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MINIREVIEW

New Drugs against Tuberculosis: Problems, Progress, and Evaluation of Agents in Clinical Development[▽]

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One-third of the world population is infected with *Mycobacterium tuberculosis* (MTB) and hence at risk of developing active tuberculosis (TB). Each year, 8.8 million patients are newly diagnosed with active TB and 1.6 million patients die of TB. The rapid spread of the human immunodeficiency virus (HIV) has fueled the TB epidemic, especially in sub-Saharan Africa, where 28% of TB patients are HIV positive (176). The current first-line treatment for TB is a multidrug regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol (RHZE). It must be taken for at least 6 months to achieve high cure rates (more than 95% in experimental settings).

PROBLEMS WITH CURRENT TUBERCULOSIS TREATMENT

There are several major problems associated with the currently available TB treatment. First, the duration and complexity of treatment result in nonadherence to treatment. This leads to suboptimal response (failure and relapse), the emergence of resistance, and continuous spread of the disease (168). Second, adverse events in response to anti-TB drugs are common and contribute to the problem of nonadherence (19, 168). Third, the increasing incidence of multidrug-resistant (MDR; resistance to at least rifampin and isoniazid) and extensively drug-resistant (XDR; MDR resistance plus resistance to a fluoroquinolone and an aminoglycoside) TB is a serious concern. Resistant TB occurs in the presence of partially suppressive drug concentrations that enable replication of bacteria, the formation of mutants, and overgrowth of wild-type strains by mutants (selective pressure) (175). The prevalence of MDR TB in new TB cases ranged from 0% in some Western European countries to more than 22% in Azerbaijan (2002 to 2007 survey); 14 of 72 participating countries reported an MDR TB prevalence of more than 5% (177). Second-line drugs for drug-resistant TB are not available everywhere and are less effective, more toxic, and require longer use than first-line drugs (61). Fourth, coinfection of TB and HIV is a problem by itself. Combined treatment of TB and HIV involves a high pill count with associated adherence problems, overlapping toxicity profiles of the antiretroviral and anti-TB drugs, drug interactions between rifampin and the antiretroviral protease inhibitors, and the risk of immune reconstitution syndrome (104). Fifth, prophylactic therapy of latent TB (TB infection without symptoms) with isoniazid is also associated with problems of nonadherence (180). Attempts to shorten treatment with alternative drugs resulted in severe adverse events (64, 150, 155).

The World Health Organization (WHO) has developed the directly observed therapy short course (DOTS) strategy to optimize response and adherence to TB treatment. However, DOTS is labor-intensive and expensive. It causes a high burden on public health programs, especially in developing countries with limited human resources (49). In addition, TB diagnosis in the DOTS strategy is based on sputum microscopy, rather than sputum culture (173). Only advanced pulmonary TB is detected by sputum microscopy, and it requires qualified microscopists (115). Consequently, TB detection rates are suboptimal and resistant *M. tuberculosis* strains are not detected (62, 115).

Clearly, there is an urgent need to improve treatment by either enhancing the application of existing agents or introducing new drugs. Potential new agents should reduce treatment duration, have an acceptable tolerability profile, be active against MDR/XDR TB, be of use in HIV-infected patients with TB, and be active against latent TB (Table 1). The aim of this article is to review the challenges of developing new anti-TB drugs, to present an up-to-date and critical evaluation of new agents in the phase of clinical testing, and to suggest ways forward to improve TB treatment.

CHALLENGES OF DEVELOPING NEW ANTI-TB DRUGS

The rapid development of new anti-TB drugs has been hampered by several obstacles. First of all, the TB drug market is associated with insufficient profit opportunity or investment return to instigate pharmaceutical industries to develop new drugs. The cost of developing a new drug is estimated at $115 to $240 million (39). To be profitable, market prices of new drugs should be relatively high, whereas the cost of the standard regimen is only about $11 per patient (115). In response to the reluctance of pharmaceutical industries, governments and nongovernmental organizations have started to invest in TB drug research and development. In the 1990s, the United States Centers for Disease Control and Prevention (CDC)

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TABLE 1. Required properties of new anti-TB drugs

What a new drug should do	Characteristic(s) required
Simplify treatment or reduce treatment duration	Strong (early) bactericidal and sterilizing activity Low pill count, fixed-dose combinations Allow for intermittent therapy
Have an acceptable toxicity profile	Low incidence of treatment-limiting adverse events No overlapping toxicity profile with other TB drugs
Be active against MDR/XDR TB	No cross-resistance with first-line drugs
Be useful in HIV-infected patients with TB	Minimal interactions with antiretroviral drugs No overlapping toxicity profile with antiretroviral drugs
Be active against latent TB	Activity against dormant bacilli Favorable toxicity profile

established the Tuberculosis Trials Consortium (TBTC). In 2000, private and public sector partnerships formed the Global Alliance for TB Drug Development (GATB), a nonprofit venture that supports the discovery and development of cost-effective new drugs (49). Various other research consortia are testing new drugs in preclinical and clinical trials. Large funding agencies, such as the European & Developing Countries Clinical Trials Partnership (EDCTP) and the Bill & Melinda Gates foundation are supporting these initiatives.

A second challenge in TB drug development is the difficulty to identify new compounds with activity against *M. tuberculosis*. Regimens against TB should kill both the rapidly growing mycobacteria (bactericidal activity) and the persisting mycobacteria in lesions (sterilizing activity) (97). The molecular mechanisms responsible for mycobacterial dormancy (mycobacteria in a state of low metabolic activity and not forming colonies), persistence (drug-susceptible mycobacteria that manage to survive despite continuous exposure to TB drugs), and drug resistance are not yet fully understood (180). The deciphering of the mycobacterial genome in 1998 has been of help in elucidating regulatory mechanisms of metabolic pathways and thereby revealing new drug targets (6, 24).

A next challenge rises with the evaluation of new compounds, as there are currently no animal models available that predict with accuracy the required treatment duration with newly identified compounds (98). The guinea pig model is being explored as an alternative for the mouse model since it resembles TB pathology in humans more closely (73).

The phase of clinical testing of new anti-TB drugs is time-consuming, as the current "gold standard" to assess efficacy of anti-TB regimens in phase III clinical trials is the relapse rate 2 years after completing treatment. In phase II clinical trials, the sputum culture conversion rate after 2 months of treatment is used as a surrogate marker for relapse rate, but the value of this surrogate marker is controversial (95, 120). Several other surrogate markers are under evaluation (120). Large sample sizes are needed in phase III clinical trials to compare the effective standard regimen to a new regimen, even in trials that use a noninferiority design. This contributes to the length of the TB drug development process (45).

Another challenge is the scarcity of trial sites with sufficient research capacity to conduct clinical trials with large sample sizes. Trials should be performed in countries where the TB burden is highest, but the human and infrastructural capacity for performing large, high-quality phase III clinical trials is usually limited in these settings (45). Despite the challenges of TB drug development, studies are being conducted with higher doses of the rifamycins and several new drug candidates have reached the phase of clinical testing.

