New drug therapies for the management of drug-resistant tuberculosis

Tuberculosis is one of the leading causes of mortality globally. In 2015, there were an estimated 10.4 million incident cases and it was responsible for more deaths worldwide than HIV (World Health Organization, 2016a). Despite this, significant gains have been made in global tuberculosis control; the tuberculosis mortality rate fell by 47% between 1990 and 2015. In September 2015, the World Health Organization announced that Millennium Development Goal 6c – to halt and reverse tuberculosis incidence – was successfully achieved in each of the World Health Organization's six regions.

A concerning development has been the emergence of drug-resistant tuberculosis, which threatens to undermine the gains made in the global strategy to control tuberculosis. Multidrug-resistant tuberculosis is caused by organisms that are resistant to the two most effective first-line drugs: rifampicin and isoniazid. Extensively drug-resistant tuberculosis, first described in 2006, harbours additional resistance to fluoroquinolones and at least one of the three injectable second-line agents: amikacin, capreomycin or kanamycin.

In 2015, there were an estimated 10.4 million incident cases of tuberculosis globally (range 8.7–12.2 million); of these 580 000 (range 520 000–640 000) were estimated to be rifampicin-resistant or multidrug-resistant tuberculosis. An estimated 3.9% of new cases and 21% of previously treated cases are thought to be either rifampicin-resistant or multidrug-resistant. Extensively drug-resistant tuberculosis had been reported in 117 World Health Organization member states by the end of 2015, and 9.5% of multidrug-resistant tuberculosis cases fulfilled the criteria for extensively drug-resistant tuberculosis in 2015 (World Health Organization, 2016a).

Globally, treatment outcomes for drug-resistant tuberculosis are significantly worse than drug-sensitive tuberculosis. Worldwide an estimated 83% of drug-sensitive tuberculosis cases achieve cure; this falls to 52% for rifampicin-resistant or multidrug-resistant tuberculosis cases and 28% for extensively drug-resistant tuberculosis cases. Of the 48% of patients that failed to achieve cure in the 2013 cohort, 17% died, 15% were lost to follow-up, 9% experienced treatment failure and 7% had no recorded outcome (World Health Organization, 2016a).

Several challenges exist which hamper successful multidrug-resistant tuberculosis management. The detection of drug resistance requires access to good quality diagnostic facilities. Drug susceptibility testing methods include phenotypic (conventional) and genotypic (molecular) methods. The most widely available method of drug susceptibility testing is Xpert MTB/RIF (Cepheid Inc), a polymerase chain reaction test which detects rifampicin resistance.

Detecting resistance to antibiotics besides rifampicin using conventional drug susceptibility testing can be difficult and lengthy. It requires extended incubation periods, can be expensive and uses specialized equipment and personnel (Parsons et al, 2011). The World Health Organization has updated its guidance to recommend the use of line probe assays (a method of polymerase chain reaction and reverse hybdridization) to detect second-line agent resistance in a more timely fashion, although this technique does not eliminate the need for phenotypic drug susceptibility testing (World Health Organization, 2016b).

The duration of treatment, which may be administered for up to almost 2 years, can result in high health-care costs, economic loss for the patient who may be unable to work and a greater risk of drug toxicity. In particular, aminoglycosides can cause serious side effects related to nephrotoxicity and ototoxicity. Additionally, the second-line agents required to treat multidrug-resistant tuberculosis can be costly and difficult to source. Therefore there has been much interest in the use of novel anti-tuberculous agents. As part of efforts to improve outcomes from multidrug-resistant or extensively drug-resistant tuberculosis, at least 70 countries had started using bedaquiline and 39 countries had used delamanid by 2015 (World Health Organization, 2016a).

Treatment regimens

World Health Organization (2016c) guidelines recommend a total of 20 months' duration of treatment for patients with multidrug-resistant tuberculosis. The initial 'intensive phase', which lasts a minimum of 8 months, should include five drugs. Thereafter, four drugs can be used during the 'continuation phase', until a total of 20 months of treatment has been reached. However, in patients with pulmonary rifampicin-resistant-tuberculosis or multidrug-resistant tuberculosis previously untreated with second-line agents and confirmed (via conventional drug susceptibility testing) or very likely (via molecular methods) to be susceptible to fluoroquinolones and aminoglycosides, then a shorter treatment duration of 9–12 months may be considered (although the World Health Organization notes that the evidence to support this is not robust) (World Health Organization, 2016c).

