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New drugs for tuberculosis treatment

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ABSTRACT

Available data on anti-tuberculosis drug research reveal different properties of the agents and provoke speculation about future directions. Higher doses of the rifamycins are promising and are currently being evaluated in regimens of shorter duration that the isoniazid plus rifampin-based, six-to-nine month-course therapy. Moxifloxacin and gatifloxacin might shorten tuberculosis treatment as well, possibly in combination with rifapentine, while SQ109 could enhance the activity of rifampin-containing regimens. On the other hand, co-administration of moxifloxacin and PA-824 could be active against latent tuberculosis, whereas linezolid, PA-824 and TMC207 are candidates for a rifampin-free regimen in multidrug-resistant and extensively-resistant tuberculosis. Unfortunately, shorter than existent 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.

Nuevos fármacos para el tratamiento de la tuberculosis

Palabras clave:
Altas dosis de rifamicinas
Nuevas combinaciones de fármacos

RESUMEN

Los datos disponibles en el proceso de investigación de nuevos fármacos antituberculosos han descubierto diferentes propiedades de los compuestos que permiten crear expectativas acerca de sus futuras indicaciones. Modelos terapéuticos que incluyan altas dosis de rifamicinas y pautas que asocien rifapentina con moxifloxacino o gatifloxacino podrían acortar el tratamiento de la tuberculosis, mientras que SQ109 incrementaría la actividad de las combinaciones basadas en esta rifamicina. Por otra parte, la tuberculosis latente podría tratarse adecuadamente con la asociación de moxifloxacino y PA-824, y la tuberculosis multirresistente y extensamente resistente con linezolid, PA-824 y TMC207, en pautas sin rifampicina. Desgraciadamente, tratamientos más cortos que los existentes, basados en asociaciones de los fármacos que se comentan en este trabajo, llevarán al menos otra década para ser completamente desarrollados e introducidos en la práctica clínica.

In every bit of honest writing in the world there is a base theme: Try to understand men.[1] But for every bit of research, to be properly done, there should be a base theme as well: Try to comprehend Nature.

From mice to men I. Old drugs, higher doses, and new combinations

Required properties of tuberculosis drugs are summarized in Table 1.

Rifampin

Rifampin is considered to be the cornerstone in the current treatment of tuberculosis (TB).[2] Results from studies with mice and early bactericidal activity (EBA), in which the fall in colony forming units (CFU) during the first 2 days of therapy is measured, suggest that the standard dose of rifampin in TB treatment is at the lower end of the concentration-response curve.[3] Rifampin inhibits the β-subunit of the RNA polymerase, a multisubunit enzyme that transcribes bacterial RNA.[2] Mycobacterial resistance to the rifamycins results from mutations in the *rpoB* gene that codes for that β-subunit,[4] and its increasing prevalence concurrently with isoniazid resistance (multidrug-resistant tuberculosis [MDR-TB]) is a serious concern.[5] The pharmacokinetics (PK) and pharmacodynamics (PD) of rifampin

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Table 1
Required properties of new anti-tuberculosis (TB) drugs

What a new drug should do?	Characteristics required
Simplify treatment or reduce treatment duration	Strong early bactericidal and sterilizing activity
	Low pill count, fixed-dose combination
	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-TB/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 antiretrovirals
Be active against latent TB	Active against dormant bacilli
	Favorable toxicity profile

HIV: human immunodeficiency virus; MDR-TB: multi-drug resistant tuberculosis; XDR-TB: extensively drug-resistant tuberculosis.

