

New Tuberculosis Therapeutics: A Growing Pipeline

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Novel chemotherapeutic drugs are needed to improve tuberculosis (TB) control, especially in the developing world. Given the magnitude of the problem and the resources available in countries that have the highest burden of disease, the present standards of care for the treatment of drug-susceptible TB, drug-resistant TB, TB/human immunodeficiency virus (HIV) coinfection, and latent TB infection are all unsatisfactory. Because no truly novel compounds for the treatment of TB have been discovered in the past 40 years, the recent enhanced activity in the research and development of new TB drugs is extremely encouraging. Seven compounds are presently in clinical development specifically for the treatment of TB. Other known antibiotic compound families are being investigated preclinically, in an attempt to identify new antimicrobial drugs with specific antituberculous activity. In addition, novel targets have been identified and are the subject of efforts to validate their potential usefulness in the treatment of TB.

Fueled by the growing incidence of HIV infection, the tuberculosis (TB) epidemic is becoming a greater global public health emergency. With one-third of the world's population harboring the tuberculous bacillus, 2 million deaths due to TB occurring each year, 3 million people becoming infected with both HIV and *Mycobacterium tuberculosis*, and the growing incidence of both multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), the need for more effective chemotherapy for the treatment of TB has never been greater [1]. Unfortunately, the last truly novel drug that was approved for the treatment of TB was discovered >40 years ago; this partially explains the inadequacy of the present armamentarium of antituberculous drugs.

CURRENT TB THERAPY

The currently recommended treatment regimens for active pulmonary TB are both lengthy and cumbersome. The treatment duration is a minimum of 6

months, with 4 drugs (isoniazid, rifampin, pyrazinamide, and ethambutol) typically given daily for the first 2 months and with 2 drugs (isoniazid and rifampin) administered for 4 additional months [2]. In part because of this lengthy and complex treatment regimen, the World Health Organization (WHO), in 1993, introduced a global strategy for TB control known as "directly observed therapy, short-course" (DOTS) [3]. One of the crucial components of this strategy is the direct observation by trained personnel of patients taking their medications, to ensure compliance and to help prevent the emergence of drug resistance. Although the direct observation and monitoring of patient adherence to the regimen is important to treatment success, it also increases the cost of treatment and makes TB therapy more burdensome.

One additional difficulty associated with the presently available treatment regimens is the potential for drug-drug interactions, primarily those between rifampin and many of the antiretroviral drugs used for the treatment of AIDS. Rifampin induces some of the cytochrome P-450 enzymes that metabolize certain of the protease inhibitors and nonnucleoside reverse-transcriptase inhibitors commonly used to treat HIV/AIDS. Therefore, it is difficult to coadminister effective treatment for TB and AIDS.

The treatment of MDR-TB is characterized by relatively less effective, poorly tolerated, and expensive drugs that may need to be administered for years.

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Table 1. Tuberculosis (TB) clinical development programs.

Compound	Development stage	Sponsor/coordinator
Gatifloxacin	Phase 3	European Commission; IRD; WHO/TDR; Lupin
Moxifloxacin	Phase 2/3	Bayer; TB Alliance; CDC; University College London; Johns Hopkins University
TMC207 ^a	Phase 2	Johnson & Johnson (Tibotec)
OPC67683 ^b	EBA	Otsuka Pharmaceutical
PA824 ^b	EBA	TB Alliance
LL3858 ^c	Phase 1	Lupin
SQ109 ^d	Phase 1	Sequella

NOTE. CDC, Centers for Disease Control and Prevention; EBA, early bactericidal activity; IRD, Institut de Recherche pour le Developpement; TDR, Special Programme for Research and Training in Tropical Diseases; WHO, World Health Organization.

^a Diarylquinoline.

^b Nitroimidazole.

^c Pyrrole.

^d Diamine.

