed as an open label extension to trial 204. An additional 6 months of delamanid with OBR was given to 213/481 trial 204 participants, a minimum of 4 weeks after the end of study 204. Study 116 studied an observation cohort of 421/481 trial 204 participants who were followed up to the end of their MDR-TB treatment or to 24 months after the first dose of delamanid in trial 204 whichever came first. Despite the weakness of the study designs for trial 208 and study 116,¹³ most importantly the possibility of selection bias, these studies showed promising results among patients who received 6–8 months of delamanid compared to those who received 0–2 months of delamanid, with significantly higher proportion of favorable outcomes (cure or treatment complete) (75.5% versus 55%) and lower mortality (1% versus 8.3%).¹²

A multicenter, double-blind Phase III placebo-controlled trial in MDR-TB patients to assess the efficacy and safety of the addition of 6 months of delamanid to a WHO-recommended OBR, has recently completed recruitment.¹⁴

Bedaquiline, previously called TMC 207, is a diarylquinoline that acts by specifically inhibiting mycobacterial adenosine triphosphate synthase and has a long half-life of approximately 5 months.¹⁵ A Phase IIb A clinical trial (C208 study) compared a second-line background regimen with or without 24 weeks of bedaquiline (Table 2).¹⁶

Notably, a higher numbers of deaths were reported in the bedaquiline treatment arm, with ten deaths occurring in bedaquiline-treated patients versus two deaths in the placebo arm ($P=0.017$).

None of these deaths were attributed to bedaquiline. All but one occurred after bedaquiline had been stopped, although, given the drug's long half-life, a potential role in these deaths cannot be excluded. Other side effects noted with bedaquiline included liver toxicity and QT prolongation.¹⁶ The planned Phase III trial of bedaquiline, STREAM II (Table 3), has yet to start.¹⁷

Table 1 Results of trial 204 for delamanid in MDR-TB patients

Drug + dose	Number of patients in mITT group	2-month sputum conversion (on liquid culture)	P-value	Prolonged QT*
Del 100 mg (2 times/day) + OBR	141	45.40%	0.008	9.9%
Del 200 mg (2 times/day) + OBR	136	41.90%	0.04	13.1%
Placebo + OBR	125	29.60%		3.8%

Notes: *No cases of prolonged QTc interval resulted in syncope or arrhythmia and no patient stopped delamanid due to QTc prolongation. Data devised from Gler et al.¹¹
Abbreviations: Del, delamanid, MDR-TB, multidrug-resistant tuberculosis; mITT, modified intention to treat; OBR, optimized background treatment regimen.

Table 2 Results of trial C208 for bedaquiline

Drug + dose	Number of patients in mITT group	6-month sputum conversion	P-value	Median time to culture conversion
Bedaquiline ^a + 5 drug regimen	66	78.80%	0.009	12 weeks
Placebo + 5 drug regimen	66	57.60%		18 weeks

Notes: ^aGiven at 400 mg daily for the first 2 weeks, followed by 200 mg three times per week for the remaining 22 weeks. Data devised from Diacon et al.¹⁶

Abbreviation: mITT, modified intention to treat.

For both delamanid and bedaquiline, there is little information on their use in HIV coinfecting patients, including those on antiretroviral treatment. An ongoing pediatric trial, with results expected in 2017, is evaluating pharmacokinetics, safety, tolerability, and antimycobacterial activity of delamanid in children, including some who are HIV infected and others with “probable” TB.¹⁸ A pediatric trial for bedaquiline is due to start in 2015.

Current guidance for clinical use

WHO has issued interim guidance for both bedaquiline in 2013¹⁹ and delamanid in 2014²⁰ and expanded on this guidance in the companion guidelines.²¹ These guidelines

specify five conditions that must be in place prior to the introduction of each drug (Table 4).