Table 2
Summary of pharmacokinetics/pharmacodynamics and activity of rifampin and rifapentine*

Drug dose	Bio availability (%)	AUC (mg·h/l)	Cmax (mg/L)	$t_{1/2}$ (h)	Plasma protein binding (%)	MIC (mg/L)	AUC/MIC ratio
Rifampin (10 mg/Kg)	68	21.5	8-20	2-5	85	0.15	70.8
Rifapentine (600 mg)	Unknown	319-394	10-18	13-20	97	0.02-0.125	76.6

AUC: area under the curve; Cmax: maximum concentration; MIC: minimal inhibitory concentration.
*Drug concentrations estimated for single compounds, not in combination.

in adults treated with the licensed dose (10 mg/Kg of body weight) are summarized in Table 2. In the 1960s and 1970s, PK 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.[6] More recently, PK 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]).[7] Increasing the dose by 30%, the maximum concentration (Cmax) increased by 49%, and the area under the 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 certain time period. A higher dose of rifampin is not likely to affect the PK 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.[8] The minimal inhibitory concentration (MIC) of rifampin is 0.15 mg/L in broth culture.[9] Rifampin exhibits concentration-dependent activity that correlates best with the AUC/MIC ratio, as was shown in the mouse model. Results from an efficacy study in mice predicted a one-third reduction in TB treatment duration when the rifampin dose was increased by 50%.[10] 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.[11] All patients remained culture negative for up to 1 year, but sixteen percent of patients relapsed after 12 to 24 months. 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,[12] however, the EBA of 1,200 mg rifampin daily was studied in 14 patients with pulmonary TB in another study and the mean 2-day EBA was almost twice as high as that of 600 mg rifampin.[3]

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.[2] Daily rifampin at 13 mg/Kg was tolerated well by Indonesian patients.[7] 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. 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).[13,14] 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.[15]

Available data suggest that higher daily doses of rifampin can shorten TB treatment. The maximum tolerable dose of rifampin and the EBA of a range of higher doses of rifampin given alone and in combination are planned to be investigated more extensively in phase II and III clinical trials in different multidrug regimens. 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 is a cyclopentyl rifamycin, whose activity and resistance mechanisms are the same as rifampin and other rifamycins.[16] PK of rifapentine in the standard dose is shown in Table 2.[17] 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.[18] Rifapentine induces the CYP450 enzyme system to a lesser extent than rifampin.[2] Rifapentine autoinduction —the phenomenon that induction of the CYP450 enzyme system also increases metabolism of the drug itself— was 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.[19] Rifapentine (900 mg thrice weekly) reduced the AUC of moxifloxacin (400 mg daily) by 17% in the same study. The MIC of rifapentine ranges from 0.02 to 0.125 mg/L, i.e., two to four times lower than that of rifampin.[20] When adjusted for protein binding, the AUC/MIC ratio for rifapentine in standard dose is 76.6 (AUC/MIC ratio for rifampin, 70.8).[21]

Table 3
Overview of anti-tuberculosis (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	Interaction with rifampin
High-dose rifampin	II	Yes	To be established	Limited	Yes but not with protease inhibitors	Yes, but not first choice	–
High-dose rifapentine	II	Yes	To be established	Limited	To be established	Yes	–
Moxifloxacin	III	Yes	Yes	Yes	Yes	Yes	Reduced AUC of moxifloxacin by 30%
Gatifloxacin	III	Yes	Caution in elderly	Yes	Yes	Unknown	Possible
TMC207	II	Yes	To be established	Yes	Unknown	Unknown	Reduced serum TMC207 concentration by 30%
PA-824	II	Doubtful	Moderate increase in creatinine observed	Yes	Unknown	Yes	No
OPC-67683	I/II	Yes	To be established	Yes	Unknown	Unknown	No
SQ 109	I/II	Yes	To be established	Yes	Unknown	Unknown	Synergism in vitro
LL3858	I	Yes	Unknown	Yes	Unknown	Unknown	Synergism in vitro

AUC: area under the curve; HIV: human immunodeficiency virus; MDR-TB: multi-drug resistant tuberculosis.