Equally inadequate is the treatment available for latent TB infection. It has been estimated that 2 billion individuals are infected with *M. tuberculosis*, so there is an enormous human reservoir of the infecting organism. The currently recommended treatment for latent TB infection is isoniazid given for 6–9 months. Because of the long duration of this therapy and the potential toxicities of isoniazid, there is a major compliance problem associated with the treatment regimen. Although new drugs are needed to shorten the duration of treatment of latent TB infection, the safety profile for these drugs must be excellent, because most patients with latent infection are destined never to experience activation of their TB.

Therefore, the need for newer, more effective drugs that can achieve multiple goals in improving TB control is pressing. Treatment of active disease needs to be shortened and simplified. TB drug regimens should not interfere with the administration of antiretroviral agents. Markedly improved therapy is needed for the treatment of MDR-TB and XDR-TB, and the treatment of latent TB infection needs to be dramatically shortened.

THE EMERGING PIPELINE OF NEW ANTI-TB DRUGS

For the first time in decades, there is now a pipeline of new compounds or classes of compounds that are being specifically tested for their potential effectiveness in the treatment of TB. Although some of these compounds, such as rifapentine, belong to classes that have already been approved for the treatment of TB, the majority belong to novel classes that have not yet been approved for TB therapy. Within this category, there are chemical classes that have been approved for the treatment of other bacterial infections; these include the fluoroquinolones, macrolides, oxazolidinones, and nitroimidazoles. There are also

novel chemical classes that have never been approved for use in humans; these include the pyrroles, pleuromutilins, and diarylquinolines. In addition to the known compounds that are being tested or optimized for their use in TB treatment, novel potential TB drug targets are also being identified, validated, and assayed for potential inhibitors.

Within this growing pipeline of potential new TB drugs, there are presently 7 novel compounds, unapproved for the treatment of TB, that are in various stages of clinical development (table 1). The most advanced of these drugs are the fluoroquinolones, specifically gatifloxacin and moxifloxacin, which are currently being evaluated in phase 2 and 3 clinical trials. Two other compounds (TMC207 and OPC67683) have completed phase 1 clinical trials and early bactericidal activity (EBA) studies, PA824 has completed its phase 1 program, and 2 other compounds (LL3858 and SQ109) are currently being evaluated in phase 1 clinical studies.

FLUOROQUINOLONES (MOXIFLOXACIN AND GATIFLOXACIN)

Over the past decade or so, the fluoroquinolones have come to play a prominent role in the treatment of MDR-TB. This increasing role has developed in spite of the lack of formal clinical data supporting the indication. Recently, however, attention has shifted to investigation of the use of the fluoroquinolones to try to shorten the treatment duration for drug-susceptible disease. Perhaps the greatest initial stimulus for this change was the report of a clinical trial by the Tuberculosis Research Centre in Chennai, India [4]. This trial randomly allocated patients with newly diagnosed pulmonary TB to receive 1 of 4 regimens containing ofloxacin. Of note, because there was no standard therapy arm in this study, the ability to interpret the results was limited. However, the rates of sputum

conversion at 2 months, which is probably the best currently available surrogate marker for the relapse rate [5, 6], ranged from 92% to 98%, which is superior to the expected rate of ~80% noted with standard therapy [7]. Perhaps more impressive were the reported relapse rates. Patients assigned to receive daily therapy with isoniazid, rifampin, pyrazinamide, and ofloxacin for 3 months, followed by twice-weekly therapy with isoniazid and rifampin for 1 month, experienced a 4% relapse rate, whereas patients assigned to receive twice-weekly treatment with isoniazid and rifampin for 2 months after the 3-month phase of daily treatment experienced a relapse rate of only 2%. This study was especially encouraging, because the newer fluoroquinolones, such as moxifloxacin and gatifloxacin, are more potent antimycobacterials than is ofloxacin [8–11].