Interim policy guidance states that bedaquiline can be used when an effective treatment regimen containing four second-line drugs (in addition to pyrazinamide) including a FQ and a second-line injectable agent cannot be designed. This includes patients with known resistance, adverse drug reactions, poor tolerance, or contraindication to any component of the regimen.¹⁹

The interim policy guidance for delamanid is similar to that of bedaquiline, recommending its use when an effective treatment regimen cannot be designed due to resistance or intolerance to existing drugs. However, it goes further,

Table 3 Ongoing and planned clinical trials of new drugs in new regimens for treating MDR-TB^a

Study name	Study summary	Description	Status	Study investigator (organization)
STREAM I trial	Evaluation of a Standardized treatment regimen of anti-TB drugs for patients with MDR-TB	Comparison of standard WHO MDR-TB regimen with 9-month modified Bangladesh regimen	Open to recruitment	Andrew Nunn, Sarah Meredith (The Union)
STAND trial: PA-824/Mfx/Z (GATB NC-006)	Treatment shortening trial of PA-824/Mfx/Z for 4 or 6 months compared to HRZE for 6 months	Study of PA-824/Mfx/Z for DS-TB; one arm enrolling patients with MDR-TB whose isolates are susceptible to FQ and Z	Expected to begin enrolling Q2 2015	Dan Everitt (TB Alliance)
Bdq/PA-824/Z (GATB NC-005)	8-week SSCC study of Bdq + PA-824 + Z	Study of Bdq/PA-824/Z for DS-TB. One MDR-TB arm adds moxifloxacin to Bdq-PA-824-Z	Now enrolling	TB Alliance
Nix-TB	PA-824, Lzd, and Bdq; single arm for 6 or 9 months duration depending on rate of sputum culture conversion	Salvage regimen for patients with XDR-TB	Enrolling patients in South Africa	Dan Everitt (TB Alliance)
STREAM II trial	STREAM stage II: multicountry clinical trial evaluating the shortened MDR-TB regimen	Comparison of 6- vs 9-month Bdq-containing regimens to WHO and Bangladesh regimens	Expected to begin enrolling Q4 2015	Andrew Nunn and Sarah Meredith (The Union)
PRACTECAL	Novel short course, 6-month regimens without injectables; uses new and repurposed drugs	3 regimens with Bdq + PA-824 + Lzd	Protocol finalized Expected start Q3 2015	Dr Bern-Thomas Nyang'wa (MSF)
End TB	9 month: novel short course regimens without injectables; uses new and repurposed drugs	Novel, no injectables, regimens with 4–5 drugs including Bdq and/or Dlm	Protocol near finalized	Franics Varaine, Carole Mitnik (MSF/PIH/HMS)
NEXT Trial	Evaluating new treatment regimen for patients with MDR-TB – a randomized controlled Phase III trial	Open label RCT of a 6–9 month injection-free regimen with Bdq, Lzd, Lfx, ethionamide/high dose H, and Z	Waiting for MCC approval, expected enrollment at five sites in South Africa	Keertan Dheda, Akther Goolam-Mohamed

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Abbreviations: Bdq, bedaquiline; Dlm, delamanid; DS, drug sensitive; FQ, fluoroquinolone; H, isoniazid; HMS, Harvard Medical School; HRZE, isoniazid, rifampicin, pyrazinamide, ethambutol; Lfx, levofloxacin; Lzd, linezolid; Mfx, moxifloxacin; MDR-TB, multidrug-resistant tuberculosis; MMC, Medicines Control Council; MSF, Médecins Sans Frontières; PIH, Partners in Health; Q2, second quarter of; Q3, third quarter of; SSCC, serial sputum colony counting; TB, tuberculosis; WHO, World Health Organization; Z, pyrazinamide.

Table 4 Criteria for introduction of new TB drugs

Category	Specific criteria
Proper patient inclusion	Special caution required in people ≥ 65 years old; in adults living with HIV. Use in children and in pregnant or breast-feeding women not advised.
Effective treatment and monitoring	Treatment must be closely monitored for effectiveness and safety, using sound treatment and management protocols approved by relevant national authorities.
Treatment regimen must adhere to WHO recommendations	Use of new drugs must follow all principles underlying WHO-recommended MDR-TB treatment regimens, particularly inclusion of four effective second-line drugs plus pyrazinamide. New drugs should not be introduced singly into regimens that do not show effectiveness.
Informed consent	Patients must be fully aware of new drug's potential benefits and harms; must give informed consent before starting treatment.
Pharmacovigilance and management of adverse events	Active pharmacovigilance measures must be in place to ensure early detection and proper management of adverse drug reactions and potential drug–drug interactions.

