INT J TUBERC LUNG DIS 16(8):1005–1014

http://dx.doi.org/10.5588/ijtld.12.0277

STATE OF THE ART SERIES
New Tools, *Series editor:* Wing-Wai Yew
NUMBER 2 IN THE SERIES

New drugs for the treatment of tuberculosis: hope and reality

J. H. Grosset, T. G. Singer, W. R. Bishai

Center for Tuberculosis Research, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; and KwaZulu-Natal Research Institute for Tuberculosis and HIV, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa

SUMMARY

The objective of this review is to report evidence about the efficacy and potential of currently licensed drugs and new molecules beyond pre-clinical development for improving the chemotherapy of tuberculosis (TB). Rifapentine, a rifamycin with low minimum inhibitory concentration, long half-life and potent sterilizing activity in mice did not confirm its potential in a recent short-term clinical trial and is being extensively re-evaluated. Moxifloxacin, a fluoroquinolone, improved the activity of the standard drug regimen when substituted for ethambutol (EMB). It is being studied to shorten the duration of treatment for fully drug-susceptible TB (Remox study). Clofazimine, a fat-soluble dye with experimental activity against TB, but used only for leprosy in the last 50 years, requires further study because it has been included in a successful short 9-month combined drug regimen for the treatment of multidrug-resistant TB. The diarylquinoline TMC207 is the most promising among the new TB drugs because of its experimental and clinical rate of culture conversion. Also exciting, 200 mg daily doses in humans of the nitroimidazo-oxazine PA-824 and the nitro-dihydro-imidazooxazole OPC-67683 were safe and induced a bactericidal effect of respectively 0.098 ± 0.072 $\log_{10}$ and 0.040 ± 0.056 $\log_{10}$ per day. The new oxazolidinones PNU-100480 and AZD-5847 might be at least as active as linezolid and much less toxic. SQ109 is an EMB analogue that does not have cross-resistance with EMB and might have synergistic activity in combined regimens. Benzothiazinones and dinitrobenzamides show exciting in vitro anti-microbial activity and deserve careful attention.

KEY WORDS: rifapentine; moxifloxacin; clofazimine; TMC207; PA-824 and OPC-67683; PNU-100480 and AZD-5847; SQ109; BTZ043

IN CONTRAST to the previous 30 years, the last 10 years have seen a renewal of efforts and promises[1,2] in the development of new drugs for the chemotherapy of tuberculosis (TB). This was triggered by the increasing prevalence of multidrug-resistant (MDR), extensively drug-resistant (XDR) and even totally drug-resistant TB in highly endemic countries.[3] During the previous 30 years, the success of TB control in industrialized countries resulted in social, industrial and scientific demobilization. Despite the hurdles involved in delivering a new drug, and still more a new drug regimen,[4,5] some amount of optimism[6] is permitted when one contemplates the long list of new molecules of potential interest for TB chemotherapy that are beyond pre-clinical development: TMC207, PA-824 and OPC-67683, PNU-100480 and AZD-5847, SQ109 and 1,3-benzothiazin-4-ones (BTZ) 043. Furthermore, currently licensed drugs are being re-evaluated to optimize their efficacy, such as rifapentine (RPT) or repurposed for anti-tuberculosis treatment, such as the fluoroquinolones, particularly moxifloxacin (MXF), and clofazimine (CFZ), a drug originally developed for TB but now almost exclusively used for leprosy.

The objective of the present article is to review current evidence about all of these drugs, beginning with the latter three, and to try to distinguish for the reader between wild and reasonable hopes of how these drugs might impact patient outcomes and TB control, particularly in countries highly endemic for TB and the human immunodeficiency virus (HIV).

We collected all references relating to the drugs listed above, but selected in the writing of this review

All authors have contributed equally to this article.