Further encouraging data regarding the potential of the fluoroquinolones to shorten treatment duration come from a series of in vitro and in vivo studies [12–14]. The most surprising and exciting of these findings is that, in the mouse model, the combination of rifampin, pyrazinamide, and moxifloxacin had sterilizing activity that substantially exceeded not only that of the standard regimen but, also, that of the standard regimen with the addition of moxifloxacin.

The technique of examining EBA has also been used to study moxifloxacin. Two moxifloxacin EBA studies have demonstrated that moxifloxacin has EBA superior to that of rifampin and perhaps comparable to that of isoniazid [15, 16].

The fluoroquinolones gatifloxacin and moxifloxacin are both currently being studied in phase 2 and/or 3 trials for the shortening of the treatment duration for active, drug-susceptible pulmonary TB. Both compounds are being tested in combination regimens in which they replace ethambutol during the initial 2-month phase of intensive therapy, whereas moxifloxacin is also being studied in a combination regimen replacing isoniazid.

Studies of gatifloxacin are being conducted by a product development team supported by the European Commission, the Institut de Recherche pour le Développement, the World Health Organization/Special Programme for Research and Training in Tropical Diseases, and Lupin. A completed phase 2 study randomized patients to receive 8 weeks of therapy with either conventional treatment or the combination of isoniazid, pyrazinamide, and rifampin with either ofloxacin, moxifloxacin, or gatifloxacin. In that study, serial sputum colony count measurements appeared to indicate that the patients in the moxifloxacin and gatifloxacin arms cleared their sputum more quickly than did patients receiving conventional therapy or the regimen containing ofloxacin [17]. Rates of sputum conversion at 2 months were not improved in any of the experimental arms. The ability of gatifloxacin, substituted for ethambutol, to shorten the duration of treatment of active smear-positive disease from 6 months to 4 months is now being tested in a

phase 3 trial in multiple African countries, including Senegal, Benin, South Africa, Kenya, and Guinea.

The moxifloxacin clinical development program is being coordinated through a joint partnership between Bayer and The Global Alliance for TB Drug Development (TB Alliance). Clinical trials within the moxifloxacin program are sponsored by the Tuberculosis Trials Consortium of the Centers for Disease Control and Prevention, Johns Hopkins University, and University College London. In a completed phase 2 trial investigating the impact of substituting moxifloxacin for ethambutol for the first 8 weeks of therapy, the Tuberculosis Trials Consortium reported that, even though the primary end point of an increase in the rate of sputum conversion at 8 weeks was not met, a post hoc analysis of sputum conversion at earlier points in time suggested that a quicker time to sputum conversion was associated with the regimen containing moxifloxacin [18]. Ongoing or planned studies include a phase 3 trial to test whether a 4-month regimen in which moxifloxacin is substituted for ethambutol is equally as effective as the standard 6-month course of therapy, as well as phase 2 studies investigating whether substituting moxifloxacin for isoniazid for 8 weeks will increase the sputum conversion rate. The latter studies are based on the preclinical findings of Nuermberger et al. [14], who found that substituting moxifloxacin for isoniazid shortens the duration of therapy for active disease much better than does substituting moxifloxacin for ethambutol. The gatifloxacin and moxifloxacin projects are the most advanced of the TB clinical development programs.

DIARYLQUINOLINE (TMC207)

In 2004, Andries et al. [19] first described the work done by Johnson & Johnson on the research and development of TMC207 (then referred to as “R207910”), a novel diarylquinoline, for potential use in the treatment of TB. TMC207, which is now being clinically developed by Tibotec, a Johnson & Johnson subsidiary, has many characteristics, both in vitro and in vivo, that make it a very attractive anti-TB drug candidate. It has very potent in vitro activity against both multidrug-resistant and drug-susceptible strains of *M. tuberculosis*. Although it also shows potent activity against other *Mycobacterium* species, such as *M. avium*, *M. marinum*, *M. fortuitum*, and *M. abscessus* (it is also active against *M. smegmatis*, with its original discovery having occurred during screening against that organism as a surrogate for *M. tuberculosis*), the compound has only weak activity against a variety of gram-positive and gram-negative organisms. The data on in vitro activity against multidrug-resistant strains of *M. tuberculosis* are consistent with a novel mechanism of action for TMC207. TMC207 works through targeting the proton pump of ATP synthase, as shown by Andries et al. [19]. The genomes of TMC207-resistant mutants of *M. tuberculosis* (1 strain) and *M. smegmatis* (2 strains) were

