Newer Anti-TB Drugs and Drug Delivery Systems

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Chapter 86

INTRODUCTION

Tuberculosis (TB) has been a leading cause of death since time immemorial and it continues to cause immense human misery even today. As per the currently available Global Tuberculosis Control Report 2012 of the World Health Organization (WHO) in the year 2011, there were 8.7 million incident cases of TB and 1.4 million deaths. Effective predictable treatment of TB became available only in the mid-1940s with the introduction of streptomycin. In the late 1970s, TB appeared to be fading away from being a major public health problem at least in the developed countries. The human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) pandemic in the early 1980s resulted in a global resurgence of TB. The recent years have also witnessed the emergence and global presence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) that are highly lethal, extremely expensive and complicated to treat and have been causing concern worldwide.

A major paradigm shift in the treatment of TB occurred with the introduction of rifampicin, the last landmark drug introduced for TB treatment. Based on the data from studies conducted in the 1970s, the standard treatment duration of anti-TB treatment could be shortened to 9 months. Rediscovery of pyrazinamide and combining it in a reduced dosage to rifampicin-containing regimens facilitated the emergence of currently used short-course treatment regimens. The currently used anti-TB drugs have been listed in Table 1.

In spite of being a global public health problem, TB has remained a neglected disease. Since the introduction of rifampicin, anti-TB drug discovery has been sluggish. Since then, no new drug has become available that can be compared to rifampicin in terms of utility and safety. In the era of M/XDR-TB, there is an urgent need for new anti-TB drugs that are more effective and have less toxicity. There is also a need for newer and innovative anti-TB drug delivery systems. In this review, we have attempted to summarize evidence regarding the efficacy and potential of repurposed existing anti-TB drugs and emerging new anti-TB drug molecules in the treatment of active TB disease.

ANTITUBERCULOSIS DRUG PIPELINE

The current concepts and processes of drug discovery and development are shown in Flow chart 1. Several approaches, such as genome-derived, target-based approaches, phenotypic screens at a whole bacterial cell level, multi-target "pathway" screens and redesign/engineering existing scaffolds have been utilized for newer anti-TB drug discovery. Presently, several newer or repurposed drugs are in pipeline in various stages of development as anti-TB drugs (Table 2). Some of the potentially useful anti-TB drugs beyond preclinical development have been discussed in this chapter.

Repurposed Existing Antituberculosis Drugs

Fluoroquinolones

Fluoroquinolones are deoxyribonucleic acid (DNA) gyrase inhibitors. As these drugs are also active against non-replicating, persistent mycobacteria, they are considered to be potentially useful and believed to be important for shortening the duration of TB drug
Among the newer fluoroquinolones, there have been several phase IIb trials assessing the utility of substituting moxifloxacin (400 mg once-a-day) in place of any of the first-line drugs with varying results. In a study,\textsuperscript{13} addition of moxifloxacin to isoniazid, rifampicin and pyrazinamide did not affect the 2-month sputum culture conversion. In another study,\textsuperscript{14} a small but nonsignificant increase in the week 8 culture negativity was documented. In other studies,\textsuperscript{15,16} a shorter time to culture conversion has been reported. In a randomized, open-label trial conducted in newly diagnosed sputum smear-positive pulmonary TB patients with moxifloxacin, gatifloxacin or high-dose levofloxacin compared with isoniazid for 7 days has shown good early bactericidal activity (EBA) that was almost comparable to that of isoniazid.\textsuperscript{17} Several studies are also underway to ascertain the utility of substituting gatifloxacin or moxifloxacin for ethambutol or isoniazid in shortening the duration of treatment from the standard 6 months to 4 months. The outcomes of the ongoing controlled clinical trial comparing the potential of two moxifloxacin-containing regimens to shorten treatment in pulmonary TB (REMOX TB) is likely to further clarify the status of moxifloxacin in the treatment of TB.