OLD DRUGS REVISED: HIGHER DOSES OF RIFAMYCINS

Rifampin. Rifampin is considered to be the cornerstone in the current treatment of TB (16). Its standard dose in TB treatment is 10 mg/kg of body weight, corresponding to 600 mg in most populations. Results from studies with mice and early bactericidal activity (EBA) studies in which the fall in CFU during the first 2 days of treatment is studied suggest that the standard dose of rifampin in TB treatment is at the lower end of the concentration-response curve (30, 65, 96).

(i) Mechanism of action. Rifampin inhibits the β-subunit of the RNA polymerase, a multisubunit enzyme that transcribes bacterial RNA (16). Mycobacterial resistance to the rifamycins results from mutations in the *rpoB* gene that codes for the β-subunit of the RNA polymerase (40). About 95% of mutations occur in a region of less than 100 bp of the *rpoB* gene (52). The increasing prevalence of resistance to rifampin and isoniazid (MDR TB) is a serious concern (177).

(ii) Pharmacokinetics. The pharmacokinetics of rifampin in adults treated with the licensed dose (10 mg/kg of body weight) are shown in Table 2 and have been reviewed elsewhere (16). In the 1960s and 1970s, the pharmacokinetics of higher single doses (up to 30 mg/kg) and repeated doses (up to 16 mg/kg) of rifampin in adults were assessed, showing nonlinear increases in exposure (1, 74). More recently, the pharmacokinetics of daily rifampin at 13 mg/kg have been compared with 10 mg/kg in 50 Indonesian patients with pulmonary TB who were treated with the standard regimen (2 months of RHZE followed by 4 months of rifampin and isoniazid [2RHZE/4RH]) (133). Increasing the dose by 30% increased the peak concentration of rifampin in plasma (C_{max}) by 49%; the area under the plasma concentration-time curve (AUC) increased by 65%. AUC is an important parameter for concentration-dependent killers such as the rifamycins. It indicates total exposure to the drug over a

TABLE 2. Pharmacokinetics of rifampin, rifapentine, moxifloxacin, and gatifloxacin

Drug (dose)	Bioavailability (%)	AUC (mg · h/liter)	C_{max} (mg/liter)	t_{max} (h)[a]	$t_{1/2}$ (h)[b]	Plasma protein binding (%)	Reference
Rifampin (10 mg/kg)	68	21.5	8–20	1.5–2.0	2–5	85	1, 16
Rifapentine (600 mg)	Unknown	319–394	10–18	4.8–9	13–20	97	16, 63, 75–77, 102; rifapentine (Priftin) package insert (Hoechst Marion Roussel)
Moxifloxacin (400 mg)	86	26.9–39.3	2.5–4.3 (5.9)[d]	1–2 (0.7)[d]	9.2–15.6 (6.5)[d]	50	88, 119, 146
Gatifloxacin (400 mg)	96	30–51.3[c]	3.4 (3.7)[d]	1.5 (2.4)[d]	6.5–7.8 (5.0)[d]	20	88, 119, 139, 178

[a] t_{max}, time to C_{max}.
[b] $t_{1/2}$, half life.
[c] In steady state.
[d] Multiple doses in patients with pulmonary TB.

certain time period. In a recent EBA study, a 71% increase in AUC was seen with a 67% increase in rifampin dose from 12 to 20 mg/kg after 5 days of monotherapy (30). A higher dose of rifampin is not likely to affect the pharmacokinetics of other anti-TB drugs and antiretroviral drugs more strongly than the standard dose, as rifampin's inductive effect on the cytochrome P450 (CYP450) enzyme system appears to be maximal at a daily dose of 300 mg (105).

(iii) Pharmacodynamics and efficacy. The MIC of rifampin is 0.15 mg/liter in broth culture (16, 53). Rifampin exhibits concentration-dependent activity that correlates best with the AUC/MIC ratio, as was shown in the mouse model (16, 108).

Results from an efficacy study in mice predicted a one-third reduction in TB treatment duration when the rifampin dose was increased by 50% (65). Only a few data are available on the efficacy of regimens based on a higher dose of rifampin in humans. A short regimen of a high dose of rifampin (1,200 mg daily or every other day) with a high dose of isoniazid (900 mg) and streptomycin (1,000 mg) daily yielded almost 100% sputum culture conversion after 3 months (80). All patients remained culture negative for up to 1 year. Sixteen percent of patients relapsed after 12 to 24 months. If pyrazinamide was included in the regimen, treatment response might have improved, as pyrazinamide accelerates sputum culture conversion rates significantly (14). Another study in TB patients did not show a difference in efficacy between 600 mg or 750 mg rifampin daily combined with 300 mg isoniazid for 20 weeks (84). Recently, the EBA of 1,200 mg rifampin daily was studied in 14 patients with pulmonary TB. The mean 2-day EBA was almost twice as high as that of 600 mg rifampin (30).

(iv) Safety and tolerability. Little is known about the tolerability of higher than standard doses of rifampin. Past attempts to use large intermittent rather than daily doses of rifampin were met with a high incidence of the flu-like syndrome. This was ascribed to the intermittency of dosing rather than the size of the dose (16). Daily rifampin at 13 mg/kg was tolerated well by Indonesian patients (133). Grade 1 and 2 hepatotoxicity was more common in the higher-dose group (46% versus 20%; $P = 0.054$), but none of the patients developed serious hepatotoxicity. Five days of rifampin monotherapy at 1,200 mg was tolerated well by patients in the EBA study (30). Higher doses of rifampin did not cause tolerability problems in patients with brucellosis (900 mg, 45 days) or cutaneous leishmaniasis (1,200 mg, divided in two doses, 28 days) (79, 143). The tolerability of rifampin in other diseases was reviewed in 650 patients; it was good with doses up to 1,200 mg but less favorable with doses of 1,800 mg (78).

(v) Discussion. Available data suggest that higher daily doses of rifampin can shorten TB treatment. The maximum tolerable dose of rifampin should be assessed when administered alone and in combination with currently available drugs. The EBA of a range of higher doses of rifampin given alone and in combination should be investigated more extensively, and phase II and III clinical trials with higher than standard doses of rifampin in different multidrug regimens should be performed. Rifampin is cheap and widely available, and physicians have experience with this drug. If increasing the dose of rifampin proves to be safe and effective, this intervention could be implemented broadly and quickly. Drawbacks of rifampin are its inductive effect on the CYP450 enzyme system, which is involved in the metabolism of many other drugs, and the increasing rate of mycobacterial resistance to rifampin.