Rifapentine (10 mg/Kg) was approved for the treatment of pulmonary TB by the U.S. Food and Drug Administration (FDA) in 1998 (Priftin, Hoechst Marion Roussel, Kansas City, MO), but it has not been approved by the European Medicines Agency (EMEA). Based upon its long half-life, rifapentine allows for intermittent dosing at wider intervals, which facilitates observed treatment. 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.[22] A high rate of mycobacterial monoresistance to rifamycins was seen in human immunodeficiency virus (HIV)-infected patients treated with rifapentine and isoniazid.[23] 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.[24] Higher than standard doses of rifapentine have shown the potency to shorten TB treatment in mice, especially when combined with moxifloxacin.[25] 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).[26] 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. 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.[27] A recent study in mice showed that the main sterilizing component in regimens containing rifapentine, moxifloxacin, and pyrazinamide is rifapentine, rather than moxifloxacin.[28] 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.[29] The optimum higher dose of rifapentine has not yet been defined, but it is assumed that rifapentine will cause fewer problems of drug-drug interactions than rifampin.

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.[30] 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.[31] 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).[19]

There is a renewed rifapentine registration trial, conducted by the Tuberculosis Trials Consortium (TBTC), in which rifapentine 600 mg, daily dose, substitutes rifampin in the standard intensive phase, four-drug regimen, for treating smear-positive, pulmonary TB (TBTC study 29). On the other hand, 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.[32] 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.[33] TBTC study 26 is also a clinical trial comparing rifapentine plus isoniazid (900 mg each), administered weekly for 12 weeks, to the standard regiment of daily isoniazid (300 mg) during 9 months. Summarizing, increasing the dose of rifapentine could shorten TB treatment, especially in combination with moxifloxacin, and may be useful against latent TB as well.

From mice to men II. New agents under clinical investigation

Table 3 provides an overview of new anti-TB drugs in the clinical pipeline, and new indications and combinations of anti-TB drugs currently assessed in clinical trials are summarized in Table 4.

Table 4
Summary of clinical trials on going as 31st of May, 2010

Study Title	Characteristics	Sponsor
TBTC Study 26	Phase III randomized, open-label clinical trial of ultra short-course treatment of latent TB infection among contacts of active cases, using a 3-month once-weekly regimen of isoniazid and rifapentine, compared to standard 9-month daily therapy with isoniazid. Enrolment of main populations is completed (more than 8,100 participants have been enrolled and are in follow-up). Extended enrollment for HIV+ and children closed as December 15th, 2010	CDC
TBTC Study 29	Phase II randomized, open-label clinical trial assessing the antimicrobial activity and safety of substituting rifampin for rifapentine in standard intensive phase TB treatment regimen	CDC
TBTC Study 29PK	Substudy to characterize rifapentine PK parameters in patients with TB	CDC
TBTC Study 30	Phase I/II randomized, placebo-controlled, double-blind clinical trial assessing the safety and microbiological activity of linezolid added to OBT for MDR-TB or XDR-TB	CDC
TBTC Study 30PK	Substudy to characterize to characterize linezolid PK and linezolid time over the MIC in patients with MDR-TB and XDR-TB	CDC
Rifaquin Study	Phase II, open-label 3-arm clinical trial powered to demonstrate non-inferiority of the two trial arms compared with the standard 6-month TB regimen. Trial regimens are: 2 months of daily ethambutol, moxifloxacin (400mg/qd), rifampin and pyrazinamide, followed by *a)* 2 months of twice weekly moxifloxacin (400 mg) and rifapentine (900mg) (2EMRZ/2P2M2) or *b)* 4 months of once weekly moxifloxacin (400mg) and high dose rifapentine (1,200mg) (2EMRZ/4P1M1)	INTERTB Biomedical Research and Training Institute, Zimbabwe
Linezolid for XDR-TB	Phase 2a, randomized, 2-arm, open-label, clinical trial of the efficacy of linezolid combined with anti-TB therapy in subjects with XDR-TB	NIAID
4-month quinolone for treating pulmonary TB	Phase III, randomized open-label controlled trial of a 4-month gatifloxacin-containing regimen versus standard regimen for the treatment of adult patients with pulmonary TB	IRD
TMC207 in patients with MDR-TB	Phase II, placebo-controlled, double-blind, randomized trial to evaluate the anti-bacterial activity, safety, and tolerability of TMC207 in subjects with newly diagnosed sputum smear+ pulmonary infection with MDR-TB	Tibotec-Virco Virology BVBA
OPC 67683 in patients with MDR-TB	Phase II, double-blind, placebo-controlled clinical trial, to evaluate OPC 67683 in patients with sputum culture-positive, MDR-TB	Otsuka Pharmaceutical
RE-MoxTB study	Phase III, double-blind controlled trial, comparing two moxifloxacin-containing treatment shortening regimens in pulmonary TB	University College, London
Levofloxacin and moxifloxacin for MDR-TB	Phase III, randomized, multicentre, open-label, with parallel groups comparing the effect between levofloxacin and moxifloxacin among MDR-TB patients	Seoul National University Hospital
Rifapentine plus moxifloxacin for treatment of pulmonary TB	Phase II randomized, open-label trial of a rifapentine plus moxifloxacin-based regimen for intensive phase treatment of smear+ pulmonary TB	Johns Hopkins University
Evaluation of early bactericidal activity in pulmonary TB	Phase II-dose ranging trial to evaluate the extended early bactericidal activity, safety, tolerability, and pharmacokinetics of PA-824 in adults with newly diagnosed, uncomplicated, smear+, Pulmonary TB	TB Alliance
Study of daily rifapentine for pulmonary TB	Phase II-randomized, open-label trial of daily rifapentine 450mg or 600mg in place of rifampicin 600mg for intensive phase treatment of smear+ pulmonary TB	Johns Hopkins University