**Rifamycins**

The newer rifamycins—rifalazil, rifabutin and rifapentine have the same mechanism of action and a significantly improved minimum inhibitory concentration (MIC) as rifampicin.\textsuperscript{8} Rifalazil has been abandoned due to severe toxicity. Rifabutin has been used as a rifampicin substitute when there is a significant risk of drug-drug interactions. Rifapentine appeared promising drug for shortening the duration of treatment for smear-positive, drug-susceptible pulmonary TB. However, published data suggest that rifapentine has not performed better than rifampicin in the 2-month culture conversion rate raising concerns.\textsuperscript{5-9} In a phase III treatment-shortening trial in progress twice-weekly rifapentine with moxifloxacin during the continuation phase is being evaluated. Replacement of rifampicin with high-dose rifapentine in the standard first-line regimen is also being evaluated in phase IIb studies.\textsuperscript{4}

The currently used rifampicin daily dose of 600 mg is considered not to be on the optimal part of the dose-response curve and some workers have suggested that higher doses may be needed to achieve treatment-shortening goals in patients with drug-sensitive TB.\textsuperscript{18} Several studies are assessing the efficacy of high-dose rifampicin. These include the Rifaquin study (http://rifaquin.wordpress.

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**TABLE 2**  Newer and repurposed antituberculosis drugs in pipelines\textsuperscript{12}

<table>
<thead>
<tr>
<th>Drugs in preclinical development</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>Nitroimidazole</td>
<td>AZD58847</td>
<td>Nitroimidazole oxazine</td>
<td>Fluoroquinolones</td>
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<tr>
<td>TBA-354</td>
<td></td>
<td>PA-824</td>
<td>Gatifloxacin</td>
</tr>
<tr>
<td>Caprazene nucleoside</td>
<td></td>
<td>Oxazolidinone</td>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>CPZEN-45</td>
<td></td>
<td>Sutezolid (PNJ-100480)</td>
<td>Nitro-dihydro-imidazo-oxazole</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td></td>
<td>Linezolid</td>
<td>Delamanid (OPC67683)</td>
</tr>
<tr>
<td>Quinolone DC-159a</td>
<td></td>
<td>Diarylquinoline</td>
<td></td>
</tr>
<tr>
<td>Dipiperidine</td>
<td></td>
<td>Bedaquiline (TMC207)</td>
<td>4-Thioureaideo-iminomethylpyridinium</td>
</tr>
<tr>
<td>SQ609</td>
<td></td>
<td>Ethylenediamine</td>
<td>Perchlorate</td>
</tr>
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<td>Capuramycin</td>
<td></td>
<td>SQ109</td>
<td>Perchlorzone</td>
</tr>
<tr>
<td>SQ641</td>
<td></td>
<td>Rifamycin</td>
<td></td>
</tr>
<tr>
<td>Benzothiazinone</td>
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<td>Rifapentine</td>
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<td>Q201</td>
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<tr>
<td>Mepenzolate bromide</td>
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<td>SPR-10199</td>
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therapy.\textsuperscript{5-9} These drugs also have the advantage of having minimal or no interaction with the cytochrome P450 enzyme system. Their long-term safety and tolerability is also good. However, resistance to these drugs develops quickly and cross-resistance among them is frequently evident.
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com/); the HIGHRIF project which is a series of 4 trials of high-dose rifampicin (http://www.edctr.org); and National Institutes of Health (NIH) supported study in Brazil and Peru. Adjuvant therapy with high-doseisoniazid has also been tried for MDR-TB.