Abbreviations: TB, tuberculosis; WHO, World Health Organization; MDR-TB, multidrug-resistant TB.

recommending delamanid use in patients with high risk of poor outcome (ie, extensive or advanced disease), meaning that delamanid is potentially suitable for a larger number of patients.²⁰

Caution is recommended when using these new drugs in people living with HIV or other comorbidities (ie, diabetes, renal, or liver dysfunction) and in people reporting alcohol or substance abuse, due to a lack of data. A single drug should not be added to a failing MDR-TB regimen, and this also applies to new drugs. Today, they cannot be combined with one another. With regard to concerns over potential impact on QTc, baseline testing and monitoring for QTc prolongation are recommended for both drugs. Bedaquiline and delamanid are classed as group 5 drugs in the WHO classification system.

Importance of accompanying drugs

A growing body of evidence indicates a potential role for some existing antibiotics in the treatment of complex drug-resistant patients also classed by WHO as group 5.^{21,22} The main drugs of interest are clofazimine, linezolid, and imipenem (Table 5).

Clofazimine is thought to have promise as an antimycobacterial due to its long half-life (65–70 days), slow metabolic elimination, high concentration in macrophages, and rapid localization within phagocytes.²³ Recent *in vitro* and *in vivo* trials in mice have shown low toxicity and good efficacy against drug-resistant TB (DR-TB) strains.²⁴ Several systematic review articles have highlighted the potential beneficial role of clofazimine in DR-TB regimens.^{8,23} Additionally, recent studies noted successful outcomes of shortened DR-TB treatment regimes containing clofazimine;^{25,26} these findings are being further investigated as part of the larger STREAM randomized control trial²⁷ (Table 3). However, a recent EBA study showed no efficacy at all at 14 days in humans.²⁸

Linezolid is thought to act by competitive inhibition of the enzyme that binds incoming transfer RNA to messenger RNA.²⁹ A systematic review found that treatment outcomes with linezolid-containing regimens for complicated cases of MDR-TB were equal to or better than those reported for uncomplicated MDR-TB,³⁰ and also better than those reported among patients treated for XDR-TB.³¹ A randomized controlled study in patients with XDR-TB not responding to treatment who had linezolid added into their regimen showed that 87% had a negative sputum culture within 6 months after linezolid had been added to their drug regimen.³²

Carbapenems (imipenem/cilastatin or meropenem) have an extremely wide spectrum of activity that includes Gram-positive, Gram-negative, aerobic, and anaerobic bacteria. Data on carbapenem use against drug-resistant forms of TB are slim, but the limited evidence available from mouse models suggests anti-TB activity; several case reports^{33,34} are consistent with this view. However, these drugs must be

Table 5 Characteristics of clofazimine, linezolid, and imipenem

Drug	Class	Route of administration	Main side effects	Indication for TB treatment
Clofazimine	Rimino-phenazine	Oral with loading schedule	Skin discoloration; GI effects; QT prolongation potential; long half-life	No
Linezolid	Oxazolidinone	Oral	Peripheral neuropathy; hematological effects, particularly thrombocytopenia	No
Imipenem/cilastatin	Carbapenem	Intravenous	Generally well tolerated. Reactions around injection site	No

Abbreviations: GI, gastrointestinal; TB, tuberculosis.

administered intravenously, which would limit their large-scale use against MDR-TB.

Experience with the new drugs in compassionate use programs

Despite an estimated 48,000 patients globally with XDR-TB and at least double that with pre-XDR-TB and MDR-TB that would fulfill the WHO criteria for new drugs, the unfortunate reality is that fewer than 1,000 patients have received bedaquiline outside of clinical trials;³⁵ the majority of whom accessed the drug through compassionate use or equivalent programs rather than through routine programmatic use. To our knowledge, delamanid – despite its much broader indication – has been used outside clinical trials by approximately 100 patients.

From both a patient and a public health perspective, access through compassionate use pathways has several restrictions and additional requirements compared with typical routine programmatic use. Compassionate use (also referred to as “clinical access” or “expanded access” programs) is intended as a way of providing lifesaving experimental treatments to patients suffering from a disease for which no satisfactory approved therapy is available, or who cannot enter a clinical trial. However, to take advantage of this access route, patients must reside in a country with appropriate legislation or authorization must be given allowing the compassionate use of new, unregistered therapies. Another restriction is that the drug developer makes final decisions on whether the drug will be supplied for compassionate use and under which conditions. No data collection is required except for the reporting of adverse events. Janssen first provided bedaquiline for compassionate use in 2011, and Otsuka provided delamanid in 2014.