CDC: Centers for Diseases Control and Prevention; HIV: human immunodeficiency virus; IRD: Institut de Recherche pour le Développement; MIC: minimum inhibitory concentration; MDR-TB: multi-drug resistant tuberculosis; NIAID: National Institute of Allergy and Infectious Diseases; OBT: optimized background therapy; PK: pharmacokinetics; TB: tuberculosis; TBTC: Tuberculosis Trials Consortium; XDR-TB: extensively drug-resistant tuberculosis.

Fluoroquinolones

The fluoroquinolones are registered as second-line anti-TB drugs.[34] Moxifloxacin and gatifloxacin are candidates for shortening TB treatment, since they have the lowest MICs [35]and greatest bactericidal activity, as expressed in the rate of fall in CFU count.[36]

Moxifloxacin is a broad-spectrum 8-methoxy fluoroquinolone with activity against both gram-positive and gram-negative bacteria, including anaerobes.[37] It inhibits bacterial DNA gyrase, an enzyme that is essential for the maintenance of DNA supercoils, which are necessary for chromosomal replication.[38] The development of mycobacterial resistance to fluoroquinolones has been described in MDR strains[39] and in strains from HIV-infected TB patients with a low CD4 count.[40] Fluoroquinolone resistance is due to stepwise mutations in the quinolone resistance-determining region of the mycobacterial *gyrA* and *gyrB* genes.[41] No cross-resistance with the first-line anti-TB drugs has been shown, but cross-resistance within the group of fluoroquinolones was proved.[42] 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.[43] Other studies did not find such an association.[44] Moxifloxacin is metabolized by glucuronidation and sulfation (phase II metabolism) rather than by CYP450-mediated (phase I) metabolism.[45] Up to 20% of moxifloxacin is excreted unaltered in urine and 25% in feces. The AUC from 0 to 24 h (AUC 0-24) of moxifloxacin decreased by 27 to 31% when coadministered with rifampin.[46] This could be due to induction of phase II metabolic enzymes (uridine diphosphatase, glucuronosyltransferase, and sulfotransferase) by rifampin. The clinical relevance of this interaction is unknown. *In vitro* studies with moxifloxacin show MICs of 0.25 to 0.50 mg/L. The bactericidal activity of fluoroquinolones is generally considered to be concentration dependent,[47] although a recent report showed time-dependent killing as well. The ratio of AUC to MIC is thought to be the best predictor of fluoroquinolone efficacy in gram-negative, fast-multiplying bacteria. It was shown *in vitro* and *in vivo* that the greatest bactericidal activity occurs at AUC/MIC ratios of 100 to 125 or more. 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). Aside from the AUC/MIC ratio, the other important indicator of efficacy of