sequenced to near completion. In addition, the parental *M. smegmatis* strain was similarly sequenced. Point mutations were identified that were associated with resistance. In the 3 resistant strains studied, only 1 gene was found that was commonly affected. This was the gene encoding atpE, part of the F0 subunit of ATP synthase. Follow-up of these studies revealed that wild-type *M. smegmatis* was transformed with a construct expressing the F0 subunit from one of the mutant *M. smegmatis* strains. This transformation caused resistance similar to that noted in the primary resistant strain.

In pharmacokinetic/pharmacodynamic studies of TMC207 in a chronic murine infection model of *M. tuberculosis* (H37Rv), dose-fractionation experiments revealed that antimycobacterial activity was independent of the dosing regimen but dependent on the cumulative area under the concentration-time curve (AUC). The optimal correlation with a reduction in the bacterial counts was for the AUC/MIC [21].

Phase 1 studies in humans have also been performed with TMC207. Single doses (10 mg, 30 mg, 100 mg, 300 mg, 450 mg, or 700 mg given to cohorts of volunteers) were given to healthy male subjects immediately after a meal. Tolerability was described as very good, and pharmacokinetics were linear over the dose range studied. A phase 1 study of multiple ascending doses was then performed with TMC207 given to 3 cohorts of normal volunteers in doses of 50, 150, or 450 mg/day for 14 days. Accumulation was seen with increases in the AUC by a factor of ~2 between day 1 and day 14. The “effective half-life” was calculated to be on the order of 24 h. Of importance, the average concentrations seen in the cohorts were greater than the concentrations needed in mice to achieve optimal activity in the established infection model. An EBA study has also been performed with ascending doses of TMC207. The compound is about to enter a randomized phase 2 study in a population of patients with MDR-TB.

NITROIMIDAZOLES (OPC67683 AND PA824)

Another class of compounds that has been the subject of considerable interest because of their potential in TB therapy is the nitroimidazoles. Currently, 2 nitroimidazoles are in clinical development. These are the nitroimidazo-oxazine PA824, which is being developed by the TB Alliance, and the dihydroimidazo-oxazole OPC67683, which is being developed by Otsuka Pharmaceutical. Of note, this class of compounds can trace its history back to at least the 1970s, when Ciba-Geigy in India investigated a series of nitroimidazoles for their potential role as radiosensitizing agents. It was later discovered that many of these compounds possessed antimicrobial activity, including activity against *M. tuberculosis*. However, when the lead compound (CGI-17341) was found to be mutagenic in the Ames assay, further development was halted.

It was not until the 1990s that the small pharmaceutical

company Pathogenesis explored this series further, modifying the furan ring structure of the Ciba-Geigy compounds and thereby describing the nitroimidazo-oxazines, or nitroimidazopyrans. Pathogenesis studied >700 novel compounds and determined that PA824 was the most active of these compounds against *M. tuberculosis* in a murine infection model [22]. PA824 was found not to be mutagenic. Potential mutagenicity, as well as other potential genotoxicity, has since been evaluated not only by the Ames assay, both with and without S9 activation, but also by chromosomal aberration, mouse micronucleus, and mouse lymphoma tests, all of which have been negative [23]. PA824 has been licensed to the TB Alliance, which has completed preclinical development of the compound and phase 1 studies involving healthy volunteers [24].