The three countries with the most patients to benefit from the use of bedaquiline via compassionate use programs were France, South Africa, and Armenia. France, which has a well-developed mechanism for expanded-access use, began compassionate use of bedaquiline in 2011. An interim analysis of the first 35 patients in a French cohort was published in 2014.³⁶ South Africa first needed to establish the appropriate legislative framework for compassionate use of bedaquiline, but after approval of a clinical access program it quickly overtook France as the biggest user of bedaquiline. After South Africa and France, Armenia has the third largest compassionate use cohort, through a program supported by Médecins Sans Frontières (MSF).

Although all these programs have very different patient profiles and programmatic means, they all are starting to

share very similar early outcome results. Published data is available from the French cohort, and very recently from South Africa.³⁷ Data from Armenia has been presented at the 4th Annual TB symposium in Yerevan, hosted by the Ministry of Health of Armenia and MSF.³⁸ Table 6 summarizes the profiles of patients from these three cohorts.

All three programs have treated adult pulmonary XDR-TB or pre-XDR-TB patients, most of whom were resistant to FQ. The French cohort was able to include patients without FQ or injectable resistance (2/35 patients) in the published analysis; although the South African Clinical Access Program inclusion criteria included MDR-TB patients without additional resistance to second-line drugs but with intolerance to other group 1–4 drugs (such as ototoxicity or renal toxicity), it did not report any cases benefiting from this access.

The majority of treated patients in all cohorts were male. The most important difference among cohorts was the rate of HIV coinfection: very high (59.3%) in South Africa, compared with no HIV-positive patients in France and only 2 (4%) in Armenia. Accompanying drugs in the regimen also varied: linezolid was used extensively in Armenia (100%) and France (94%), and in 70% of patients in South Africa. Imipenem was not used in South Africa, and clofazamine is used much less in France (14%) than in Armenia (74%) or South Africa (74.7%).

While the end-of-treatment outcomes for MDR-TB patients are in general poor, close to 50% success, the treatment of the difficult-to-treat subgroup, XDR-TB patients,

Table 6 Description of three cohorts of patients started on bedaquiline-containing treatment regimens

Period reported	France ³⁶	South Africa ³⁷	Armenia ³⁸
	January 2010–July 2013	March 2013–July 2014	March 2013–January 2015
Number of patients	35 ^a	91	53
XDR-TB	54.3%	37.4%	45%
Pre-XDR-TB (FQ)	28.6%	45.1%	49%
Pre-XDR-TB (Inj)	11.4%	17.6%	6%
Median age (years)	39	35	42.5
Sex, male	80%	60.4%	87%
HIV positive	0	59.3%	4%
Lzd ^b	94.3%	70.3%	100%
Imp ^b	65.7%	0%	75%
Cfz ^b	14.3%	74.7%	74%

Notes: Pre-XDR-TB (FQ): MDR with additional resistance to fluoroquinolones, pre-XDR-TB (Inj): MDR with additional resistance to second-line injectable drugs; ^afrom March 2011 to June 2014, 53 patients started bedaquiline treatment but descriptive results have been published for 35 patients; ^bdata shown are percentage of patients whose regimen included the indicated drug.

Abbreviations: Cfz, clofazamine; FQ, fluoroquinolone; Imp, imipenem; Inj, injectable; Lzd, linezolid; MDR-TB, multidrug-resistant TB; TB, tuberculosis; XDR-TB, extensively drug-resistant TB.

Table 7 Summary of available culture conversion and safety data from three cohorts of patients given bedaquiline-containing regimens

	France ³⁶	South Africa ³⁷	Armenia ³⁸
Culture conversion at 6 months among patients culture positive at baseline	28/29 (97%)	33/43 (77%)	22/26 (84%)
Early mortality (<24 weeks bedaquiline) ^a	1/35 (3%)	1/63 (1.6%)	4/53 (7.5%)
Increase in QTcB/F (ms)	1.96 ^b	8 ^c	Not reported
QTcB/F increase	7/35 (20%) >60 ms	24/91 (26.3%) >50 ms	Not reported
QTcB/F >500 ms	3/35 (9%)	3/91 (3.2%)	Not reported
Discontinuation of bedaquiline	2/35 ^d (6%)	1/91 ^e (1%)	Not reported
Patients with serious adverse events reported (unrelated to bedaquiline)	1/35 (3%)	9/91 (9.9%)	4/53 (8%)

