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New drugs and regimens for treatment of TB

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Abstract

Tools for effective TB control have been available for years. Case finding, active medications, case management and directly observed therapy are the foundations for the management of TB. The current TB epidemic, centered in resource-limited settings is fueled by the HIV-1 epidemic. Lack of ability to diagnose and treat drug-resistant TB has led to development of more extensive patterns of resistance. Among the currently available drugs, there is reason to hope that rifamycins paired with fluoroquinolones will lead to shorter treatment regimens for drug-susceptible TB. As the result of novel public-private collaborations and investments of resources, new drugs are being developed. These include TMC207, already shown to have activity early in the treatment of multidrug-resistant TB and others that are likely to be active against persistor organisms, and have the prospect to dramatically shorten treatment courses for active and latent TB. Given that these drugs have novel mechanisms of action, combinations have the prospect to be highly active even against multidrug-resistant organisms.

Keywords

fluoroquinolones; rifamycin; tuberculosis

TB has afflicted humans for millennia [1–3] and was a leading cause of death in Europe for centuries [4]. In 1680 John Bunyan called it “the captain of all these men of death” [5]. TB rates were falling in the west long before the introduction of antibiotics, and even before the demonstration that TB is an infectious disease and the implementation of public health measures that followed [6]. Introduction of anti-tuberculous medication with streptomycin in 1944 proved that patients with TB could be cured and led to the hope that TB would be eliminated [7]. Introduction of rifampin-based short-course therapy brought this hope closer to reality. Modern short-course therapy has a cure rate over 95% in individuals with drug-susceptible organisms [8]. Despite the availability of effective treatment, rates of TB have remained high in developing countries and are rising across Sub-Saharan Africa – associated with challenges of drug resistance and HIV co-infection [9].

Mycobacterium tuberculosis organisms develop spontaneous resistance mutations that can interfere with a drug’s mechanism of action, activation or entry into the cell. Resistance emerges as a consequence of selective pressure caused by monotherapy. Treatment with multiple drugs to which the organism is susceptible will prevent this selection [10,11]. As

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rates of drug resistance rise in the community, the potential for inadvertent monotherapy and subsequent emergence of more advanced drug resistance increases [12]. Multidrug resistant TB (MDR-TB) is harder to treat because second-line drugs are less effective, more toxic and more expensive than first-line drugs and require a prolonged treatment course [13]. Drug resistance is an important global problem. Of 9 million new TB cases per year, 500,000 are MDR-TB, defined as disease caused by an organism resistant to both isoniazid (INH) and rifampin [14]. Perhaps 10% of patients have extensively drug-resistent TB (XDR-TB) defined as resistance to first-line drugs along with an injectable drug and a fluoroquinolone [15]. In some places the situation is more dire. A recent report from Kwa-Zulu Natal, South Africa, showed a 41% MDR-TB rate and a 10% XDR-TB rate among a cohort of 544 patients with positive cultures [16]. Avoiding the programmatic shortcomings that can lead to drug resistance is crucial in TB control. Since drug resistance has become more common, there is a clear need for new drugs for TB.

Human infection with *M. tuberculosis* and the disease TB represent a complex interaction between the metabolism of the organism and the defenses of the host. *M. tuberculosis* exists in a variety of environments including within granulomas, intracellularly within phagocytic cells and extra-cellularly within cavities [17]. In each of theses states the interaction of the organism with the environment is different.

During drug treatment of human TB, susceptible organisms can be eradicated from sputum rapidly, usually within 2 months, but a continuation phase for months of treatment after cultures are negative is required to prevent re-emergence of the disease [10]. Organisms that are still viable after months of treatment to which they are susceptible are termed persistors [17]. Currently available TB drugs target mechanisms of cell growth and metabolism. Persistent organisms are metabolically less active, or differently active, making attacks on growth and metabolism less effective. It is unclear what signals initiate and maintain this less metabolically active state, but hypoxia and starvation within granulomas or phagocytic cells have been proposed [17].

Rifampin is somewhat active against persistors [18]. This property may be what makes it critical to short course therapy. For a drug to kill persistors it will need to target some aspect of cell metabolism that remains vital in the less metabolically active state. A new drug active against these metabolic pathways could have the potential to shorten the continuation phase of treatment of active TB. This would enhance adherence and greatly reduce the cost of days of treatment.

Even if all active cases of TB could be eliminated, the large pool of latently infected individuals would serve as a significant, reservoir for development of active cases for decades [19]. Because the metabolic pathways in latent TB may be similar to those in persistors, a drug active against persistors would have the potential to revolutionize TB control by making treatment of latent infection shorter and more effective [17].

HIV infection leads to depletion of CD4 lymphocytes and defects in cell-mediated immunity. In an HIV infected patient with pulmonary TB, failure to develop a CD4 alveolitis limits effective immune response to TB [20]. TB within the lung creates conditions favorable to local HIV replication [21,22].