World Health Organization (2016c) guidelines divide their multidrug-resistant tuberculosis treatments into four groups

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(A–D) (*Table 1*). They advise the intensive period should use pyrazinamide, plus one medication from each of groups A and B, and two from group C, to make a total of five medicines. If pyrazinamide or any medications from groups A–C cannot be used, then those from group D2 or D3 should be used until the total of medications is five. The regimen should also be further strengthened by using add-on medicines ethambutol and/or high-dose isoniazid (D1 medicines) if they are considered to add benefit (e.g. high-dose isoniazid can be added to patients with low-level isoniazid resistance).

Table 1. Medicines recommended for the treatment of multidrug-resistant tuberculosis

Group A	Fluoroquinolones (in order of decreasing preference)	Levofloxacin
		Moxifloxacin
		Gatifloxacin
Group B	Second line injectable agents	Amikacin
		Capreomycin
		Kanamycin
		Streptomycin
Group C	Other core second line agents (in order of decreasing preference)	Ethionamide or prothionamide
		Cycloserine or terizidone
		Linezolid
		Clofazimine
Group D	Add on agents	D1: pyrazinamide, ethambutol, high dose isoniazid
		D2: Bedaquiline, delamanid
		D3: p-aminosalicylic acid, meropenem-clavulanate, imipenem-cilastatin, amoxicillin-clavulanate, thioacetazone

From World Health Organization (2016c)

Novel agents

Bedaquiline is a novel oral agent used in the treatment of tuberculosis. It is a member of the antibiotic class known as diarylquinolines. These drugs target a subunit of mycobacterial ATP synthase, interfering with mycobacterial ATP production and resulting in cell death. Human ATP synthase is 20 000-fold less sensitive to diarylquinolines than mycobacterial ATP synthase, thereby allowing these drugs to be used in humans (Haagsma et al, 2009).

In a phase II trial (TMC207-C208), patients with pulmonary multidrug-resistant tuberculosis were treated with a regimen containing bedaquiline or a placebo for 24 weeks. Those on the bedaquiline arm demonstrated higher rates of sputum culture conversion at 24 weeks (79% *vs* 58%) and cure at 120 weeks (58% *vs* 32%) (Diacon et al, 2014). The results are very promising and many other studies are using bedaquiline as a trial agent in the treatment of multidrug-resistant tuberculosis. One of these is the STREAM trial, which is using bedaquiline in two of their treatment regimens to see whether treatment duration can be reduced to 6 or 9 months (Moodley et al, 2016).

Bedaquiline is mostly well tolerated, but some concerns over safety have been raised. It can prolong the QT interval on electrocardiography. In the TMC207 trial, there were more deaths in patients randomized to bedaquiline than those who received placebo (10 *vs* 2 patients). This outcome is not thought to be related to bedaquiline but is still awaiting further explanation (Diacon et al, 2014).

Another new oral drug being used in tuberculosis treatment is delamanid, a nitroimidazole. Its action lies in its ability to inhibit synthesis of mycolic acid, a vital component of mycobacterial cell walls. Similarly to bedaquiline, delamanid has shown improved sputum culture conversion compared to placebo. A randomized controlled trial, those taking delamanid in their treatment regimen had 45.4% sputum culture conversion compared to 29.6% taking placebo (Gler et al, 2012).

Multiple studies are currently underway to assess the efficacy of delamanid. One of these, the endTB trial, which is due to report in 2019, is using delamanid and bedaquiline in new all-oral treatment regimens for multidrug-resistant tuberculosis (Sloan and Lewis, 2016).

Like bedaquiline, delamanid can also prolong the QT interval. Delamanid's DM-6705 metabolite confers this prolongation effect, and its generation is mediated by serum albumin. Therefore, delamanid should not be used in patients with hypoalbuminaemia (Sloan and Lewis, 2016).