Rifapentine. Rifapentine (10 mg/kg) was approved for the treatment of pulmonary TB by the U.S. Food and Drug Administration (FDA) in 1998 (rifapentine [Priftin] package insert, Hoechst Marion Roussel, Kansas City, MO). It allows for intermittent dosing at wider intervals, which facilitates observed treatment (102). However, regimens with rifapentine and isoniazid once weekly in the continuation phase of treatment are slightly inferior to regimens with rifampin and isoniazid twice weekly, especially in patients with cavitary TB (152, 165; rifapentine [Priftin] package insert, Hoechst Marion Roussel, Kansas City, MO). A high rate of mycobacterial monoresistance to rifamycins was seen in HIV-infected patients treated with rifapentine and isoniazid (9). The use of rifapentine once weekly has therefore been restricted to HIV-negative pulmonary TB patients without cavitation and with a negative sputum culture after the intensive phase of treatment (63). Higher than standard doses of rifapentine have shown the potency to shorten TB treatment in mice, especially when combined with moxifloxacin (130).

(i) Mechanism of action. Rifapentine is a cyclopentyl rifamycin that, like other rifamycins, inhibits mycobacterial RNA synthesis by binding to the β-subunit of DNA-dependent RNA polymerase (63, 102). Mutations in the gene coding for the β-subunit (*rpoB*) of the mycobacterial RNA polymerase lead to complete resistance to all rifamycins (100, 172).

(ii) Pharmacokinetics. The pharmacokinetic properties of rifapentine in the standard dose in adults are summarized in Table 2 and described elsewhere (16, 76, 77, 101, 102, 123, 127,

151; rifapentine [Priftin] package insert, Hoechst Marion Roussel, Kansas City, MO). When the dose of rifapentine was increased from 600 to 900 or 1,200 mg in 35 TB patients, the AUC increased by 39% or 61%, respectively (170). Rifapentine induces the CYP450 enzyme system to a lesser extent than rifampin (16). Rifapentine autoinduction—the phenomenon that induction of the CYP450 enzyme system also increases metabolism of the drug itself—was recently shown in a phase I study: rifapentine AUC decreased by 20% after 7 days of thrice-weekly rifapentine at 900 mg in 13 healthy volunteers (34). Rifapentine (900 mg thrice weekly) reduced the AUC of moxifloxacin (400 mg daily) by 17% in the same study.

(iii) Pharmacodynamics and efficacy. The MIC of rifapentine ranges from 0.02 to 0.125 mg/liter, i.e., two to four times lower than that of rifampin (8, 18, 31, 32, 101). When adjusted for protein binding, the AUC/MIC ratio for rifapentine in standard dose is 76.6 (AUC/MIC ratio for rifampin, 70.8) (108).

Rifapentine is being evaluated with moxifloxacin as a companion drug. A higher dose of rifapentine (15 mg/kg) with moxifloxacin (100 mg/kg twice per day) in a once-weekly continuation-phase regimen in mice showed better sterilizing activity than once-weekly rifapentine (15 mg/kg) and isoniazid (75 mg/kg) or twice-weekly rifampin (10 mg/kg) and isoniazid (75 mg/kg) (131). A twice-weekly regimen in mice containing rifapentine (15 or 20 mg/kg), pyrazinamide (300 mg/kg), and moxifloxacin (100 mg/kg), preceded by 2 weeks of daily rifampin (10 mg/kg), pyrazinamide (150 mg/kg), and moxifloxacin (100 mg/kg), resulted in stable cure after 4 months of treatment (130). Substitutions of rifampin (10 mg/kg) by rifapentine (10 mg/kg) and of isoniazid (25 mg/kg) by moxifloxacin (100 mg/kg twice per day) in a daily standard regimen in mice lead to bacillus eradication rates twice as fast as the standard regimen (132). A recent study in mice showed that the main sterilizing component in regimens containing rifapentine, moxifloxacin, and pyrazinamide is rifapentine, rather than moxifloxacin (110). An experiment in mice revealed a dramatic increase of bactericidal activity with increased rifapentine dose up to 80 mg/kg in a regimen of rifapentine, moxifloxacin (100 or 400 mg/kg), and pyrazinamide (150 or 600 mg/kg), indicating the potential of higher doses of rifapentine to shorten TB treatment (129).

The International Consortium for Trials of Chemotherapeutic Agents in Tuberculosis (INTERTB) is currently conducting the RIFAQUIN trial with moxifloxacin (400 mg) instead of isoniazid (300 mg) in the standard regimen and with rifapentine once weekly (20 mg/kg for 4 months) or twice weekly (15 mg/kg for 2 months) in the continuation phase.

Rifapentine is also a candidate drug for latent TB. A once-weekly, 3-month regimen of rifapentine (15 mg/kg) plus either moxifloxacin (100 mg/kg) or isoniazid (75 mg/kg) was as active as 6 months of daily isoniazid (25 mg/kg) in monotherapy in a mouse model for latent TB (112). A regimen of rifapentine (900 mg) plus isoniazid (900 mg) once weekly for 12 weeks was tolerated better than daily rifampin (450 to 600 mg) plus pyrazinamide (750 to 1,500 mg) for 8 weeks by patients with latent TB. The regimen protected well against active TB (138).

(iv) Safety and tolerability. A study in 150 HIV-negative TB patients treated with either 600, 900, or 1,200 mg rifapentine plus isoniazid at 15 mg/kg once weekly in the continuation phase showed good tolerability of the 900-mg dose and an insignificant trend towards more adverse events in the 1,200-mg arm (12). In another study (35 patients), no association between the occurrence of adverse events and a higher dose of rifapentine (up to 1,200 mg) was found (170). Two of 14 healthy volunteers developed adverse events (grade 2 hepatitis and a flu-like syndrome with rash) after treatment with daily moxifloxacin (400 mg) and thrice-weekly rifapentine (900 mg) (34).

(v) Discussion. Increasing the dose of rifapentine could shorten TB treatment, especially in combination with moxifloxacin, and may be useful against latent TB as well. Rifapentine will cause fewer problems of drug-drug interactions than rifampin. The optimum higher dose of rifapentine has not yet been defined. The start of renewed rifapentine registration trials with higher doses has been announced by Sanofi-Aventis (presentation by D. Leboulleux at TBTC meeting, 16 to 17 May 2008, Toronto, Canada).

Rifabutin. Rifabutin is mainly used for the prevention and treatment of disseminated *Mycobacterium avium* complex disease in patients with advanced HIV infection (15). The MIC of rifabutin against rifampin-susceptible MTB strains is $\leq$0.08 mg/liter, 8 times less than the MIC of rifampin against the same strains (31, 54, 156). In TB patients, the activity of rifabutin was not greater than that of rifampin (50, 94). Furthermore, the occurrence of dose-related ($\geq$450 mg) adverse events, such as polyarthralgia, uveitis, flu-like syndrome, and hepatitis (125, 142), is likely to deter any investigation into the efficacy of higher than standard doses of rifabutin in TB treatment.