In TB patients with HIV co-infection, especially those with low CD4 cell counts, *M. tuberculosis* organisms are at greater risk of development of rifampin resistance during treatment. [23] Intermittent therapy of TB in HIV-infected patients can lead to the emergence of rifamycin resistance even during the continuation phase [24–26]. A suggested mechanism is that because of differences in half-life between INH and the rifamycin, patients were essentially receiving intermittent rifamycin monotherapy. HIV-negative

patients under similar circumstances do not develop resistance [27]. Guidelines are now explicit in recommending against highly intermittent therapy for patients with advanced HIV [10]. Thrice-weekly therapy for both 6- and 9-month courses are associated with acquired rifampin resistance [26]. Ensuring that selective pressures are avoided will be critical in any new regimen.

The introduction of multidrug highly active antiretroviral therapy (HAART) revolutionized the prognosis for HIV-infected people [28,29]. Interactions among rifamycins, protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are complex and clinically relevant. Rifamycins are potent inducers of the cytochrome P450-3A (CYP3A) system. Of these, rifampin is most potent and rifabutin the least. Rifabutin, but not rifampin or rifapentine, is metabolized by CYP3A [30]. Protease inhibitors and NNRTIs are metabolized by CYP3A and NNRTIs induce CYP3A [30].

The use of HAART in patients with advanced TB leads to better outcomes [31,32], and because of this the option of holding HAART during treatment is not favorable. Given that rifamycins are the cornerstone of TB therapy, the option of treating with a regimen without rifamycins is not favorable. Guidelines for management are frequently updated [201]. When to add HAART to the anti-TB drug regimen is an area of intense interest. Adding it immediately has been shown to improve outcomes but is associated with increased risk and severity of immune reconstitution inflammatory syndrome [33,34].

Drug development

Rifampin is the last novel drug for TB and was developed over 40 years ago. New drugs are needed. Ideally these drugs should be administered orally, safe, effective, easily tolerated and inexpensive. They should have novel mechanisms of action so that they are active against drug-resistant strains. Their potential to interact with existing TB drugs and with HAART must be defined. Drugs without interactions would be vastly preferable. Drugs with a long half-life to match that of rifampin (or even rifapentine) might allow intermittent therapy even in individuals infected with HIV infected with HIV Drugs active against persistor organisms might allow for shorter treatment courses.

The Global Alliance for TB Drug Development (TB Alliance) was formed in 2000 as an outgrowth of an international TB conference in South Africa [35]. The TB alliance is a not-for-profit, product development partnership accelerating the discovery and development of new TB drugs. Half of their funding, over 250 million dollars, has come from the Bill and Melinda Gates Foundation. The balance is from the US Agency for International Development, UK Department for International Development, The Netherlands Ministry of Foreign Affairs, Rockefeller Foundation, Irish Aid and others [202]. The TB alliance has agreements with a large number of pharmaceutical partners to develop and license new promising drugs for TB. Largely through their efforts, there are over 20 projects in various stages of development, more than at any time in the past [203]. Because most drugs fail in the development process, many candidates are needed for every success and the cost of development remains a significant challenge [36].

The TB Clinical Trials Consortium (TBTC), a collaboration of researchers supported by the CDC, conducts clinical trials of candidate drugs and regimens. Critically important guidance for the treatment of TB has come from these studies and the TBTC continues to lead with important advocacy and research [24,27,204]. Their leadership will be critically important as new drugs enter complex human trials.

The TB Antimicrobial Acquisition and Coordinating Facility was established by NIAID to screen compounds for activity against *M. tuberculosis*. It provides no-cost preclinical drug

screening and efficacy testing services intended to accelerate new TB drug development. This program encourages academic researchers and pharmaceutical company investigators to explore TB research. More than 82,000 compounds have been screened and over 200 have been sufficiently promising to go on to animal testing [205].

TB drug development has come a long way since Waksman had Schatz test pathogens on plates of organisms from soil [37]. High throughput testing has made it easier and faster to screen candidate chemicals for *in vitro* antimycobacterial activity [38].

Drug target identification by stress-induced gene expression analysis can be used to identify vital pathways that may be targets for drug development [39,40]. Selection for resistant mutants and identification of the mutant gene product can also identify important metabolic pathways [41]. X-ray crystal structure analysis of the target proteins, along with a detailed understanding of the chemical structure of the candidate drug and structure–activity relationship allow modifications to be made to bring out desired characteristics [42]. Computer modeling of the structure of a drug target can be used to try to rationally design drugs using virtual screening [43]. High throughput screening of candidate chemicals for activity against these targets or pathways can be used to identify the most promising potential lead chemicals [38].