Both drugs are costly. Bedaquiline costs £18 700 for a 24-week course. Clearly this price is too expensive for regular use in many less economically developed countries (where the burden of multidrug-resistant tuberculosis is highest). Delamanid is similarly priced to bedaquiline, but the Stop TB partnership and delamanid's manufacturer Otsuka have developed an initiative whereby delamanid will be supplied for $1700 per 6-month course, where multidrug-resistant tuberculosis treatment can be accessed via the Global Drug Facility (Stop TB Partnership, 2016).

For both bedaquiline and delamanid, there is a lack of data on their use in many different cohorts, e.g. HIV co-infected, pregnant women. There is also a lack of data on their concomitant use and until these data are available, the World Health Organization's current position is to recommend against co-prescription. Bedaquiline has an extremely long half life (5.5 months) and so it is recommended that those requiring delamanid after bedaquiline need to wait for a 6-month washout period (delamanid's half-life is only 38 hours, and so conversely only a 5-day washout period is required) (Gualano et al, 2016; Sloan and Lewis, 2016).

KEY POINTS

- The emergence of drug-resistant tuberculosis threatens to undermine gains made in global control.
- Drug-resistant tuberculosis treatment courses are lengthy, medications are toxic and outcomes much worse than for drug-sensitive tuberculosis.
- Novel oral agents bedaquiline and delamanid, and the repurposing of known antibiotics, provides new hope in the global battle against drug-resistant tuberculosis.

In summary, bedaquiline and delamanid are two novel oral agents which have thus far shown great promise in the treatment of multidrug-resistant tuberculosis. More data are required on their safety profiles and use in certain patient groups, and there are still issues around how these medicines will be distributed to areas most in need of their effect.

Repurposed drugs

Linezolid, an oxazolidinone, is an oral antibiotic used mostly to treat Gram-positive bacterial infection, especially in cases of antibiotic resistance (e.g. in vancomycin-resistant enterococcus). It works by binding to bacterial ribosomes and interfering with protein synthesis. There is evidence supporting linezolid's anti-tuberculous effect; for example, a study looking at the treatment of 65 extensively drug-resistant tuberculosis patients in China showed those who had linezolid added in to their treatment regimen were more likely to attain sputum culture conversion by 24 months than those who did not (78.8% *vs* 37.6%) (Tang et al, 2015). However, one problem with linezolid use is its high side-effect profile, the most detrimental being bone marrow toxicity and peripheral neuropathy. In the aforementioned study, 81.8% of patients developed clinically significant adverse drug effects attributed to linezolid. This was dealt with by temporary cessation of the drug or dose reduction, and subsequently most side effects resolved (Tang et al, 2015). A lower dose of linezolid may be appropriate for the treatment of tuberculosis (Koh et al, 2012), although more large-scale data to support this are lacking.

The phenazine dye clofazimine, primarily used as an anti-leprotic agent, has demonstrated some activity against tuberculous infection. A systematic review of its use in patients with multidrug-resistant tuberculosis found that it may improve long-term outcomes, but there are also data suggesting that it has limited bactericidal effect (Gopal et al, 2013).

> “Novel oral agents and the repurposing of known antibiotics provide new hope in the global battle against drug-resistant tuberculosis.”

Carbapenems have also been used, but there are only limited data to support their efficacy. For example, in a case-controlled series of 37 patients, 83.8% achieved sputum culture conversion, compared to 62.5% of controls when meropenem-clavulanate was added to their treatment regimens (which already contained linezolid). A 2016 systematic review analysed seven studies using carbapenem-based treatments (either meropenem, ertapenem or imipenem) and reported sputum culture conversions between 60% and 94.8%, with good safety and tolerability (Sotgiu et al, 2016). These preliminary data are promising, but more robust studies are required to further demonstrate their efficacy (De Lorenzo et al, 2013).

Conclusions

Drug-resistant tuberculosis is an infectious disease of major public health concern, associated with significant morbidity and poor treatment outcomes. Challenges to treatments include long treatment courses, the need to administer drugs intravenously and troublesome side-effect profiles. Novel oral agents and the repurposing of known antibiotics provide new hope in the global battle against drug-resistant tuberculosis. **BJHM**

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