NEW DRUGS FOR TB TREATMENT

Fluoroquinolones. The fluoroquinolones are a promising class of drugs for the treatment of TB (43). In particular, they are distributed broadly throughout the body, including within cells, which explains their efficacy against intracellular mycobacteria (10, 46, 117, 148). The fluoroquinolones are registered as second-line anti-TB drugs (11, 103, 174). Moxifloxacin and gatifloxacin are candidates for shortening TB treatment, since they have the lowest MICs (3, 38, 41, 44, 108) and greatest bactericidal activity, as expressed in the rate of fall in CFU count (44, 56, 66, 140). The approved dose for moxifloxacin and gatifloxacin is 400 mg/day (Avelox [moxifloxacin hydrochloride] tablets, final draft package insert; FDA). While the potential of moxifloxacin and gatifloxacin to shorten TB treatment is being investigated in clinical trials, a new generation of quinolones, including the promising TBK 613, is being developed in preclinical research (M. Spigelman, presented at the 1st International Workshop on Clinical Pharmacology of Tuberculosis Drugs, Toronto, Canada, 2008).

(i) Moxifloxacin. *(a) Mechanism of action*. Moxifloxacin is a broad-spectrum 8-methoxy fluoroquinolone with activity against both gram-positive and gram-negative bacteria, including anaerobes (146, 147). It inhibits bacterial DNA gyrase, an enzyme that is essential for the maintenance of DNA supercoils, which are necessary for chromosomal replication (25, 92, 141, 145). The development of mycobacterial resistance to fluoroquinolones has been described in MDR strains (13, 58, 163) and in strains from HIV-infected TB patients with a low

CD4 count (47, 48). Fluoroquinolone resistance is due to stepwise mutations in the quinolone resistance-determining region of the mycobacterial *gyrA* and *gyrB* genes (46). No cross-resistance with the first-line anti-TB drugs has been shown (46, 47, 56), but cross-resistance within the group of fluoroquinolones was proved (2, 46, 72). A study in newly diagnosed TB patients showed higher rates of *M. tuberculosis* resistance to fluoroquinolones in patients with prior exposure to fluoroquinolones than in patients who were fluoroquinolone naïve (45). Other studies did not find such an association (13, 58).

(b) Pharmacokinetics. The pharmacokinetic properties of moxifloxacin in humans are summarized in Table 2. Moxifloxacin is metabolized by glucuronidation and sulfation (phase II metabolism) rather than by CYP450-mediated (phase I) metabolism (106). Up to 20% of moxifloxacin is excreted unaltered in urine and 25% in feces (146). The AUC from 0 to 24 h (AUC_{0-24}) of moxifloxacin decreased by 27 to 31% when coadministered with rifampin (106, 171). This could be due to induction of phase II metabolic enzymes (uridine diphosphatase, glucuronosyltransferase, and sulfotransferase) by rifampin (106). The clinical relevance of this interaction is unknown.

(c) Pharmacodynamics and efficacy. In vitro studies with moxifloxacin show MICs of 0.25 to 0.50 mg/liter (41, 66, 128, 140). The bactericidal activity of fluoroquinolones is generally considered to be concentration dependent (10, 178), although a recent report showed time-dependent killing as well (140). The ratio of AUC to MIC is thought to be the best predictor of fluoroquinolone efficacy in gram-negative, fast-multiplying bacteria (46, 140, 178). It was shown in vitro and in vivo that the greatest bactericidal activity occurs at AUC/MIC ratios of 100 to 125 or more (178). While it is unclear whether this also applies to the slowly multiplying *M. tuberculosis*, this observation would suggest that moxifloxacin is the fluoroquinolone with greatest efficacy, followed by gatifloxacin (AUC/MIC ratios of 96 and 68, respectively, derived from in vitro and in vivo work) (46). Aside from the AUC/MIC ratio, the other important indicator of efficacy of concentration-dependent killers is the C_{max}/MIC ratio, which should be more than 8 to 12 for effective killing of gram-negative bacteria (36, 108, 124, 178). Data adapted from a single-oral-dose study in healthy volunteers showed that the C_{max}/MIC_{90} ratio of moxifloxacin (400 mg) is 8.6 (88, 108).

In vitro studies and studies in mice showed enhanced bactericidal activity of moxifloxacin and isoniazid when coadministered (41, 66, 85, 99, 179). Ethambutol adversely affected the activity of moxifloxacin in vitro: it reduced moxifloxacin efficacy by 80% (85). Moxifloxacin (100 mg/kg) was able to reduce the time to culture conversion in mice by 2 months when replacing isoniazid in the standard 6-month regimen (113, 114). This reduction was not found when moxifloxacin was either added to the standard regimen or when it replaced any of the other drugs. It is hypothesized that the superior activity of 2 months of rifampin plus moxifloxacin plus pyrazinamide followed by 4 months of rifampin plus moxifloxacin (2RMZ/4RM) to 2RHZ/4RH is caused by a synergistic activity of rifampin, moxifloxacin, and pyrazinamide or antagonistic activity of rifampin, isoniazid, and pyrazinamide (113).

Moxifloxacin efficacy has also been shown in humans. EBA studies in newly diagnosed pulmonary TB patients showed comparable activity of moxifloxacin (400 mg) and isoniazid (300 mg or 6 mg/kg) (51, 122). The VT_{50} (the time needed to kill 50% of viable bacteria) of isoniazid was lower than that of both rifampin and moxifloxacin. The EBA and VT_{50} of combined moxifloxacin and isoniazid did not differ significantly from the two drugs in monotherapy. Based on these results, no antagonistic effect of adding moxifloxacin to the standard, isoniazid-containing regimen is expected, nor will it enhance the bactericidal activity of the regimen (42). The effect of replacing ethambutol with moxifloxacin in the standard regimen on the 2-month sputum culture conversion rate was analyzed in 277 patients with pulmonary TB from African and North American sites (17). No difference in percentage of negative cultures after 2 months of treatment (71% and 71%) was found. However, more patients treated with moxifloxacin had negative cultures after 4 weeks of treatment than patients treated with ethambutol (37% versus 26%; $P = 0.05$). A comparable study is ongoing in Brazil (71). The Gatifloxacin for TB Study Team (OFLOTUB) performed a phase II clinical trial in which ethambutol in the standard regimen was replaced by gatifloxacin, moxifloxacin, or ofloxacin (135). The regimen with moxifloxacin caused the fastest decrease in CFU during the early phase of a biexponential fall (in a nonlinear model that differentiates between quickly and slowly eliminated bacilli) (28, 135). Both moxifloxacin and gatifloxacin accelerated bacillary elimination significantly in the late phase. The percentage of negative sputum cultures after 2 months of treatment did not differ significantly between the treatment groups (82% versus 77% on solid medium and 40% versus 44% on liquid medium [in MGIT] for moxifloxacin versus gatifloxacin, respectively) (135). Two-month sputum culture conversion rates have also been evaluated in a double-blind randomized controlled trial in which isoniazid in the standard regimen was replaced with moxifloxacin (TBTC study 28). Culture conversion after 8 weeks of treatment was achieved in 60% of patients treated with the moxifloxacin-containing regimen and in 55% of patients using isoniazid (J. Grosset, presented at the 1st International Workshop on Clinical Pharmacology of Tuberculosis Drugs, Toronto, Canada, 2008). A multicenter three-armed REMoxTB trial in which the standard regimen is compared to (i) a regimen of 2RHZM/2RHM and (ii) a regimen of 2RMZE/2RM has recently started. The possibility of combining moxifloxacin with rifapentine, two agents with a long half-life, is explored in the RIFAQUIN trial (see section about rifapentine) (85, 130, 131, 167). Finally, moxifloxacin could be of use in the treatment of latent TB. The combination of 3 months of once-weekly moxifloxacin and rifapentine was as effective as 6 months of isoniazid monotherapy in a mouse model for latent TB (112).