The early bactericidal activity (EBA) of a drug is a measure of potency against rapidly dividing organisms. Among currently available TB drugs, INH, which works on cell wall synthesis in rapidly dividing organisms, has the best EBA. In fact the EBA of a combination of INH, rifampin, pyrazinamide (PZA) and ethambutol is no better than that of INH alone [44]. The ability to kill persistors is distinct from EBA, and is less crucial in initial treatment and in rendering the patient culture negative. Killing persistors contributes to ultimate cure and determines length of treatment needed to ensure very low relapse rates. Models mimicking persistors have been developed involving microaerophilically adapted cultures or hypoxic cultures. These allow testing of drugs for activity against persistors *in vitro* [45–48]. A model of nutrient starvation may also be relevant to the biology of persistors [49]. Organisms grown in nutrient-poor conditions enter a nonreplicating state like those in the hypoxic model, have changes in ATP homeostasis and maintain reduced intracellular ATP levels [50].

The murine model is the most commonly used animal model because of low costs, experience and convenience. Mice are infected by aerosol or by venous injection. Candidate drugs are added after the infection is established and mice are sacrificed at intervals and lung and spleen homogenates are plated and assayed for colonies of *M. tuberculosis*. This model allows preliminary estimates of efficacy, of effective serum concentrations, toxicities and drug interactions [51,52].

There are disadvantages to the murine model. Various strains are used but these have not been compared with their response to *M. tuberculosis* infection. The pathologic changes in mouse lung are not considered; neither are host pathogen interactions [53]. While treated mice do harbor persistor organisms [54], mice with TB do not form the same sort of well-formed necrotizing granulomas as humans [55]. Organisms rendered persistent by drugs may not grow when plated [56], giving the false impression that infection is truly eradicated.

Other animal models may be of value. Guinea pigs, rabbits and rats infected by low dose aerosol exposure to *M. tuberculosis* develop pathologic lung changes more similar to those in human TB [53]. These might be better models for studies of host response, sterilization and/or latency. These animals are more expensive as are the facilities needed for this model. Nonhuman primates with TB have pathology most similar to humans [57], but are extremely expensive as an experimental model.

Once a drug is active in an animal model and a dose range is defined, Phase I studies of pharmacokinetics and toxicity follow. Bactericidal activity can be assayed *in vitro*, in animal models, and in humans by following changes in colony counts in sputum in response to treatment. EBA studies in humans are typically limited to a few days to 2 weeks to ensure that the research participant receives effective therapy promptly, and to minimize emergence of resistance because the growth characteristics of the organism change over time [18].

Phase II studies of efficacy in humans are more demanding. Since the time frame for treating TB is months, long trials are needed. Since monotherapy leads to resistance, the new drug is added to an adequate background regimen. This prevents the emergence of resistance and ensures adequate therapy for the research participant, but makes it difficult, even with an appropriate control group, to discern the effect of the individual drug being tested and its interactions with other drugs [58].

Ultimately, a highly promising drug will need to be tested as part of a regimen. This requires large, long trials comparing different regimens. These trials are expensive. As the TBTC and TB Alliance have argued, there is a significant lack of trial capacity in terms of study participants, study personnel and funding for these large trials. These deficits must be overcome to proceed to evaluate the promising drugs that are anticipated over the next several years [58]. Many of the forthcoming trials will likely be conducted in sub-Saharan Africa where there will be a need to develop experience and laboratory capacity for conducting and administering large trials [59].

Rifamycins

Rifamycins are potent inhibitors of RNA polymerase. Rifampin has been the cornerstone of TB treatment since it was introduced more than 40 years ago. Only rifamycins allow short course therapy. Rifapentine has a dramatically longer half-life than rifampin and so has been studied for use in intermittent regimens. Because HIV co-infected patients develop rifamycin resistant organisms when treated with intermittent therapy with combinations of INH and either rifampin or rifapentine, rifapentine use is limited to the continuation phase of treatment in HIV-negative patients Only [24,25,27].

Studies in mice have suggested that daily or three times weekly rifapentine dramatically shortens the treatment course required for cure. Mice treated with regimens of rifapentine and PZA, along with either INH or moxifloxacin, achieved stable cure at 10–12 weeks, whereas mice treated with INH rifampin and PZA for 12 weeks relapsed [60]. A total of 6 months of treatment with a regimen of INH rifampin and PZA are required to prevent relapse [61]. These findings suggest that rifapentine, when dosed more frequently, may be more active against persistor organisms than rifampin and may have the potential to dramatically shorten treatment duration. It is unclear if the superiority of rifapentine in this model is because it is a superior drug or because a higher effective dose of a rifamycin was delivered. Serum levels of rifapentine exceeded MIC for much longer than levels of rifampin [61].