Notes: Data shown as n/N (%). ^aOne death in France due to malignancy, three deaths in total in South Africa reported as unrelated to Bedaquiline, four deaths in Armenia also reported as unrelated to bedaquiline (J Faqirzai, Médecins Sans Frontières, Armenia, personal communication, June, 2015); ^bincrease in median QTcB; ^cincrease in median QTcF; ^drelated to increase in QTcB; ^eatrial fibrillation, unclear if related to bedaquiline.

is even worse in general. Although a retrospective study of XDR-TB patient treatment outcomes from Tomsk showed 14/29 (48.3%) patients had a successful end of treatment outcome,³⁹ most other analyses reported much lower success rates. For example, only 12/107 (11%) XDR-TB patients from South Africa had a favorable outcome at 60 months,⁴⁰ while WHO has reported 22% favorable end of treatment outcomes among 1,269 XDR-TB patients from 40 countries.¹ Although there are no published results on the subgroup of pre-XDR-TB (FQ) patients, given that resistance to FQ is associated with failure and lack of culture conversion, the outcomes are likely to be closer to XDR-TB patients than MDR-TB patients without FQ resistance.^{41,42}

One of the challenges to developing better treatment for MDR-TB is the long treatment duration and therefore the long time needed to analyze end of treatment outcomes. Clinicians use the conversion of culture from positive to negative to guide their clinical management of patients. In MDR-TB patients, it has been reported that no culture conversion by the third month of treatment is an independent predictor of death and failure⁴¹ and that treatment outcomes were worse in patients who did not convert by 2 months.⁴³ In the subgroup of XDR-TB patients, Pietersen et al⁴⁰ found net culture conversion was associated with survival, whereas O'Donnell et al⁴⁴ found culture conversion by 2 months associated with survival, although time to conversion was not a good predictor of favorable outcomes. Therefore, while acknowledging the weakness of this indicator, culture conversion at 6 months has been used as an early proxy for the assessment of treatment outcomes.

Previous published data on cohorts of treated XDR-TB patients have shown low culture conversion rates at 6 months. O'Donnell et al⁴⁴ found 36.8% of their cohort of 114 XDR-TB patients culture converted and Pietersen et al⁴⁰ found only 9.3% (10/107) of 107 patients had culture converted by

6 months. In contrast, the 6-month culture conversion rates for the new bedaquiline compassionate use cohorts (Table 7) show a vast improvement over these earlier results using other treatment regimens: 77% (33/43) for patients treated in South Africa, 84% (22/26) in Armenia, and 97% (28/29) in France. Although the patients in all three of these cohorts were not all XDR-TB patients, they are almost all FQ-resistant MDR-TB patients for whom we could anticipate similar outcomes.⁴⁵

Early mortality in the 24 weeks of bedaquiline treatment was low in general, and all deaths were evaluated as being unrelated to bedaquiline.

None of the projects has identified significant adverse events, although in all cases patients were managed with enhanced monitoring. As expected, an increase, although small in QTcB/F was reported by the French and South African cohorts, but without adverse outcomes for the patients. Elevated liver enzymes were reported in 14% of patients in France, which is similar to the findings from the clinical trials.^{16,36} No reported adverse events linked to hepatotoxicity were reported the South African cohort which is very reassuring considering the majority of patients were also taking anti-retro viral drugs in particular nevirapine, a known hepatotoxic drug. Armenia did not report on hepatotoxicity although their analyses may not be complete.

The South African cohort analysis has significantly contributed to reducing the lack of data on the use of bedaquiline in HIV infected persons, and in combination with antiretroviral drugs. The excellent results, both in terms of safety and effectiveness, are reassuring for both clinicians and patients.³⁷ These results must be interpreted with caution because they are only interim findings and because culture conversion is only a first indication of treatment response; clinical outcomes can only be known when patients have completed their treatment course and been followed up for at least a year post-treatment in order to detect relapses.

Because of the very recent introduction of bedaquiline into routine programmatic use, there are no routine results to report so far. Similarly, for delamanid there are no published or presented data on delamanid use outside clinical trials, although the manufacturing company reports that approximately 100 patients around the world have benefited from this drug. MSF began a compassionate use program using delamanid with the first patients starting treatment in February 2015.

However, as stated earlier, compassionate use programs provide a useful interim step to providing access and experience in using new drugs, but the conditions attached to these programs limit the number of patients who can be included. For the tens of thousands of patients who urgently need these new drugs, and for the drugs' full public health benefit to be realized, it is essential that they become incorporated into routine programmatic use. The reasons why this may not be happening are discussed later in the article.