(d) Safety and tolerability. A single dose moxifloxacin of up to 800 mg was tolerated well (88, 146, 147). Little is known about the long-term tolerability in TB patients. Moxifloxacin (400 mg, administered for an average of 6.3 months) was withdrawn in 4 of 38 TB patients because of a major adverse event (including nausea, vomiting, muscle pain, tremors, insomnia, and dizziness), but no irreversible or fatal events occurred (23). In another study, no toxicity was experienced by patients who were treated with moxifloxacin, rifampin, and isoniazid for 6 months (164). Prolongation of QT time has been seen in patients using moxifloxacin for a variety of other bacterial infec-

tions (Avelox [moxifloxacin hydrochloride] tablets, final draft package insert; FDA). In February 2008, Bayer distributed a "Dear Doctor" letter warning physicians about rare but severe hepatological and dermatological adverse events associated with moxifloxacin. In July 2008 the European Medicines Agency (EMEA) sent out a review on the association of moxifloxacin and hepatological problems. It was concluded that the benefits of moxifloxacin in treatment of respiratory tract infections outweigh the risks, but its use should be restricted (37).

(e) Discussion. Moxifloxacin is a promising drug that could shorten TB treatment. However, the optimal dose of moxifloxacin in TB treatment must be evaluated with respect to the recently observed decrease in AUC_{0-24} when coadministered with rifampin. Furthermore, concerns have been raised about the development of mycobacterial resistance against fluoroquinolones and the association between resistance and the widespread use of fluoroquinolones for other infections (35). The efficacy studies in mice and humans revealed ambiguous results. While culture conversion rates increased in mice when isoniazid was replaced by moxifloxacin in the standard regimen, this was not shown in humans, nor did moxifloxacin show better early bactericidal activity than isoniazid in humans. Replacing ethambutol by moxifloxacin in the standard regimen in humans also did not improve culture conversion rates convincingly. The optimal moxifloxacin-including regimen has yet to be found. Finally, the adverse events of moxifloxacin require extended evaluation.

(ii) Gatifloxacin. *(a) Mechanism of action*. Like the other fluoroquinolones, gatifloxacin blocks the bacterial DNA gyrase, thereby preventing chromosomal replication (25, 92, 141, 145). Gatifloxacin and moxifloxacin show cross-resistance (2, 46, 72). The mechanism of resistance is described in the section on moxifloxacin.

(b) Pharmacokinetics. Table 2 shows the pharmacokinetic properties of gatifloxacin. The elimination route of gatifloxacin is predominantly renal; 77% of the oral dose is excreted in urine (88). The elimination time of gatifloxacin was prolonged in 22 healthy volunteers who received a single dose of a fixed-dose combination of rifampin, isoniazid, pyrazinamide, and gatifloxacin (600, 300, 1,600, and 400 mg, respectively). It led to a 14% increase in AUC of gatifloxacin (and a 19% reduction of rifampin AUC) (93).

(c) Pharmacodynamics and efficacy. The MICs of gatifloxacin range from 0.2 to 0.5 mg/liter (38, 108, 128, 153, 154), resulting in AUC/MIC_{90} ratios of 60 to 68 and C_{max}/MIC_{90} ratios of 6.8 to 8.4 (adapted from results of studies in mice and healthy volunteers) (46, 108).

In vitro studies and studies in mice showed improved activity of rifampin and isoniazid when gatifloxacin was added and even more when the regimen also included pyrazinamide (26, 81, 87). Ethambutol interfered with gatifloxacin in vitro as it did with moxifloxacin: it caused a remarkable increase in the MIC_{90} of gatifloxacin (87). When gatifloxacin (100 mg/kg) was combined with ethionamide (75 mg/kg) and ethambutol (100 mg/kg) in mice, greater bactericidal activity was achieved than with a 20 mg/kg rifampin plus 25 mg/kg isoniazid regimen (3). The addition of pyrazinamide (150 mg/kg) to gatifloxacin/ethionamide/ethambutol did not improve activity but yielded stable cures after 12 weeks of treatment and 8 weeks of observation, whereas the regimen without pyrazinamide did not (27).

A multicenter trial of the OFLOTUB consortium is enrolling patients at five African sites. It compares the efficacy and tolerability of a 4-month regimen of 2 months of rifampin plus isoniazid plus pyrazinamide plus gatifloxacin followed by 2 months of rifampin plus isoniazid plus gatifloxacin (2RHZG/2RHG) to the standard 2RHZE/4RH regimen (71). The OFLOTUB consortium also evaluated the fall in CFU count in patients enrolled in the same trial (see section on moxifloxacin) (135).

(d) Safety and tolerability. A single dose of gatifloxacin (400 mg) was tolerated well (88). Only mild adverse events were reported in patients with respiratory tract infections who were treated with gatifloxacin at 100 to 400 mg/day for 5 to 12 days (169). An increased risk of dysglycemia was described in elderly patients using gatifloxacin for a variety of bacterial infections (118). Elderly patients with hypoglycemia or hyperglycemia were 4 or 17 times more likely to have used gatifloxacin than controls. The results of this study forced the OFLOTUB study group to tighten their exclusion criteria and to strengthen their monitoring of dysglycemic events (71). No dysglycemic events related to gatifloxacin use were reported in an earlier study that focused on the fall in CFU (135).

(e) Discussion. Gatifloxacin has many of the favorable features of moxifloxacin. However, the risk of mycobacterial resistance development and the recently found association between gatifloxacin and dysglycemic events are concerns. In vitro studies and studies in mice revealed contradictory results. While ethambutol reduced gatifloxacin activity in vitro, the combination of ethambutol, ethionamide, and gatifloxacin was highly effective in mice.

Diarylquinolines. Diarylquinolines have been identified in a process of screening various compounds for potential anti-TB activity (4). The most active diarylquinoline (TMC207, also called R 207910, or compound J) is currently being evaluated in phase II clinical trials at a dose of 400 mg/day (71).

(i) TMC207. *(a) Mechanism of action*. TMC207 inhibits the mycobacterial ATP synthase enzyme (4, 29). TMC207 has shown equal activity in susceptible and MDR strains. No cross-resistance with available drugs is expected since the target of the diarylquinolines differs from that of the currently available anti-TB drugs (4, 161). Mycobacteria that are resistant to TMC207 in vitro show mutations in the *atpE* gene, which encodes subunit c of ATP synthase (121).