High-dose rifamycin use, especially when given intermittently, has been associated with the rifamycin hypersensitivity syndrome, an illness that manifests as fever myalgia and thrombocytopenia that has been described as ‘flu like’ but which can be fatal [62]. A Phase I study of pharmacokinetic interactions between daily 400 mg moxifloxacin and three -imes weekly 900 mg rifapentine was done in normal volunteers. Rifapentine modestly reduced moxifloxacin concentration and induced its own metabolism. Importantly, adverse reactions in two out of 13 participants may have been ascribable to rifamycin hypersensitivity syndrome [63].

TBTC 29 is a Phase II study of daily rifapentine with INH, PZA and ethambutol compared with rifampin, INH, PZA and ethambutol in the intensive phase. Time to culture conversion and safety and tolerability of daily rifapentine will be evaluated [206]. A study being conducted by researchers at Johns Hopkins, MD, USA, and the Federal University of Rio de Janeiro, Brazil, compares daily rifapentine and moxifloxacin along with INH and PZA to a standard regimen of rifampin INH, PZA and ethambutol in the intensive phase [207].

The Rifaquin study is being conducted by The International Consortium for Trials of Chemotherapeutic Agents in TB. This study of participants with fully susceptible TB is intended to explore the roles of rifapentine and moxifloxacin in both the initiation and continuation phases of treatment in both HIV co-infected and uninfected individuals. Moxifloxacin is substituted for INH in the initiation phase. The continuation phase is either rifapentine and moxifloxacin twice weekly for 2 months or rifapentine and moxifloxacin weekly for 4 months. HIV infected individuals with CD4 cell counts below 200/cm^3 are excluded. This study will evaluate whether higher doses of rifapentine allow shortening of the treatment course and if combining moxifloxacin with rifapentine will prevent the emergence of rifamycin resistance [208].

Fluoroquinolones

Fluoroquinolones are broad spectrum antibiotics that act on DNA gyrase. Ciprofloxacin was shown to be useful in drug resistant TB in 1984 [64]. Fluoroquinolones have been widely used in the treatment of drug resistant TB since the late 1980s. As each newer generation of fluoroquinolones has been developed and shown to be more effective against TB [65–67] it has supplanted the prior generation in TB therapy. Use of fluoroquinolones in MDR-TB correlates with outcome [68] and the definition of XDR-TB includes resistance to fluoroquinolones [69]. Currently, moxifloxacin and gatifloxacin are the most potent, fluoroquinolones in use in drug resistant TB. Each has good EBA [70–72].

Moxifloxacin has a long half-life, making it an attractive companion drug for use with rifapentine. A regimen of moxifloxacin, rifapentine and INH was active in a murine model, but less sterilizing than a regimen of INH rifampin and PZA [73]. In the murine model a regimen of moxifloxacin, rifampin and PZA led to more rapid sterilization than a regimen of TNH, rifampin and PZA [74], and a regimen of rifapentine, Moxifloxacin and PZA achieved culture conversion faster than INH, rifapentine and PZA. Both groups achieved stable cure at 10–12 weeks, whereas all mice treated with INH rifampin and PZA relapsed [60].

Moxifloxacin has excellent activity against nonreplicating organisms *in vitro* [71] and in human studies of late bactericidal activity [70,75]. This property raises hopes that moxifloxacin might one day be proven to shorten the duration of effective TB therapy.

There are data to support the value of moxifloxacin in the initiation phase of treatment in human TB. In a Phase II study of moxifloxacin substituted for ethambutol in 170 participants, 59 out of 74 (80%) participants in the INH, rifampin, PZA and moxifloxacin group had documented culture conversion at 8 weeks compared with 45 out of 72 (63%) participants in the INH, rifampin, PZA and ethambutol group [76]. In TBTC study 26, a regimen of rifampin, PZA and ethambutol, and moxifloxacin was compared with INH, rifampin, PZA and ethambutol for culture conversion at 8 weeks. Out of 165 participants in the moxifloxacin group 99 (60%) had documented negative cultures at 8 weeks compared with 90 out of 164 (55%) participants in the INH group [77]. In an open label study, addition of moxifloxacin to INH, rifampin, PZA and ethambutol was associated with 82% culture conversion at 6 weeks compared with 61% without moxifloxacin [78].

A Phase III trial comparing a regimen of INH, rifampin, PZA and gatifloxacin for 2 months followed by INH, rifampin and gatifloxacin for 2 months with a regimen of INH, rifampin, PZA and ethambutol for 2 months followed by INH and rifampin for 4 months is ongoing in several African countries. Results of an interim analysis are expected in 2010 [209].

New fluoroquinolones being developed holds promise for treatment of TB. DC159a has been shown to be more active *in vitro* against both drug susceptible and drug resistant *M. tuberculosis* isolates than levofloxacin, gatifloxacin and moxifloxacin [79].

TMC207

TMC207 is a diarylquinoline. Diarylquinolines are related to, but structurally and mechanistically different from quinolones. TMC207 was formerly named R207910, and much of the early enthusiastic literature is under this name [80].