Maximizing the benefit of the new drugs

Another key step in realizing the promise of these new drugs is to incorporate them into better combination regimens, since no single drug can cure TB. New regimens for drug-resistant forms of TB must be shorter, more effective, and safer (fewer adverse events).⁴⁶

Several planned clinical trials will investigate new TB regimens that incorporate new drugs, including delamanid and bedaquiline (Table 3). These trials are crucial for establishing the best ways to use these new drugs and maximize their potential. However, results are likely to be at least 5 years away, and the use of the new drugs should not be delayed until these data are available. In the meantime, countries can and should add these new drugs to the arsenal available in their programs as per WHO guidance.

Duration

Clinical trials data for bedaquiline and delamanid are currently available for only 24 weeks of use. For this reason, WHO and stringent regulatory authorities have recommended limiting treatment with both drugs to a 24-week maximum,^{19,21} a strategy that potentially compromises their effectiveness in certain patients. Considering the very positive early responses of XDR-TB and pre-XDR-TB patients treated with bedaquiline in compassionate use programs, is it appropriate to stop an effective drug, potentially weakening the treatment regimen? The other effective drugs in these therapeutic regimens also

have major drawbacks: linezolid is associated with serious side effects, especially hematological and neurological toxicity,^{30,47,48} while imipenem is difficult to administer – it must be given intravenously twice daily through central catheters. Given these serious limitations for the drugs now in use, bedaquiline may be essential for maintaining an effective regimen over the duration of treatment.

While guidelines for WHO do not allow extension of bedaquiline beyond 24 weeks, the French compassionate use program allows clinicians extensions on a case-by-case basis. This exception has been made for patients with fewer than three effective drugs in the regimen, resulting in a current median treatment time of 36 weeks as of February 2015 and increasing as bedaquiline is continued in these patients.⁴⁹ The US Centers for Disease Control⁵⁰ and European Medical Agency⁵¹ have also left open the possibility of case-by-case extension of bedaquiline beyond 24 weeks. Despite these agencies allowing flexibility in treatment duration, WHO guidance preserves the 24-week limitation in both the interim policy guidance and the more recent implementation plan for bedaquiline.^{19,21,52} Although at the time of the initial expert recommendations in 2013 this conservatism was understandable, it may be unnecessarily restrictive in 2015 considering both the accumulated experience with these drugs since then (and specifically with extended use of bedaquiline) and the positive initial outcomes data. While it is obviously preferable to have a strong evidence base for recommending extension of treatment, the risks and benefits must be appropriately evaluated, along with the availability of alternatives on a case-by-case basis. Furthermore, many other drugs used today for treating MDR-TB also lack a strong evidence base: for example, the effectiveness of the group 5 drugs linezolid, imipenem, and clofazamine against MDR-TB has never been tested in a clinical trial, nor has clinical experience on their extended use been published.²¹ In our view, these factors, along with the very poor outcomes of current treatment for XDR-TB, shift the risk–benefit in favor of extending bedaquiline and delamanid use beyond 24 weeks in patients who have limited alternatives, a good response to treatment, and no adverse effects.

Continuation of both bedaquiline and delamanid treatment for selected patients is a crucial next step in the learning curve on these drugs. For support in these efforts, providers in most countries can access expert advice on patients, either through the ERS/WHO TB Consilium forum⁵³ or from other such committees. With access to technical support from such groups, countries should have the flexibility to extend treatment durations, as appropriate,

to ensure that MDR-TB patients can remain on the strongest regimen.

Drug combinations

Since successful TB treatment depends on successful regimens, and not individual drugs, the most important new drug combination with the greatest potential to really make inroads into improving DR-TB treatment of drug-resistant forms of TB would be the combination of delamanid and bedaquiline, two completely new classes of drugs. In patients with limited treatment options, such as XDR-TB patients, the use of these drugs together could be an option. However, due to the potential overlap in the two drugs' toxicities, particularly QTc prolongation, and the lack of any studies investigating this combination, at this point it is not recommended to combine these two drugs.²¹ A drug–drug interaction study that has been planned by NIH has yet to commence, but until the results are available and the concerns about the prolonged QT interval caused by both drugs have been resolved, it is unlikely that the guidance will be changed. However, could certain exceptions be considered, where the benefits of combining these two drugs outweigh the possible risks? Another option is to use the two drugs sequentially, and WHO gives guidance on this.²¹ Considering the long half-life of bedaquiline, patients could be started on delamanid for 24 weeks and then switched to bedaquiline for an additional 24 weeks, giving just over a year of benefit from the new drugs. The long half-life of bedaquiline makes reverse sequence (bedaquiline followed by delamanid) a more risky combination.