(b) Pharmacokinetics. Oral administration with a meal results in a twofold increase of serum TMC207 concentrations (71). The C_{max} is reached after 5 h; the half-life is long: about 24 h in humans. The pharmacokinetics of TMC207 show linearity with dose (4). TMC207 is metabolized by the CYP450 3A4 enzyme to an active *N*-monodesmethyl metabolite (M2) (134). Rifampin reduces plasma TMC207 concentrations by 50%; however, a recent study in mice showed significant activity of TMC207 even with a 50% reduction in exposure, indicating that the relevance of this interaction is questionable (71, 86). No drug-drug interactions were observed between TMC207 and isoniazid plus pyrazinamide (K. De Beule and R. van Heeswijk, presented at the 1st International Workshop on Clinical Pharmacology of Tuberculosis Drugs, Toronto, Canada). Steady-state concentrations in

humans take more than 7 days to establish due to the extensive tissue distribution of TMC207 (71).

(c) Pharmacodynamics and efficacy. In vitro studies show MICs ranging from 0.030 to 0.120 μg/ml in both fully susceptible and MDR strains (4, 59). The in vitro activity of TMC207 did not increase with increasing drug concentration, suggesting time-dependent rather than concentration-dependent killing. The activity of TMC207 is limited to mycobacterial species only (4).

Treatment with TMC207 (25 mg/kg), isoniazid (25 mg/kg), and pyrazinamide (150 mg/kg), and with TMC207, rifampin (10 mg/kg), and pyrazinamide yielded 100% negative lung cultures in mice after only 2 months of treatment. When any of the drugs in the standard regimen was replaced with TMC207 (25 mg/kg), the bactericidal activity improved (4). Regimens based on the standard anti-TB drugs and/or moxifloxacin that contained both pyrazinamide and TMC207 were more active than regimens without these two drugs. A 2-month regimen of once-weekly TMC207 (125 mg/kg), pyrazinamide (300 mg/kg), and rifapentine (15 mg/kg) was more active than rifampin (10 mg/kg), isoniazid (25 mg/kg), and pyrazinamide (150 mg/kg) five times per week (166). These results suggest synergistic activity of TMC207 and pyrazinamide in mice (60).

The guinea pig model was used to demonstrate sterilizing activity of TMC207. Almost complete eradication of primary and secondary lung lesions was achieved after 6 weeks of TMC207 monotherapy (15 mg/kg), whereas the standard regimen had limited effect (83).

An EBA study was done in which patients with pulmonary TB received various doses of TMC207, rifampin, or isoniazid in monotherapy for 7 days. The EBA of both rifampin and isoniazid was better than that of TMC207. Only a dose of 400 mg TMC207 showed an EBA between days 4 and 7 of the same magnitude as that of rifampin and isoniazid in the same period (134). Because of the pharmacokinetic interaction between rifampin and TMC207, the primary focus in the development of TMC207 is now on regimens without rifampin. Recently, a multicenter phase II study in 200 patients with MDR TB was started in which a standard second-line, rifampin-free regimen is compared with the same regimen plus TMC207 (71).

(d) Safety and tolerability. No serious adverse events were reported in single-dose (up to 700 mg) and multiple-dose (up to 400 mg) studies in healthy, male volunteers (see suppporting data in reference 4). In the EBA study, no adverse events related to the study drugs were encountered (71, 134).

(e) Discussion. TMC207 is a new, promising compound that has greater bactericidal activity than the standard first-line regimen in mice. It is active in susceptible and MDR strains. However, the EBA of TMC207 in humans is not as good as that of rifampin and isoniazid. The variability of serum TMC207 concentrations with food intake is a disadvantage. TMC207 could be of use in rifampin-free regimens against MDR and XDR TB. Interactions between TMC207 and rifapentine, another agent with a long half-life, should be investigated.

Nitroimidazopyrans. The nitroimidazopyrans have been derived from the bicyclic nitroimidazofurans that were originally developed for cancer chemotherapy but also exhibited activity against actively growing and dormant *M. tuberculosis* (116, 149). The compounds are structurally related to metronidazole (7, 149). PA-824 (a nitroimidazo-oxazine) and OPC-67683 (a dihydroimidazo-oxazole) are currently being investigated in clinical trials (144).

(i) PA-824. *(a) Mechanism of action*. PA-824 is a prodrug that needs the mycobacterial glucose-6-phosphate dehydrogenase (FDG1) or its cofactor, coenzyme F_{420}, to be transformed into an active form (89, 149). Activated PA-824 inhibits the synthesis of proteins and cell wall lipids. PA-824 activity is limited to *M. tuberculosis* complex (90, 149). PA-824 is active in susceptible and resistant *M. tuberculosis* strains. No cross-resistance with standard anti-TB drugs has been observed (149). Mutations in the mycobacterial genes *fbiA*, *fbiB*, and *fbiC* lead to impaired coenzyme F_{420} synthesis and therefore resistance to PA-824 (21, 22). Mutations in the Rv3547 gene, encoding a protein with unknown function, have been described in PA-824 resistant strains. Complementing these mutants with intact Rv3547 fully restored the ability of the mutants to metabolize PA-824. This suggests mediation of a highly specific protein, next to FGD1 and coenzyme F_{420}, in PA-824 activity (89).

(b) Pharmacokinetics. Serum PA-824 concentrations in mice are not influenced by coadministration of rifampin, isoniazid, and pyrazinamide in various combinations, and PA-824 does not influence concentrations of the latter drugs in serum (109). PA-824 is currently being investigated in phase I clinical trials under the auspices of the GATB. Studies in healthy volunteers showed a half-life of about 18 h and a time to reach C_{max} of 4 to 5 h. About 65% of PA-824 is excreted in urine and 26% in feces (71).

(c) Pharmacodynamics and efficacy. In vitro studies showed MICs of PA-824 against fully susceptible and MDR strains ranging from 0.015 to 0.25 μg/ml. PA-824 activity is concentration dependent (82, 149, 162).

The bactericidal activity of PA-824 (25 to 50 mg/kg) was comparable to that of isoniazid (25 mg/kg) in mice and guinea pigs (82, 149, 159, 162) and to those of rifampin (20 mg/kg) and moxifloxacin (100 mg/kg) in mice (82). PA-824 showed greater activity than isoniazid and moxifloxacin in vitro and in mice and comparable activity to combination therapy with rifampin and isoniazid (57, 82, 162). PA-824 (100 mg/kg) has been incorporated in the standard regimen in mice to evaluate its potential to shorten treatment duration. Only the regimen in which isoniazid was replaced with PA-824 achieved faster lung culture conversion and a lower CFU count after 2 months of treatment than the standard regimen. However, relapse rates were the same in these regimens (109). The sterilizing activity of a regimen containing PA-824 (100 mg/kg), moxifloxacin (100 mg/kg), and pyrazinamide (150 mg/kg) was recently found to be better than that of rifampin (10 mg/kg), isoniazid (25 mg/kg), and pyrazinamide (150 mg/kg) in mice, indicating that PA-824 could be incorporated in a rifampin-free regimen to treat MDR TB (111).