Diarylquinolines were identified by screening prototype chemicals for inhibition of growth of *Mycobacterium smegmatis*, a rapid grower. TMC207 works by inhibition of the membrane spanning component of ATP synthase. While ATP synthase is highly conserved, mycobacterial ATP synthase is 2×10^4 more sensitive to TMC207 than human mitocondrial ATP synthase [81]. TMC207 was the most potent of the diarylquinolines. When tested for activity against *M. tuberculosis*, TMC207 was active against both susceptible and MDR strains, implying that it had a distinct mechanism of action. Mutations cause resistance and spontaneous mutations occur at a rate comparable to rifampin [80]. TMC207 is active against many species of mycobacteria, though not *Mycobacterium Xenopi* owing to a difference in ATP synthase [82].

Mouse and guinea pig data suggest better activity against *M. tuberculosis* than first-line TB drugs [80]. Safety trials in humans have shown it to be safe and bioavailable following oral administration [83].

Early bactericidal activity is good at a dose of 400 mg daily [83]. Late bacterial activity is better than rifampin, suggesting that TMC207 may kill nonreplicating organisms and so potentially shorten the continuation phase [80,84,85].

Its long half-life makes TMC207 an attractive companion drug for other drugs that also have a long half-life. In a murine model, a combination of TMC207, rifapentine and PZA given once weekly was more active than a regimen of INH, rifampin and PZA given fivetimes per week over a 2-month period [86,87].

TMC207 is metabolized by the cytochrome P450 system. Drugs that induce function of cytochrome P450, such as rifampin, will reduce concentrations of TMC207. This will increase the complexity of regimens that might contain both drugs and will likely create interactions with other drugs affected by cytochrome P450 including HAART [88].

A murine study compared TMC207 plus various combinations of INH, rifampin and PZA for 4 months against 6 months of INH, rifampin and PZA. All mice were culture negative at 4 months. Regimens with INH and TMC207 led to culture conversion at 2 months. The relapse rate 3 months after completion of the standard 6 month regimen was 17%. The best regimen, INH rifampin, PZA and TMC207, had a relapse rate of 6% 3 months after completing the 4 month course. Without INH the rate rose to 13%. Without rifampin the rate rose to 29%. The combination of rifampin moxifloxacin and PZA was vastly inferior with a relapse rate of 42% [89].

Results of a Phase lib randomized, double blind, placebo controlled study of the use of TMC207 in humans with MDR-TB were recently published [90]. Participants received a five-drug second-line regimen of kanamycin, ofloxacin, ethionamide, cycloserine and PZA. They were randomized to TMC207 versus placebo for the first 8 weeks of therapy. Patients with organisms resistant to the study drugs and those with advanced HIV disease were excluded. The dose of TMC207 was 400 mg daily for the first 2 weeks and then 200 mg every other day for the next 6 weeks. This dosing was chosen to maximize EBA [83] for the first 2 weeks, then to maintain a serum concentration of 600 ng/ml. At 2 months the TMC207 group had a culture conversion rate of 48 compared with 9% in the control group. Nonconverters had the same serum levels as converters. Nausea was noted frequently (26 vs 4% in the TMC207 and control group, respectively) but did not lead to discontinuation of the drug.

Oxazolidinones

Oxazolidinones inhibit protein synthesis by binding to a ribosomal subunit and inhibiting complex formation [91]. Linezolid was initially chosen for development because it has good efficacy against drug resistant Gram-positive organisms [92]. Oxazolidinones have antituberculous effects [93–95]. Linezolid has been used as salvage therapy in patients with MDR-TB. Numerous small case-series document cases of patients who were cured with a salvage regimen including linezolid. Dose ranges were typically 600 mg daily or twice daily. These series have also documented significant hematologic and neurologic toxicity, including cases of nonreversible neurologic toxicity [96–98].

A report from the Bellevue Chest Service described seven patients who were treated with linezolid as part of their therapy for XDR-TB. Most were treated with 600 mg twice daily. In all cases, smears and cultures converted to negative within up to 6 months. Patients were treated for up to 28 months. The most common adverse reaction was neutropenia in three of seven, which resolved with discontinuation of the medication and did not recur in two patients rechallenged with a lower dose. Two patients had evidence of peripheral neuropathy. Each continued to receive treatment with stable or improving symptoms [99].

There are suggestions that the marrow toxicity can be limited by dose reduction [100], but the neurologic toxicity might be related to duration of treatment [101]. One study recently showed that even with a dose of 300 mg daily, linezolid levels stayed above MIC [102]. Resistance to linezolid has been reported [103].

The TBTC study 30 is to be a randomized, double blind placebo controlled Phase I–II study of safety and tolerability of low dose (600 mg daily) linezolid in MDR-TB in Kwa Zulu Natal [210].