PA824 is active in vitro against a variety of both drug-susceptible strains and strains of *M. tuberculosis* with known resistance to standard TB therapies [22]. Although the mechanism of action of PA824 is not well understood, it appears that the compound functions as a prodrug requiring reductive activation of the aromatic nitro group that is mediated, at least in part, by a specific glucose-6-phosphate dehydrogenase or its deazaflavin cofactor [25].

Pharmacokinetic studies of PA824 in the rat indicate that the drug has excellent tissue penetration with tissue exposure, as measured by AUC values in organs such as the lung and the spleen, which are 3- to 8-fold higher than those in plasma. Pronounced in vivo activity has been confirmed in murine studies in which the minimum bactericidal dose of PA824 (which is defined as the minimum dose of PA824 that reduces the lung colony-forming unit count by 99%) is 100 mg/kg/day [26].

A more recently discovered nitroimidazole, OPC67683, is a dihydroimidazo-oxazole under development by Otsuka Pharmaceutical specifically for the treatment of TB. After undergoing single- and multiple-dose trials in normal volunteers, the compound is presently being tested in patients in an EBA trial.

OPC67683 has extremely potent in vitro and in vivo activity against *M. tuberculosis* [27]. In a mouse model of chronic infection, the efficacy of OPC67683 was superior to that of currently used TB drugs. The effective plasma concentration was 0.100 µg/mL, which was achieved with an oral dose of 0.625 mg/kg, confirming the remarkable in vivo potency of the compound. Furthermore, OPC67683 showed no cross-resistance with any of the currently used antituberculous drugs.

MICs against multiple clinically isolated TB strains were on the order of 0.006 µg/mL [28]. On the basis of the relatively similar chemical structure and cross-resistance between the 2 compounds, it is likely that the mechanisms of action of PA824 and OPC67683 will prove to be very similar, if not identical [29]. Furthermore, as with PA824, OPC67683 shows no evidence of mutagenic potential [30].

PYRROLE (LL3858)

Currently, the pyrrole LL3858 is being developed by Lupin and is being evaluated in a multidose phase 1 trial involving healthy volunteers in India. The activity of the pyrroles against *M. tuberculosis* was first reported in 1998 by Deidda et al. [31]. The most potent of the compounds described at that time was BM212, 1,5-diaryl-2-methyl-3-(4-methylpiperazin-1-yl)methylpyrrole, with MICs that ranged from 0.7 to 1.5 $\mu\text{g}/\text{mL}$ against several strains of *M. tuberculosis*. Although the mechanism of action for this class of compounds has not yet been established, the MICs for resistant strains are similar to those for susceptible strains. This would indicate that the pyrroles described by Deidda et al. [31] most likely work through a novel mechanism of action. Some non-TB mycobacterial strains also appeared to be susceptible to BM212, although the MICs were higher than those for *M. tuberculosis*.

On the basis of work by Deidda et al. [31], Lupin synthesized a series of pyrrole compounds, one of which (LL3858) is currently in clinical development for the treatment of TB [32]. This compound has submicromolar MICs and appears to be very active in a mouse model of TB. In combination with currently used antituberculous drugs, LL3858 is reported to sterilize the lungs and spleens of infected animals in a shorter time frame than conventional therapy [33].

DIAMINE (SQ109)

The most recent compound to enter phase 1 clinical trials for TB is SQ109, or *N*-adamantan-2-yl-*N'*-(3,7-dimethylocta-2,6-dienyl)-ethane-1,2-diamine, which is being developed by Sequella. Although originally intended to be an improvement of the first-line TB drug ethambutol, its structural dissimilarity to ethambutol and the potential differences in its intracellular target(s) suggest that it may be a truly novel antimycobacterial agent and not an ethambutol analogue. A diverse combinatorial library of compounds with the 1,2-diamine pharmacophore of ethambutol was synthesized and tested for activity against *M. tuberculosis*. SQ109 was ultimately identified as the most potent compound in the series [34]. In vitro and mouse in vivo studies of SQ109 revealed a MIC against *M. tuberculosis* that was in the range of 0.1–0.63 $\mu\text{g}/\text{mL}$ and a 2- to 2.5-log reduction in counts of colony-forming units in the lung and the spleen. Of interest is the finding that the oral bioavailability of the drug in mice is only 4% [35]. On the basis of the results of formal preclinical toxicology studies, SQ109 recently entered phase 1 studies involving human volunteers.