concentration-dependent killers is the Cmax/MIC ratio, which should be more than 8 to 12 for effective killing of gram-negative bacteria. Data adapted from a single-oral-dose study in healthy volunteers showed that the Cmax/MIC90 ratio of moxifloxacin 400 mg (the approved dose in humans) is 8.6.[23] *In vitro* studies and studies in mice showed enhanced bactericidal activity of moxifloxacin and isoniazid when coadministered.[48] Ethambutol adversely affected the activity of moxifloxacin *in vitro*: it reduced moxifloxacin efficacy by 80%.[49] 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. 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.[50] 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] The VT50 (the time needed to kill 50% of viable bacteria) of isoniazid was lower than that of both rifampin and moxifloxacin. The EBA and VT50 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.[52] 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.[53] No difference in percentage of negative cultures after 2 months of treatment 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. 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.[54] 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). 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). 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 a) a regimen of 2RHZM/2RHM and b) 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).[55] 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.[53] A single dose moxifloxacin of up to 800 mg was tolerated well. 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.[56] In another study, no toxicity was experienced by patients who were treated with moxifloxacin, rifampin, and isoniazid for 6 months. Prolongation of QT time has been seen in patients using moxifloxacin for a variety of other bacterial infections. 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.[57]

Moxifloxacin could shorten TB treatment. However, its optimal dose in TB treatment must be evaluated with respect to the recently observed decrease in AUC0-24 when coadministered with rifampin, and ambiguous results revealed from efficacy studies in mice and humans. Finally, the adverse events of moxifloxacin require extended evaluation.

Gatifloxacin has many of the favorable features of moxifloxacin.[58] However, the risk of mycobacterial resistance development and the recently found association between gatifloxacin and dysglycemic events[59] are concerns. *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,[60] but some results were contradictory: while ethambutol reduced gatifloxacin activity *in vitro*, the combination of ethambutol, ethionamide, and gatifloxacin was highly effective in mice.[61] A multicenter trial of the OFLOTUB consortium (see section on moxifloxacin) 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. As per rifapentin, gatifloxacin has not been approved by the EMEA.

Oxazolidinones

Linezolid has been the first oxazolidinone to be developed and approved for clinical use. It is active against a range of bacteria, but its primary clinical role is the treatment of infections caused by aerobic Gram-positive organisms, including resistant strains such as vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant pneumococci.[62]

In vitro studies have shown good activity of linezolid against different species of mycobacteria, including resistant strains. The linezolid MIC90 for *M. tuberculosis* was in the range 1–2 mg/L.[63] MICs of linezolid against other non-tuberculous mycobacteria are higher than the MIC for *M. tuberculosis*.[64] In experimental studies with the murine model of tuberculosis, oxazolidinones have shown an activity similar to isoniazid.[65] Clinical experience with the use of linezolid in the management of mycobacterial infections is still sparse. Some authors have reported successful results in the treatment of both multidrug-resistant *M. tuberculosis* infections[66] and non-tuberculous mycobacteria infections.[67] In addition to the lack of information on the efficacy of linezolid in the treatment of tuberculosis, toxicity is a matter of concern when the drug has to be used for long periods.[68] Clinical trials have shown that linezolid (600 mg twice daily in adults) is safe and generally well tolerated for courses of therapy of <28 days[69] but long-term linezolid use has been associated with reversible haematopoietic suppression, primarily thrombocytopenia[70] and neuropathy.[71] However, this drug is being used as salvage therapy when no better options are available, with some successful results.[72] Efficacy and safety of lower doses of linezolid[73] for treating MDR-TB and extensively-resistant tuberculosis (XDR-TB) are being assessed in phase II clinical trials by the TBTC and the National Institute of Allergy and Infectious Diseases (NIAID).