In the early reports on oxazolidinones, PNU100480 was reported to have greater activity against *M. tuberculosis* than linezolid [94]. At the time many believed that pursuit of this promising class of agents for TB would be limited. As interest in development of TB medications has increased, PNU100480 is again an attractive candidate TB drug.

In the murine model, PNU100480 has been shown to have strong bactericidal activity. Added to first-line drugs it increases bactericidal activity by two orders of magnitude. A regimen of moxifloxacin, PZA and PNU100480 was more active than a regimen of INH, rifampin and PZA [104]. Treatment with INH, rifampin, PZA and PNU100480 given for 2 months then either INH, rifampin and PNU-100480 or rifampin and PNU-100480 for 2 more months, leads to cure in 95% of mice at 4 months compared with 10% with conventional therapy. By contrast, addition of linezolid to INH, rifampin and PZA had an

antagonistic effect resulting in higher colony-forming unit counts and failure to render mice culture-negative in 4 months of treatment [105].

PNU100480 is now in active Phase 1 trials including recruiting volunteers for a Phase I study of safety and pharmacokinetics [211]. Other candidate oxazolidinones are being developed and optimized for TB treatment. RBX8700 has potent, concentration-dependent activity *in vitro* and in a cultured macrophage cell line [106,107] AZD5847 is undergoing a Phase 1 study of safety, tolerability and pharmacokinetics [212].

β-lactams

β-lactam antibiotics inhibit synthesis of bacterial cell wall peptidoglycans. *M. tuberculosis* has a potent rapidly acting β-lactamase encoded by *blaC* [108]. β-lactam antibiotics have been tried as a therapy against TB for years with very modest success. Penicillin has no activity, though amoxicillin–clavulanate and ampicillin–sulbactam have some [109,110]. Clavulanic acid is a better inhibitor of this β-lactamase than sulbactam or tazobactam [111]. Meropenem is a poor substrate for the *M. tuberculosis* β-lactamase. When meropenem and clavulanic acid are combined, they have potent sterilizing effect *in vitro* against both drug susceptible and drug resistant *M. tuberculosis* [112]. Since these drugs are licensed, it is likely that this combination will be tried as part of MDR/XDR regimens, though lack of an oral formulation will be limiting. Studies of the use of meropenem and clavulanic acid in patients with drug resistant TB are planned in South Africa and South Korea [213]. Demonstration that a β-lactam can be active against *M. tuberculosis* may spur more investigation into this class of antibiotics for treatment of TB. An orally bioavailable β-lactam that is similarly a poor substrate for the *M. tuberculosis* β-lactamase would have even greater potential value.

Nitroimidazoles

Metronidazole is a nitroimidazole antibiotic with activity against anaerobes. Some reports have shown that it has some mild activity against nonreplicating *M. tuberculosis* organisms under anaerobic conditions [113,114]. Others have not [115–117]. There is a report that in combination with rifampin, metronidazole can sterilize long dormant *M. tuberculosis* [118]. If true, this would have implications for length of treatment and for treatment of latent infection. A Phase II study of metronidazole for MDR-TB in Korea has been suspended [214].

Screening for other nitroimidazoles that might have better activity against *M. tuberculosis* has led to development of several promising candidate drugs.

PA-824

PA-824 is a nitroimidazole. Early reports highlighted PA-824's activity against *M. tuberculosis in vitro* and in animal models [119]. In 2002, the TB Alliance and Chiron Co., a biotechnology company based in California (CA, USA), signed a landmark agreement to develop PA-824 for TB. The TB Alliance received worldwide, exclusive rights to PA-824 and its analogs for the treatment of TB, and Chiron pledged to make the technology available royalty-free in endemic countries. Chiron retained the right to develop and commercialize the compounds for indications other than TB. PA-824 acts against both actively growing and nonreplicating *M. tuberculosis*.

PA-824 is a prodrug. It is converted into three metabolites by Rv3547, a deazaflavin-dependent nitroreductase [120]. PA-824 has two mechanisms of action. The first, inhibition

of mycolic acid synthesis, kills rapidly growing cells. PA-824 has excellent EBA and leads to rapid killing in animal models [121].

The second mechanism of action is responsible for its excellent activity against nonreplicating organisms [121,122]. One of the three metabolites, a desnitro product, kills by generation of reactive nitrogen species, including nitric oxide within the organism. This anaerobic killing can be prevented by nitric oxide scavengers [120]. Even in a nonreplicating cell, maintenance of an energized cell membrane and ATP homeostasis are required. The anaerobic killing is believed to work through inhibition of cytochrome c oxidase by nitric oxide, effectively poisoning cell respiration [123].

The correlation between activity and formation of imidazole-ring-reduced products at the two electron level provides a molecular understanding of this reduction pathway [124]. It is possible that a similar drug could be designed to maximize this action, yielding better treatment of nonreplicating or latent *M. tuberculosis*.