Clofazimine

Clofazimine a fat-soluble riminophenazine dye, although developed in the 1950s as an anti-TB drug, became established as a key drug for the treatment of leprosy. Clofazimine is presently being considered for the treatment of X/MDR-TB. It has been used with success in a short, 9-month combined drug regimen for the treatment of MDR-TB. Other Drugs

Among this category, the phenothiazine neuroleptic thioridazine has been used along with other drugs recently with some success in the treatment of XDR-TB. Thioridazine is thought to act by enhancing the killing of intracellular Mycobacterium tuberculosis by non-killing macrophages, inhibiting the genetic expression of efflux pumps of the TB bacillus that extrude antibiotics prior to reaching their intended targets, and by inhibiting the activity of existing efflux pumps that contribute to the multidrug-resistant phenotype of Mycobacterium tuberculosis. Several other drugs, such as amoxyccillin-clavulanic acid, clarithromycin and imipenem have also been used to treat TB with varying results.

Emerging Newer Antituberculosis Drugs

Delamanid (OPC-67683)

Delamanid (OPC67683) is a nitro-dihydro-imidazooxazole derivative that inhibits mycolic acid synthesis with potent in vitro and in vivo activity against drug-resistant strains of Mycobacterium tuberculosis. In a recently published randomized, placebo-controlled, multinational clinical trial, patients with MDR-TB (n = 481) were treated with delamanid at a dose of 100 mg twice daily (n = 161) or 200 mg twice daily (n = 160) or placebo (n = 160) for 2 months in combination with a background drug regimen developed according to WHO guidelines. Among patients who received 100 mg twice daily delamanid, 45.4% had sputum-culture conversion in liquid broth at 2 months as compared with 29.6% of patients who received a background drug regimen plus placebo (p = 0.008). Similarly, patients receiving 200 mg of delamanid twice daily also had a higher proportion of sputum-culture conversion compared with placebo (41.9% vs 29.6%; p = 0.04). These observations suggest that delamanid could enhance treatment options for patients with MDR-TB.

Bedaquiline (TMC207)

Bedaquiline (TMC207) is a diarylquinoline that targets the proton pump of adenosine triphosphate (ATP) synthase, leading to inadequate synthesis of ATP. In a randomized placebo-controlled study of patients with MDR-TB (n = 47) treated with either bedaquiline or placebo added to the first 8 weeks of a background regimen, bedaquiline significantly reduced the time to culture conversion over 24 weeks (hazard ratio, 2.253; 95% confidence interval, 1.08–4.71; p = 0.031). While only one patient receiving bedaquiline acquired resistance to companion drugs, five patients receiving placebo acquired resistance to companion drugs (4.8% versus 21.7%; p = 0.18). Resistance to ofloxacin was acquired in four patients receiving placebo and in none receiving bedaquiline (22% versus 0%; p = 0.066). These observations suggest that bedaquiline may have the potential to be effective in preventing the emergence of acquired resistance to companion drugs. Presently, bedaquiline appears to be a promising new anti-TB drug especially for the treatment of MDR-TB.

PA-824

The nitromidazole-oxazine PA-824 is a derivative of metronidazole. It is hypothesized that PA-824 acts by inhibiting the synthesis of ketomyculates that are essential components of the mycobacterial cell wall; and by donating nitric oxide during enzymatic nitro reduction within Mycobacterium tuberculosis, thereby poisoning the respiratory apparatus. A randomized EBA study in patients with drug sensitive, smear-positive pulmonary TB patients (n = 69) evaluating oral PA-824 at 200, 600, 1000 or 1200 mg doses per day for 14 days revealed that all doses were well tolerated, and had exhibited equivalent activity. A subsequent dose-ranging randomized study in drug-sensitive, sputum smear-positive adult pulmonary TB patients (n = 15) to find the lowest dose giving optimal EBA, oral PA-824 was administered in doses of 50 mg, 100 mg, 150 mg or 200 mg per kg body weight per day for 14 days. PA-824 at a dosage of 100–200 mg daily appeared to be safe and efficacious.