Diarylquinolines

Diarylquinolines have been identified in a process of screening various compounds for potential anti-TB activity.[74] 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.

TMC207 inhibits the mycobacterial ATP synthase enzyme.[75] TMC207 has shown equal activity in susceptible and MDR strains.[76] No cross-resistance with available drugs is expected since the target of the diarylquinolines differs from that of the currently available anti-TB drugs. Mycobacteria that are resistant to TMC207 *in vitro* show mutations in the *atpE* gene, which encodes subunit c of ATP synthase.[77] Oral administration with a meal results in a twofold increase of serum TMC207 concentrations. The Cmax is reached after 5 h; the half-life is long: about 24 h in humans. PK of TMC207 show linearity with dose. TMC207 is metabolized by the CYP450 3A4 enzyme to an active *N*-monodesmethyl metabolite (M2).[78] 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.[79] No drug-drug interactions were observed between TMC207 and isoniazid plus pyrazinamide (De Beule and 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. *In vitro* studies show MICs ranging from 0.030 to 0.120 mg/L in both fully susceptible and MDR strains.[80] 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. 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.[74] 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.[81] These results suggest synergistic activity of TMC207 and pyrazinamide in mice.[82] 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.[74] 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. 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 supporting data in reference 77). In the EBA study, no adverse events related to the study drugs were encountered.

TMC207 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.

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*.[84] The compounds are structurally related to metronidazole.[85] PA-824 (a nitroimidazo-oxazine) and OPC-67683 (a dihydroimidazo-oxazole) are currently being investigated in clinical trials.

PA-824 is a prodrug that needs the mycobacterial glucose-6-phosphate dehydrogenase (FDG1) or its cofactor, coenzyme F420, to be transformed into an active form.[86] Activated PA-824 inhibits the synthesis of proteins and cell wall lipids. PA-824 activity is limited to *M. tuberculosis* complex. PA-824 is active in susceptible and resistant *M. tuberculosis* strains. No cross-resistance with standard anti-TB drugs has been observed. Mutations in the mycobacterial genes *fbiA*, *fbiB*, and *fbiC* lead to impaired coenzyme F420 synthesis and therefore resistance to PA-824.[87] 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 F420, in PA-824 activity.[88] 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.[89] PA-824 is currently being investigated in phase I clinical trials under the auspices of the Global Alliance for TB Drugs Development (GATB, TB Alliance). Studies in healthy volunteers showed a half-life of about 18 h and a time to reach Cmax of 4 to 5 h. About 65% of PA-824 is excreted in urine and 26% in feces. *In vitro* studies showed MICs of PA-824 against fully susceptible and MDR strains ranging from 0.015 to 0.25 mg/L. PA-824 activity is concentration dependent.[90] 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 and to those of rifampin (20 mg/Kg) and moxifloxacin (100 mg/Kg) in mice.[91] PA-824 showed greater activity than isoniazid and moxifloxacin *in vitro* and in mice and comparable activity to combination therapy with rifampin and isoniazid. 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. 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.[92] PA-824 (100 mg/Kg) was highly active in a mouse model for latent TB when combined with moxifloxacin (100 mg/Kg).[32] 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 (Spigelman, presented at the 1st International Workshop on Clinical Pharmacology of Tuberculosis Drugs, Toronto, Canada, 2008). 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 (Spigelman, presented at the 1st International Workshop on Clinical Pharmacology of Tuberculosis Drugs, Toronto, Canada, 2008).

The potential of PA-824 to shorten TB treatment duration when combined with the standard, first-line anti-TB drugs was reassessed in the mouse model.[93] 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.