At concentrations over 1.0 ng/ml, PA-824 kills all *M. tuberculosis* in three models of hypoxia-induced latency. By contrast, even high concentrations of moxifloxacin, a drug that may be of value in shortening length of treatment, is unable to sterilize all organisms in these models. Since PA-824 is 94% plasma bound, it is unclear if this concentration can be achieved *in vivo*, particularly in cavitary lesions [125].

PA-824 has excellent tissue penetration and a long half-life. Phase I studies of absorption, distribution, metabolism and excretion have been conducted. PA-824 was tolerated well with no definitive dose-limiting adverse events [126]. In humans PA-824 causes increased creatinine. This is related to inhibition of renal creatinine secretion and is clinically benign [127]. A 14-day EBA trial of varying doses of PA-824 conducted in patients with TB reportedly suggests that PA-824 also has good EBA at low doses [128].

OPC 67683

OPC 67683 is a nitroimidazole being developed by Otsuka Pharmaceutical Co. Ltd. The major activity is against mycolic acid synthesis. OPC 67683 has an exceptionally low 14 day MIC in the range of 0.006–0.024 μg/ml against both resistant and susceptible *M. tuberculosis in vitro*. It is partially synergistic when combined with first-line drugs *in vitro*. It is as active against intracellular *M. tuberculosis* in a THP-1 macrophage model as rifampin and is better than INH. A combination of OPC 67683 and rifampin leads to sterilization in the murine model 2 months faster than a combination of INH, rifampin, PZA and ethambutol. There is no significant cytochrome P450 metabolism [129]. OPC 67683 has completed Phase I and EBA studies in humans and is now recruiting participants Phase IIb trial in MDR-TB [215].

SQ109

SQ109 is an ethylenediamine developed by Sequella Inc. as the most potent agent found through high throughput combinatorial screening of ethambutol analogs. It seems to work by inhibition of cell wall synthesis but by a mechanism different from ethambutol. It can kill ethambutol-resistant organisms [130]. *M. tuberculosis* reacts to the two drugs by activating different genes implying different intracellular targets [131]. SQ109 is more potent than ethambutol, has lower MIC and kills intracellular organisms better [132,133]. A long half-life makes this a potentially attractive companion drug to other drugs with long half-lives. It acts synergistically with rifampin *in vitro*, lowering the MIC of rifampin [134]. In animal models, INH, rifampin, PZA and SQ109 produces counts of *M. tuberculosis* colonies at 8 weeks that are 1.5-log lower than those with INH, rifampin, PZA and ethambutol [135].

Low bioavailability of SQ109 is related to first pass metabolism. An upstream prodrug produces 91% bioavailability [136]. SQ109 is metabolized by cytochrome P450 [132]. Sequella is recruiting for a Phase Ib dose escalation study of SQ109 in normal volunteers [216].

Proteasome inhibitors

A study in *Nature* described oxathiazol-2-one compounds as selective inhibitors of mycobacterial proteasomes. Proteasome inhibition leads to cell death by the novel mechanism of accumulation of toxic cell debris. Two oxathiazol-2-one compounds, GL5 and HT1171, bind irreversibly to the *M. tuberculosis* proteasome, while largely sparing the human homologue. The fact that this inhibition of the *M. tuberculosis* proteasomes is selective raises the prospect that antiproteasome agents might prove to be highly selective drugs for the treatment of TB [137].

Pyrroles

Screening of a variety of azole derivatives led to the description of a pyrrole, BM212 as having activity against *M. tuberculosis* in 1998 [138]. Development of this class of agents is ongoing. Chemical modifications have led to the design of derivatives with high activity and low cytotoxicity [139].

LL-3858, also called Sudoterb, is a pyrrole developed by Lupin Ltd. EBA studies, reported in abstract form, were done in 2005 [140,141]. While these early reports were enthusiastic, no new information has been reported and the status of the development project is unclear. Lupin is said to be in recruiting participants for a Phase II trial of bactericidal activity of Sudoterb [217].

SQ641

SQ641, from Sequella pharmaceuticals, is an inhibitor of peptidoglycan synthesis early in the development process. *In vitro*, SQ641 seems very potent against a wide variety of mycobacteria. Poor water solubility and poor intracellular activity limit use, though when dissolved in a vitamin E analog, α-tocopheryl-polyethylene glycol-1000-succinate and administered intraperitonealiy, it has strong killing and synergy with INH in a murine model [142].