PA-824 (100 mg/kg) was highly active in a mouse model for latent TB when combined with moxifloxacin (100 mg/kg) (112). An extended EBA study in humans with daily PA-824 doses of 200 to 1,200 mg over 14 days is ongoing in South Africa. Results are expected soon (M. Spigelman, presented at the 1st International Workshop on Clinical Pharmacology of Tuberculosis Drugs, Toronto, Canada, 2008).

(d) Safety and tolerability. Single PA-824 doses ranging from 50 to 1,500 mg were tolerated well by healthy volunteers, but

multiple doses of 1,000 mg were associated with a moderate, reversible increase in creatinine. This renal effect of PA-824 was found to be of insignificant clinical relevance in consecutive studies (M. Spigelman, presented at the 1st International Workshop on Clinical Pharmacology of Tuberculosis Drugs, Toronto, Canada, 2008).

(e) Discussion. In mice, PA-824 seems most promising in regimens without isoniazid. However, no regimen in which PA-824 was combined with the standard, first-line anti-TB drugs in mice has convincingly shown the potential of shortening treatment duration. No additive or synergistic activity of PA-824 with the first-line drugs has been shown. PA-824 could be developed for the treatment of latent TB together with moxifloxacin, since the combination was highly active in a mouse model for latent TB. Its activity against drug-susceptible and drug-resistant *M. tuberculosis* strains must be evaluated in regimens with second-line (or new) anti-TB drugs.

(ii) OPC-67683. *(a) Mechanism of action*. OPC-67683 is a mycolic acid biosynthesis inhibitor (137). While isoniazid inhibits the synthesis of all mycolic acid subclasses, OPC-67683 inhibits methoxy and ketomycolic acid synthesis only (91). OPC-67683 has to be activated by *M. tuberculosis* to exert its activity. Mutations in the mycobacterial Rv3547 gene found in OPC-67683 resistant *M. tuberculosis* strains suggest that this gene codes for the key enzyme in activating OPC-67683 (as well as PA-824) (91, 158).

(b) Pharmacokinetics. Studies in healthy volunteers showed a more than dose-proportional increase in systemic exposure to OPC-67683 with a stepwise increase of the dose from 5 to 400 mg (71). Absorption rates were higher when OPC-67683 was administered with a high-fat meal. OPC-67683 was consecutively analyzed in a different administration formula. This improved systemic absorption (71). The newer formula is used in ongoing evaluations of OPC-67683. OPC-67683 does not affect the activity of liver microsome enzymes, nor is it affected by activated liver enzymes (91). Interactions with drugs that are metabolized by these enzymes are therefore not expected.

(c) Pharmacodynamics and efficacy. The MICs of OPC-67683 are equal in drug-susceptible and -resistant *M. tuberculosis* strains and range from 0.006 to 0.024 μg/ml (91, 137). OPC-67683 exhibits concentration-dependent activity also against intracellular *M. tuberculosis* (91, 136).

The in vitro intracellular activity of OPC-67683 was better than that of isoniazid and PA-824 and as good as that of rifampin (91). OPC-67683 showed sterilizing activity that was superior to that of isoniazid and equal to that of rifampin in an in vitro model of drug-tolerant *M. tuberculosis*, representing semidormant bacilli (136). No antagonism of OPC-67683 with rifampin, isoniazid, ethambutol, and streptomycin was shown in vitro (91).

In mice, a regimen of OPC-67683 (2.5 mg/kg), rifampin (5 mg/kg), and pyrazinamide (100 mg/kg) achieved faster eradication of bacilli than the standard RHZE regimen (5, 10, 100, and 100 mg/kg, respectively). Whereas no mycobacterial colonies were detected after 4 months of treatment with the OPC-67683-containing regimen, colonies were still detected after 6 months of treatment with the standard regimen (91).

The EBA of 400 mg OPC-67683 in patients with pulmonary TB was low during the first 4 days. From day 4 onwards, a significant decrease in CFU was seen. This activity is currently being explored in an extended (14 days) EBA study (71).

(d) Safety and tolerability. OPC-67683 in multiple doses up to 400 mg was tolerated well by healthy volunteers. No serious adverse events were reported (71).

(e) Discussion. OPC-67683 is a promising new anti-TB drug with bactericidal and sterilizing activity in vitro and in mice. It could be useful in treatment of MDR and XDR TB. Its optimal formulation and its role in TB treatment in humans still need to be established. The low EBA is not favorable.

Diamines. A library of more than 60,000 compounds was generated by synthesizing ethambutol analogues with 1,2-diamine pharmacophore (20, 67, 70). So far, the most promising diamine candidate from this library for TB treatment is SQ109 (70).

(i) SQ109. *(a) Mechanism of action*. SQ109 inhibits mycobacterial cell wall synthesis; the exact target is not yet known (20). Since resistance rates to SQ109 are low, it is thought that two mycobacterial gene changes are needed to result in resistance. Therefore, SQ109 may have more than one target in *M. tuberculosis* (71).

(b) Pharmacokinetics. SQ109 undergoes a first-pass step in the liver before it enters the systemic circulation. Liver microsomes convert SQ109 in four predominant metabolites. CYP2D6 and CYP2C19 enzymes are involved in SQ109 metabolism; CYP3A4 has little effect on SQ109 (68). It has been suggested that SQ109 is a prodrug that needs activation by mycobacterial CYP enzymes (20). Results from a recent drug-drug interaction study in rats suggest that SQ109 induces its own metabolism (55). SQ109 binding to plasma proteins ranges from 6 to 23% in humans, mice, rats, and dogs (68). Binding to tissue proteins is higher than that to plasma proteins (20). SQ109 has a long half-life (61 h) in humans (160).

(c) Pharmacodynamics and efficacy. The MIC of SQ109 ranged from 0.16 to 0.64 mg/liter in susceptible and drug-resistant MTB isolates, including ethambutol-resistant strains (20, 71). SQ109 also exhibits bactericidal activity within macrophages (67, 69, 70). Its activity is concentration dependent (69).

Synergistic activity was shown in vitro between SQ109 and isoniazid and especially rifampin. Synergy was even present in rifampin-resistant strains. Streptomycin had an additive effect on SQ109 activity; ethambutol and pyrazinamide had no effect on the activity of SQ109 (20). Four weeks of monotherapy with SQ109 (0.1 to 25 mg/kg) in mice resulted in a reduction of mycobacterial load in spleen and lungs that was comparable to the effect of treatment with ethambutol (100 mg/kg) but less than that of treatment with isoniazid (25 mg/kg) (69). When ethambutol (100 mg/kg) was substituted for by SQ109 (10 mg/kg) in an 8-week regimen of rifampin (20 mg/kg) and isoniazid (25 mg/kg), with or without pyrazinamide (150 mg/kg), in mice with chronic TB, the mycobacterial load was 1.5 $\log_{10}$ lower than with the standard RHZE regimen (107).