In a recent prospective, randomized EBA study from South Africa, treatment-naive, drug-susceptible patients with uncomplicated pulmonary TB were randomized to receive bedaquiline; bedaquiline and pyrazinamide; PA-824 and pyrazinamide; bedaquiline and PA-824; PA-824 along with moxifloxacin and pyrazinamide; or unmasked standard anti-TB treatment (as positive control). The mean 14-day EBA of PA-824-moxifloxacin-pyrazinamide was found to be significantly higher than that of bedaquiline, bedaquiline-pyrazinamide, bedaquiline-PA-824, but not PA-824-pyrazinamide, and comparable with that of standard treatment suggesting that PA-824-moxifloxacin-pyrazinamide is potentially suitable for treating drug-sensitive and MDR-TB.

Oxazolidinones

The oxazolidinones act via competitive inhibition of the enzyme that binds the incoming transfer ribonucleic acid (RNA) with the complementary codon on the messenger RNA and inhibiting translation. Cycloserine (4-amino-1,2-oxazolidin-3-one) was the first oxazolidinone that was used as an anti-TB drug. Another oxazolidinedione, linezolid, has been used off-label in the treatment of MDR-TB. In human studies, PNU-100480 (sutezolid) was well tolerated in doses up to 1,200 mg/day. EBA study testing daily 600 mg and 1,200 mg for 14 days has been planned. AZD-5847 (posizolid) is scheduled to be evaluated in phase II studies in dosages of 500 mg once and twice daily, 800 mg twice daily and 1,200 mg once daily.

Substituted Ethylenediamines

SQ109 is a 1,2-ethylenediamine ethambutol analog. It acts by targeting the cell wall formation but by inhibition of trehalose monophosphate transferase. It exhibits no cross-resistance with ethambutol. Currently, SQ109 is undergoing safety and efficacy studies in humans.

Benzothiazinones and Dinitrobenzamides

Benzothiazinones and dinitrobenzamides act by targeting the enzymes responsible for the formation of arabinans that are essential parts of the cell wall. In view of their novel mechanism of action, these drugs appear promising as anti-TB drugs.

NEWER ANTITUBERCULOSIS DRUG DELIVERY SYSTEMS

During the last decade, newer drug delivery systems, such as liposomes, polymeric micro/nanoparticles and solid lipid nanoparticles have been developed. These newer drug delivery systems can be administered through oral, subcutaneous, intravenous or inhaled route. The newer drug delivery systems have the potential advantages of improving patient adherence, reduce pill burden and shorten the treatment duration.
The term “nanoparticle” refers to a colloidal particle with a size of less than 1 micron. Nanoparticles can be made from a wide array of biocompatible materials, like natural substances (e.g. alginate and albumin) or synthetic substances (e.g. polylactides, solid lipids).28-30

**Application of Nanotechnologies for Treatment of Tuberculosis**

Translational research has paved the way for the development of innovative nanotechnology-based drug delivery systems. Applications of nanotechnologies for the treatment of TB have been listed in **Table 3** and outlined below.

**Nanodispersions**

Nanodispersions are submicron colloidal dispersions of pure drugs stabilized with surfactants. Nanonization (reduction of the average size of solid drug particles to the nanoscale by top milling or grinding) facilitates improved solubility of drugs that are both with poor water and lipid solubility. Nanoemulsions are thermodynamically stable oil-in-water dispersions. Their drop size is between 10 nm and 100 nm and has the advantages of being generated spontaneously and ease of production in a large scale and being sterilized by filtration. Niosomes are thermodynamically stable liposome-like vesicles produced with the hydration of cholesterol, charge-inducing components like charged phospholipids and non-ionic surfactants. They can host hydrophilic drugs within the core and lipophilic ones by entrapment in hydrophobic domains.

**Polymeric and Nonpolymeric Nanoparticles**

Polymeric and nonpolymeric nanoparticles have been explored as means for drug solubilization, stabilization and targeting, and facilitate two kinds of systems, namely nanocapsules and nanospheres.