PREVIOUS TB DRUG PIPELINE

The compounds described above are in clinical development and are thus the furthest advanced in the global TB drug pipeline. There are, however, multiple other earlier-stage preclinical

and discovery programs looking specifically for new anti-TB compounds.

The preclinical and discovery TB drug programs are focused on either known classes of compounds or molecular targets that are in the process of being validated or for which inhibitors are being sought. Examples of the classes of compounds that are being investigated include the macrolides, pleuromutilins, quinolones and 2-pyridones, and oxazolidinones. These classes are being studied through whole-cell screening efforts and are mostly in the lead identification or lead optimization stages of development. Multiple molecular targets are also presently being investigated. Some targets, such as isocitrate lyase, peptide deformylase, and the enoyl acyl carrier protein reductase InhA, have been or are the subject of enzymatic screening to identify hits from which it is hoped that lead molecules can be derived. Other targets, such as malate synthase, the proteasome, specific TB proteases, ribonucleotide reductase, and the stringent response enzyme Rel_{Mtb}, are the subjects of attempts to validate the potential usefulness of inhibiting their function. Most of the validation work is based on genomic silencing of the expression of these proteins, observation of the viability of the resultant organisms, and subsequent reintroduction of the specific genomic material to prove causality. Perhaps the major focus of this early-stage target identification and validation work is the pursuit of targets that are essential to the viability of those TB organisms that are called “persisters” and are believed to be responsible for the prolonged treatment times necessary for the cure of active disease [36]. It is hoped that these projects, in addition to other initiatives, will provide a much-needed steady stream of new anti-TB compounds entering clinical development.

DISCUSSION

The enhanced research and development activity in searching for new TB drugs has raised new opportunities and challenges for the field. It is instructive to note that TB was perhaps the first field in which it was appreciated that combination therapy was critical [37]. Although the initial observation citing the need for combination therapy was based on the emergence of drug resistance when treatment consisted of streptomycin monotherapy, it has since been appreciated that a further benefit of combination therapy is also enhanced effectiveness. Thus, the standard 4-drug regimen used today and outlined above provides for more effective therapy than any one of its component drugs could provide, while it also prevents the emergence of drug resistance.

Therefore, the optimal exploitation of new TB drugs will be achieved by understanding which combination regimen or regimens will be most effective. With the growing pipeline of new compounds for the treatment of TB, the opportunity exists for progression to occur more rapidly by devising novel combi-

nations, regardless of whether the component drugs are old or new. For TB, it is necessary for all sponsors of new TB compounds to examine not only the properties of their individual compounds, as must always be done in the routine discovery and development of any novel compound, but, perhaps most importantly, to determine the optimal regimen. It is the therapeutic potential of the regimen, not any individual component, that will be the key to success.

Clinical development in the field of TB therapeutics is a lengthy process, because there are no accepted surrogate markers for efficacy and because pivotal trials must follow patients to relapse; as a result of the combination of lengthy treatment periods, at least in the control arm, coupled with long follow-up periods, years will be required for the execution of pivotal clinical trials. Therefore, new paradigms for the development of drug regimens need to be entertained and adopted to allow for much earlier investigation of significantly more active combinations of new drugs, whether the compounds are approved or experimental. Work should begin during the preclinical stages of drug development, when novel regimens, regardless of the sponsors of the individual compounds, need to be investigated. Only the best of the potential regimens would be introduced into the lengthy process of phase 2 and 3 clinical trials. The true therapeutic potential of all compounds in the field of TB chemotherapy will be fully exploited and optimized only when the focus of clinical development is the determination of the best combinations from all available drugs.

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