IFN-γ

A local T-helper-1 (Th1) immune response in the lower respiratory tract limits *M. tuberculosis*. Aerosol delivery of recombinant IFN-γ to the lung enhances this Th1 response [20]. Addition of aerosol IFN-γ to failing second-line therapy led to conversion of sputum to smear negative within 1 month in five out of five patients with MDR-TB. All had improved symptoms, time to detection of *M. tuberculosis* in the culture and chest radiographs [143]. In patients with TB who are coinfected with HIV, TB enhanced HIV-1 replication in the lung [21]. A total of 1 month of aerosolized IFN-γ led to a reduction in bronchoalveolar HIV-1 viral load in five out of five participants [144]. In a randomized, controlled clinical trial of aerosol IFN-γ added to conventional therapy in cavitary pulmonary TB, 16 weeks of 200 μg aerosolized IFN-γ three-times a week significantly increased sputum smear AFB clearance, reduced symptoms, reduced inflammatory cytokines in the BAL and led to significant radiographic improvement [145]. Subcutaneous IFN-γ was ineffective. In each of these studies, rate of culture conversion and of cure are not significantly enhanced by IFN-γ. It behaves by enhancing endogenous bactericidal activity but does not enhance sterilizing activity [Condos R. Pers. Comm.].

Summary

The TB community has promoted a full pipeline of candidate drugs at all phases of development. The majority of candidates in preclinical and early clinical development will never be brought to market. Any listing of candidates here would be rapidly out of date. There are promising ideas among inhibitors of many stages of the cell cycle and directed at specific critical metabolic pathways and enzymes. There are promising ideas among azoles [146], taxanes [147] and phenothiazines [148]. The websites of the TB alliance [218] and of the Working Group on New TB Drugs [219] provide up-to-date information.

Expert commentary

The current TB epidemic in the developing world has raised alarm owing to high case rates, very high rates of HIV coinfection and emergence of MDR-TB and XDR-TB. In this setting, with drug susceptibility testing limited or unavailable, empiric short-course therapy via days on treatment may be ineffective and may even raise the risk of more advanced drug resistance. MDR-TB and XDR-TB are difficult to treat. Second-line drugs are expensive, toxic, largely unavailable and require 18 or more months to be effective. Potent new drugs are needed. These drugs must be cheap, safe, orally administered once daily and should not interact with each other or with antiretroviral therapy.

Recent developments in diagnostics and therapeutics have significantly improved the prospects for control of TB. Extraordinary public–private partnerships have emerged and have engaged pharmaceuticals to develop these drugs. Drug development has come a long way. For the first time, many new drugs are on the horizon. These drugs have novel targets and mechanisms of action and potent bactericidal activity. They have already proven their value in *in vitro* and in murine models and they are in clinical testing. TMC207 has already proven to be of value in hastening sputum culture conversion in MDR-TB in humans. Some of the most promising new drugs are highly active against persistors. These have the potential to dramatically shorten duration of treatment courses. If these drugs are safe enough and effective enough, they could even have the potential for use in latent infection, eliminating a huge potential reservoir of disease.

Case finding, regimens that do not foster monotherapy, directly observed therapy and case management will remain central to TB control. Rapid drug susceptibility testing will minimize the potential for inappropriate regimens and allow earlier initiation of effective therapies. Better vaccines will provide more effective protection, and boosting will maintain those benefits. Vaccines may have a role in treatment of latent infection and even in the treatment of active disease.

The drug regimen of the future will include drugs with excellent EBA to rapidly render the patient noninfectious and potent sterilizing activity to produce reliable cures in a fraction of the current treatment duration. Fixed combination formulations will simplify administration and minimize the risk of monotherapy that might select for resistance. Since these regimens will be composed of novel agents, patients whose organisms are resistant to currently available drugs will share in the prospect of rapid effective treatment.

Five-year view

With many new drugs in development, the next five years will see an explosion of information. We should know if high dose moxifloxacin and rifapentine allow for shorter treatment courses with adequate safety within the next 5 years.

Given that new drugs must be evaluated as part of a multidrug regimen, complex trials will be needed. It will take years to conduct the needed Phase III trials, and several years to evaluate for relapses in participants after they complete the treatment component of the trial. The challenge of conducting these trials, particularly since they will be conducted in resource poor locations with limited infrastructure or trials experience will be considerable.

In 5 years time we should know the activity, interactions and toxicity of many of the current candidate drugs. The generation of trials after that will be devoted to evaluating regimens comprised of the truly novel drugs to define their true promise. Given current trends in TB control, this information will be desperately needed.

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Key issues

- Case management and duration of treatment are the cornerstones of TB therapy.
- As drug resistance increases, empiric therapy becomes less reliable, and drug susceptibility testing becomes more urgent.
- New affordable, safe and effective drugs are urgently needed.
- New affordable, safe and effective drugs are needed for multidrug-resistant-TB and extensively drug-resistant TB.
- New drugs are emerging as a result of public–private collaborations.
- New drugs and regimens have the potential to shorten treatment duration.
- Of the new drugs, TMC207 is the furthest in development and has activity in human multidrug-resistant TB.