Concerns about QT interval prolongation also apply to the combination of the FQ moxifloxacin with bedaquiline or delamanid. Moxifloxacin has the greatest impact on QT among the FQ;⁵⁴ WHO recommends that the use of the combination of moxifloxacin with bedaquiline and clofazimine (three drugs that strongly prolong the QT interval) should be avoided. In the French cohort of XDR-TB and pre-XDR-TB (FQ) patients, bedaquiline was combined with either moxifloxacin at standard (400 mg/day) or high dose (800 mg/day) or with levofloxacin. Their analysis found that the presence of a FQ in the treatment regimen was the only independent factor associated with a faster time to culture conversion. No cardiac arrhythmias were recorded, and three patients (9%) had a QTcB greater than 500 ms, and two patients had bedaquiline discontinued (6%) due to persistent QTcB prolongation, one who received concomitant moxifloxacin and 1 who received clofazimine and amiodarone.³⁶ In South Africa and Armenia, moxifloxacin was not used in combination with bedaquiline. As the higher generation FQ (Lfx,

Mfx) may have residual effectiveness in a small percentage of patients resistant to ofloxacin, it is essential to be able to identify these patients in whom the possible benefits of the combination of moxifloxacin with new drugs could outweigh the risks. Identifying these patients would require changes to diagnostic capacity in many countries where the only DST available for FQ is DST to ofloxacin.

Who should get what drug?

How to choose between bedaquiline and delamanid for an individual patient? WHO has given some practical advice in the most recent updated guidelines.²¹ Currently, there is more experience of using bedaquiline in XDR-TB and pre-XDR-TB (FQ) patients due to the early availability through compassionate use or equivalent programs. However, the safety profile of delamanid is better, and the data from the trials show lower mortality in patients who received delamanid.¹² This would make delamanid the drug of choice for MDR-TB patients with adverse events requiring the substitution of a drug in the treatment regimen or those with high risk of a poor outcome. Other factors apart from resistance profile should be taken into account, in particular comorbidities; delamanid has less interactions with antiretrovirals and other drugs metabolized by the cytochrome P450 enzymes like CYP3A4 and less hepatic effects, which is important in coinfecting hepatitis B and C patients.^{5,55,56}

Of concern, there is recent evidence of a possible cross-resistance between clofazimine and bedaquiline.^{57,58} With the lack of accessible DST for bedaquiline and clofazimine, delamanid may be preferred in patients with previous use of clofazimine. Further studies are required to know if the presence of the mutation Rv0678 is clinically important in predicting resistance to bedaquiline and clofazimine, only then will the significance of this finding be known.

Barriers to accessing new and repurposed drugs

Any discussion regarding how best to use these new drugs must also consider their availability in countries with a high burden of MDR-TB patients, which cannot be taken for granted. Access to new and repurposed TB drugs for programmatic use requires that several processes are in place, and several existing barriers removed.

For the drugs without an indication for TB (clofazimine, linezolid, and imipenem/cilastatin), this may present problems with importing the drug into a country as well as issues arising around using a drug as it becomes off label use. (Of note this also applies to FQ and second-line injectable

agents). The main barrier to the scaling up and use of imipenem/cilastatin is its formulation. It is only available as a twice-daily injectable agent, which creates many programmatic barriers to its widespread use.

Importation can be possible immediately in the short term through importation waivers while registration processes are under way, although registration is desirable in the long term. Janssen has submitted a number of dossiers for the registration of bedaquiline, with rapid approval processes leading to successful registrations in Russia and South Africa, two key high-burden countries. Otsuka has not currently submitted registration dossiers for delamanid in any countries outside the European Union.

The price of the drugs needs to be considered as affordability is a crucial aspect of access for patients. Price for a drug cannot be viewed in isolation but must be considered in addition to a background regimen that already has a price range of USD1,500–USD7,000.⁵⁹ For bedaquiline, Janssen has implemented a tiered pricing strategy in which low-income countries pay USD900 for a 6-month course, middle-income countries pay USD3,000, and high-income countries USD30,000.⁶⁰

However, up to now the scale-up of routine programmatic use of bedaquiline (where this pricing mechanism would come into play) has been very slow; to date, the majority of patients who received bedaquiline have done so through compassionate use programs, where the drug is usually free to patients. It is unclear why scale-up in routine programs has been so slow. The tiered pricing structure will eventually require middle-income countries with high MDR-TB and XDR-TB burdens to make a considerable financial commitment to provide access to bedaquiline to all those who would benefit from it.