**Polymeric Micelles**

Polymeric micelles are nanocarriers generated by the self-assembly of amphiphilic polymers in water above the critical micellar concentration. Dendrimers are macromolecules displaying well defined, regularly hyperbranched and three-dimensional architecture that preferentially engulfed by the alveolar macrophage, releasing the anti-TB drugs directly into the macrophage and this targeted drug delivery holds significant potential in combating the TB bacillus. Human clinical trials are awaited in near future to evaluate these innovative novel modalities of drug delivery and their impact on TB control.

**FUTURE PROSPECTS**

With X/MDR-TB emerging as a global threat to TB control, eradication of TB requires not only new drugs and treatment regimens, but newer drug delivery systems. The repurposed and emerging newer anti-TB drugs must be carefully evaluated in well designed controlled clinical trials so as to generate quality evidence regarding their efficacy. The quest for newer and more efficient anti-TB drugs must be pursued relentlessly.

**SUMMARY**

Tuberculosis (TB) has been a leading cause of death since time immemorial and it continues to cause immense human misery even today. The emergence of multdrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) has been threatening to destabilize TB control globally. TB has remained a neglected disease and since the introduction of rifampicin, anti-TB drug discovery has been sluggish. Since then, no new drug has become available that can be compared to rifampicin in terms of utility and safety. There is an urgent need for new anti-TB drugs that are more effective and have less toxicity. There is also a need for newer and innovative anti-TB drug delivery systems. Newer fluoroquinolones, especially moxifloxacin has been shown to improve the activity of standard anti-TB treatment regimen when substituted for ethambutol and is studied to shorten the treatment duration in drug-susceptible TB. Rifapentine is a rifamycin that is being extensively re-evaluated. While its potential sterilizing activity has been documented in mice, the same was not evident in a recent short-term clinical trial. Clofazimine, a fat-soluble dye with experimental activity against TB, is being evaluated for the treatment of MDR-TB. The phenothiazine neuroleptic thiordanizone has been found to be useful for XDR-TB. Among newer drugs, the nitro-dihydro-imidazooxazole derivative delamanid (OPC67683), the diarylquinoline bedaquiline (TMC207), the nitroimidazole-oxazine (PA-824) appear most promising. The newer oxazolidinones PNU-100480 and AZD-5847 have been shown to be as active as linezolid and are less toxic. The ethambutol analogue SQ109 does not have cross-resistance with ethambutol and appears to have the potential for a synergistic activity in combined regimens. Eradication of TB requires not only new drugs and treatment regimens, but newer drug delivery systems, especially those based on nanotechnologies. These newer drug-delivery systems can be administered through oral, subcutaneous, intravenous or inhaled route. The newer drug delivery systems, especially nanotechnology-based drug delivery systems have the potential advantages of improving patient adherence, reduce pill burden and shorten the treatment duration. Human clinical trials are awaited in near future to evaluate these innovative novel modalities of drug delivery and their impact on TB control.

**TABLE 3** Nanotechnologies applied to the treatment of tuberculosis

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<tr>
<th>Nanodispersions</th>
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<tr>
<td>• Nanosuspensions</td>
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<td>• Niosomes</td>
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<tr>
<td>Polymeric and nonpolymeric nanoparticles</td>
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<tr>
<td>Polymeric micelles and other self-assembled structures</td>
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**Newer Anti-TB Drugs and Drug Delivery Systems**

anti-TB drugs as well as inhalable drugs. The therapeutic efficacy of O-stearyl amylopectin (O-SAP)-coated liposomal anti-TB drugs given by intravenous route appears promising.28-30

Inhaled nanoparticle-based administration of anti-TB drugs has the advantages of direct delivery of the drugs to the site of infection, and bypassing the first-pass metabolism.32 Nanoparticle delivery of anti-TB drugs also provides sustained release in both blood plasma as well as organ tissues. Furthermore, as nanoparticles are preferentially engulfed by the alveolar macrophage, releasing the anti-TB drugs directly into the macrophage and this targeted drug delivery holds significant potential in combating the TB bacillus. Human clinical trials are awaited in near future to evaluate these innovative novel modalities of drug delivery and their impact on TB control.
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REFERENCES