(d) Safety and tolerability. No adverse events were reported in a phase I single-dose study (71). Multiple doses of SQ109 (up to 300 mg) were tolerated well by healthy volunteers (160).

(e) Discussion. SQ109 is a potential anti-TB drug that has entered phase I/II clinical trials. It has low MICs against both susceptible and resistant MTB strains. SQ109 has different and

TABLE 3. Overview of anti-TB drugs in the clinical pipeline

Drug	Trial phase	Potential to shorten treatment	Acceptable toxicity profile	Active against MDR TB	Useful in HIV-infected patients with TB	Active against latent TB[a]	Interaction with rifampin
High-dose rifampin	II	Yes	To be established	Limited	Yes, but not coadministered with protease inhibitors	Yes, but not first choice	NA[b]
High-dose rifapentine	II	Yes[c]	To be established	Limited	To be established	Yes	NA
Moxifloxacin	III	Yes	Yes	Yes	Yes	Yes[c]	Yes; reduced AUC of moxifloxacin by 30%
Gatifloxacin	III	Yes	Yes (caution: dysglycemia in elderly)	Yes	Yes	Unkown	Possible
TMC207	II	Yes[c]	To be established	Yes	Unknown	Unknown	Yes; reduced serum TMC207 concn by 50%
PA-824	II	Doubtful	Yes (moderate increase in creatinine observed)	Yes	Unknown	Yes[c]	No
OPC-67683	I/II	Yes[c]	To be established	Yes	Unknown	Unknown	No
SQ109	I/II	Yes[c]	To be established	Yes	Unknown	Unknown	Synergism in vitro
LL3858	I	Yes[c]	Unknown	Yes	Unknown	Unknown	Synergism in vitro

[a] Latent TB is the situation in which a host is infected with *Mycobacterium tuberculosis* but has not developed symptoms.
[b] NA, not applicable.
[c] Results from preclinical data.

more favorable properties than ethambutol, suggesting that it should be regarded as a truly new diamine, and not just as an ethambutol analogue. SQ109 could be included in regimens containing rifampin and isoniazid, since synergism with both drugs has been shown. Clinical trials are ongoing to establish its future role in TB treatment.

Pyrroles. In the search for compounds with activity against mycobacteria and fungi, several pyrrole derivatives have been developed. LL3858 is being investigated in phase I clinical trials (5, 71). A fixed-dose combination called LL3848, containing LL3858 and the standard, first-line anti-TB drugs, is also being developed (126).

(i) LL3858. *(a) Mechanism of action*. The mycobacterial target of LL3858 is not yet known. Since LL3858 is active against *M. tuberculosis* strains that are resistant to available anti-TB drugs, the target probably differs from the targets of the currently used drugs.

(b) Pharmacokinetics. No data about the pharmacokinetics of LL3858 in humans are available yet (157).

(c) Pharmacodynamics and efficacy. The MIC_{90} of LL3858 for MTB is 0.25 μg/ml. LL3858 exhibits concentration-dependent activity (5). LL3858 (12.5 mg/kg) reduced the mycobacterial load in mice to a greater extent than isoniazid. Regimens of 8 weeks of LL3858, isoniazid, and rifampin with or without pyrazinamide sterilized lungs and spleens of 3 of 6 and 4 of 6 mice, respectively. When the treatment period was extended to 12 weeks, complete sterilization of the target organs was achieved in 6 of 6 mice (5, 157).

(d) Tolerability. The tolerability of LL3858 is currently being investigated in phase I clinical trials (157).

(e) Discussion. The pyrroles are a new class of compounds with promising activity against *M. tuberculosis*, atypical mycobacteria, and fungi. The pyrrole derivative LL3858 has reached phase I clinical trials.

DISCUSSION: THE WAY FORWARD

Several new drugs for TB treatment are being evaluated in clinical trials. Available data reveal different properties of the agents (Table 3) and provoke speculation about future directions. Higher doses of the rifamycins are promising and may be the first to be implemented in a regimen of shorter duration. Moxifloxacin and gatifloxacin might shorten TB treatment, possibly in combination with rifapentine. Coadministration of moxifloxacin and PA-824 could be active against latent TB. PA-824 and TMC 207 are candidates for a rifampin-free regimen for treatment of MDR and XDR TB. SQ109, on the other hand, could enhance the activity of rifampin-containing regimens.

Unfortunately, shorter treatment regimens based on the new agents discussed here are likely to take at least another decade to be fully developed and implemented in clinical practice. Since not all new agents will succeed in clinically useful regimens, and since only a few drugs are currently in preclinical development, more new agents are needed. Therefore, urgent attention should be paid to the development of new drugs; this requires more involvement of large pharmaceutical industries. The development of new drugs should get a programmatic approach in which a series of consecutive studies are properly planned, while keeping the desired end product in mind (J. Gheuens, presented at the TBTC meeting, Toronto, Canada, 2008). Moreover, the development of various agents must be coordinated, since a single new drug might not be very promising in a regimen with the standard anti-TB drugs, but could be highly active in combination with other new drugs. The potential of bifunctional molecules with more than one target in MTB is currently being explored (M. Spigelman, presented at the 1st International Workshop on Clinical Pharmacology of Tuberculosis Drugs, Toronto, Canada, 2008). Initiatives such as the GATB have an important role in facilitating cooperation in drug development.

Ways to shorten clinical trials with new TB drugs should be explored. The evaluation of surrogate biomarkers that predict the likelihood of relapse, such as serial sputum colony counts and molecular markers, should be incorporated into clinical trials as much as possible. Validated surrogate markers will reduce the time it takes to assess the efficacy of new agents.

Special groups of patients should be addressed in clinical trials. Since TB is a major problem in patients with HIV, these patients should be included in clinical research on new anti-TB drugs as early as possible. Likewise, the development of improved TB treatment regimens for children should get high priority (33). Effective treatment regimens against MDR and XDR TB should be developed urgently.

To facilitate clinical trials, research capacity should be strengthened in developing countries, where the TB burden is highest.

Finally, control of the TB epidemic implies more than developing new drugs. The diagnostic and therapeutic facilities of health care centers in developing countries should be improved, and the socioeconomic status and general welfare of patients (including nutritional and HIV status) should be addressed to help eradicate TB.

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ADDENDUM IN PROOF

The potential of PA-824 to shorten TB treatment duration when combined with the standard, first-line anti-TB drugs was recently reassessed in the mouse model (R. Tasneen, S. Tyagi, K. Williams, J. Grosset, and E. Nuermberger, Antimicrob. Agents Chemother. **52**:3664–3668, 2008). Mice treated with rifampin (10 mg/kg), PA-824 (100 mg/kg), and pyrazinamide (150 mg/kg) remained free of relapse after 4 months of treatment, while 15% of mice treated with a 4-month regimen of rifampin, isoniazid (25 mg/kg), and pyrazinamide relapsed. The combinations of PA-824 and pyrazinamide and of PA-824 and rifampin displayed synergistic activity in the same study. Results from this study hold promise for PA-824 to shorten TB treatment duration in combination with first-line drugs.

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