OPC-67683 is a mycolic acid biosynthesis inhibitor.[94] While isoniazid inhibits the synthesis of all mycolic acid subclasses, OPC-67683 inhibits methoxy and ketomycolic acid synthesis only.[95] 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). 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. 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. 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.[95] Interactions with drugs that are metabolized by these enzymes are therefore not expected. The MICs of OPC-67683 are equal in drug-susceptible and -resistant *M. tuberculosis* strains and range from 0.006 to 0.024 mg/L.[94] OPC-67683 exhibits concentration-dependent activity also against intracellular *M. tuberculosis*. The *in vitro* intracellular activity of OPC-67683 was better than that of isoniazid and PA-824 and as good as that of rifampin. 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. No antagonism of OPC-67683 with rifampin, isoniazid, ethambutol, and streptomycin was shown *in vitro*. 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.[95] 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. OPC-67683 in multiple doses up to 400 mg was tolerated well by healthy volunteers. No serious adverse events were reported.

OPC-67683 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.[96] So far, the most promising diamine candidate from this library for TB treatment is SQ109.

SQ109 inhibits mycobacterial cell wall synthesis; the exact target is not yet known.[97] 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*. 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.[98] It has been suggested that SQ109 is a prodrug that needs activation by mycobacterial CYP enzymes. Results from a recent drug-drug interaction study in rats suggest that SQ109 induces its own metabolism.[99] SQ109 binding to plasma proteins ranges from 6 to 23% in humans, mice, rats, and dogs. Binding to tissue proteins is higher than that to plasma proteins. SQ109 has a long half-life (61 h) in humans. The MIC of SQ109 ranged from 0.16 to 0.64 mg/L in susceptible and drug-resistant MTB isolates, including ethambutol-resistant strains.[100] SQ109 also exhibits bactericidal activity within macrophages. Its activity is concentration dependent. 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. 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). 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 log10 lower than with the standard RHZE regimen.[101] No adverse events were reported in a phase I single-dose study. Multiple doses of SQ109 (up to 300 mg) were tolerated well by healthy volunteers.

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 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.[102] A fixed-dose combination called LL3848, containing LL3858 and the standard, first-line anti-TB drugs, is also being developed.[103]

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. No data about the pharmacokinetics of LL3858 in humans are available yet. The MIC90 of LL3858 for MTB is 0.25 mg/L. LL3858 exhibits concentration-dependent activity. 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. The tolerability of LL3858 is currently being investigated in phase I clinical trials.[104]

From mice to men III. Animal models of tuberculosis. Limits and lessons

When humans are infected with *M. tuberculosis*, they may develop primary active TB, latent TB, chronic active TB, or reactivation disease. Not all manifestations are mutually exclusive, as 10% of non-immunosuppressed individuals progress from latent to reactivation TB over their lifetimes, while HIV-infected individuals have a 10% annual risk of reactivating latent disease. Immunosuppression, HIV infection, nutritional status, intensity of exposure, BCG vaccination, and age determine, in part, individual outcomes. Less commonly

Table 5
Comparing features of common animal models of tuberculosis

Model	Histopathology			Relative susceptibility to *M. tuberculosis*	Immunologic reagents available	Laboratory space requeriments and costs	Approximates human latent TB infection	Most common experimental uses
	Necrosis	Caseation	Cavitation					
Mouse	Variable	Usually not	No	Low	Extensive	Relative small	No; Cornell model may do so	Immunology; drug efficacy
Rabbit	Yes	Yes	Yes	Very low (*M. bovis* typically used)	Moderate	Relative large	No	Pathogenesis
Guinea Pig	Yes	Yes	Infrequent	Very high	Relatively few	Moderate	No	Vaccine efficacy; airborne transmission
Nonhuman primate	Yes	Yes	Yes	High	Extensive	Large	Yes	Pathogenesis; Immunodeficiency

reported, but of increasingly recognized importance, is the role that re-exposure to TB and re-infection play in the risk of developing disease.[105] Although there are no true animal reservoirs for *M. tuberculosis*, each of these stages of infection in humans can be approached by the use of one or more of the animal models showed in Table 5.

Conclusion

To our knowledge, control of the TB epidemic implies more than developing new drugs, however experimental models as well as the aforementioned clinical assay-based initiatives to try them in humans are crucial to be successful in the global contest to eradicate TB.

Conflict of interest

The authors declare they have not any conflict of interest.

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