For delamanid there is no global price structure available, and it is not marketed or available in any low- or middle-income countries. Where it is marketed in Europe, it has a similar price to that of the high-income countries price of bedaquiline. For linezolid, there are increasing numbers of quality-assured suppliers and this is having a positive impact on the price of the product, which had until recently been priced out of reach of widespread use.

The looming price barrier for bedaquiline and delamanid has been temporarily removed in some settings with the announcements of various donation programs. Janssen has established a program with USAID⁶¹ to make 30,000 courses of bedaquiline available to global fund Global Fund-eligible countries over the next 4 years. Otsuka has announced a targeted access donation program for delamanid. The details of this donation program are yet to be announced but are focused on the 27 high-burden countries.⁶²

Such donation programs can potentially enable short-term scale-up of new drugs. However, they are not a sustainable method of ensuring access to drugs, since they are usually limited in duration and geographical scope (as in this case) – leaving patients who are ineligible for the program with few or no options for gaining affordable access. In the case of delamanid, there is no information on how countries that are not eligible for the donation program will be able to procure the drug. Nevertheless, if the donation process is straightforward and has a wide scope, then even short-term removal of the price barrier creates an opening to address additional barriers to widespread, sustainable programmatic implementation.

Another challenge for scaling up programmatic use of bedaquiline and delamanid is the issue of pharmacovigilance (PV). Since these drugs are completely new and were approved with only limited clinical trial data, it is important to collect additional safety data. This can be accomplished in a number of ways. WHO guidance²¹ on the new drugs states that “Active pharmacovigilance measures must be in place to ensure early detection and proper management of adverse drug reactions and potential interactions with other drugs”. Many countries with high MDR-TB burdens have spontaneous PV models in place and do not have extensive experience of running cohort event monitoring, which is the most robust forms of PV. Although it is critical to have a system for detecting unexpected adverse events, it is also important to recognize that all countries cannot be expected to have a functioning comprehensive cohort event monitoring system before the new drugs are introduced. The WHO companion guidelines have template CEM forms that would allow clinicians using the new drugs to report any adverse events, while the national program is setting up a central PV system, which is a longer-term process.

Barriers, including PV and regulatory strengthening, will also require technical support and adequate funding beyond the cost of the drugs, in order to be addressed. It is therefore important that global fund monies, along with national and donor funding, are used to strengthen all aspects of the programmatic management of DR-TB programs including the supply of quality companion drugs for the new drugs.

Finally, the countries need to have the necessary political will and support to ensure that these drugs are made available to all those who need them with minimal delay.

Conclusion

For clinicians and patients alike, the development of bedaquiline and delamanid after so many decades without new

TB drugs is an historic opportunity to gain ground in the fight against TB. The promise of these new medicines applies not only to patients with the most urgent, immediate needs – those with additional drug resistance, with side effects from existing drugs, or with expected poor outcomes – but also to all DR-TB patients, for whom these drugs offer the possibility of shorter, safer, and better treatment. There is work to be done by many: national programs to introduce the new drugs under reasonable conditions; governments, researchers, and manufacturers to support clinical trials of new regimens; and technical assistance from WHO and other actors.

At this point in time, there are clear recommendations from WHO on when, how, and for whom to use these new drugs, as well as both practical clinical experience from programs that have already introduced them and technical support for implementation. Yet despite all these, few patients have actually received these new drugs. This must change. New drugs should not be kept as a last resort; on the contrary, they should be introduced as soon as possible, to improve treatment outcomes and patient adherence to long and toxic regimens. Countries that have not yet introduced these drugs may be proceeding with caution, intimidated by the need for PV reporting or by their lack of experience with the new drugs. However, these factors should be weighed against the poor outcomes and toxicity of today's treatment regimens.

The current clinical experience with bedaquiline in combination with other group 5 drugs offers real hope to MDR-TB patients. Wide-scale introduction of the new and group 5 drugs has the potential to radically improve the outcomes of MDR-TB patients. Let us not miss this historic opportunity.

Acknowledgment

The authors thank Patricia Kahn for critical editorial input.

Disclosure

The authors report no conflicts of interest in this work.

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