Previous articles in this series **Editorial:** Yew W-W, Borgdorff M W, Enarson D A. New tools for global tuberculosis control: are we any closer? Int J Tuberc Lung Dis 2012; 16(7): 855–856. **No 1:** Drobniewski F, Nikolayevskyy V, Balabanova Y, Bang D, Papaventsis D. Diagnosis of tuberculosis and drug resistance: what can new tools bring us? Int J Tuberc Lung Dis 2012; 16(7): 860–870.

Correspondence to: Jacques H Grosset, Center for Tuberculosis Research, Johns Hopkins University School of Medicine, CRBII Suite 103, 1550 Orleans Street, Baltimore, MD 21231, USA. Tel: (+1) 410 502 8234. Fax: (+1) 410 614 8173. e-mail: jgrosse4@jhmi.edu; jacques_grosset@yahoo.com

[A version in French of this article is available from the Editorial Office in Paris and from the Union website www.theunion.org]

only those papers that we felt were the most relevant, given the limited number of references allowed. We have sought to provide for each drug the same information pertaining to pre-clinical in vitro data (i.e., minimum inhibitory concentration), pre-clinical in vivo data (i.e., murine model outcomes) and all up-to-date clinical data when available.

EXISTING TB DRUGS ON RE-EVALUATION

Rifapentine

RPT is the 3-[(4-cyclopentyl-l-piperazinyl) iminomethyl] rifamycin SV derivative.[7] Its minimum inhibitory concentration (MIC) for *Mycobacterium tuberculosis* is 0.06 μg/ml, while that of the most widely used rifamycin derivative, rifampicin (RMP, R), is 0.25 μg/ml.[8] Like RMP, RPT is highly protein-bound, but the protein binding of RPT is 97%, while that of RMP is only 85%.[9] As its half-life ($t_{1/2}$) is 10–15 h, i.e., five times longer than the 2–3 h $t_{1/2}$ of RMP,[10] it was assumed that RPT would provide longer exposure of *M. tuberculosis* to active rifamycin and consequently permit once-weekly treatment of TB[11] in combination with isoniazid (INH, H). In fact, once-weekly RPT+INH in the continuation phase of antituberculosis treatment[12] resulted in high rates of failure in patients with cavitary TB and/or HIV positivity and relapse with rifamycin-monoresistant bacilli.[11,13] Moreover, once-weekly RPT+INH treatment has been shown to be less active than thrice- or twice-weekly treatment with INH and RMP.[11,14] It has been suggested that the high protein binding of RPT may be partially responsible for the suboptimal activity observed in once-weekly regimens.[15,16]

Improvements in RPT-based regimens might be made by increasing the dose of RPT from 10 to 15 mg/kg[17] to augment the active drug concentration at the site of infection.[18] The 15 mg/kg dose of RPT has been well tolerated in humans,[19] and an early bactericidal activity (EBA) study of the rifamycins has suggested that the most effective dose of RPT may lie between 15 and 20 mg/kg.[20] Another possibility that has been studied to improve the effectiveness of RPT was to increase the rhythm of RPT administration to augment RPT exposure. In the mouse model of TB,[9] 5 days/week administration of 10 mg/kg RPT+INH + pyrazinamide (PZA, Z) for 3 months was found to cure mice and prevent any relapse, whereas the standard RMP-containing daily regimen (2RHZE/4RH)* required 6 months to prevent relapse in all mice. Building on the mouse data, a multicenter clinical trial was launched to compare the 2-month culture conversion rate obtained with the RHZE regimen given 5 days/week with the same drug regimen in which the 10 mg/kg dose of RMP was replaced by a 10 mg/kg dose of RPT.[21] The RPT-containing regimen was as well tolerated and as safe as the RMP-containing regimen but, surprisingly, the culture conversion rate at the 2-month time point was similar in both treatment groups. If the 2-month culture conversion rate was a surrogate marker of sterilizing activity, such a finding would suggest that the sterilizing potency of daily RPT was not superior to that of daily RMP. This clinical finding contradicts the experimental findings in the mouse model, and prompts further investigations.

Conclusion: Because of its low MIC, long $t_{1/2}$, potent activity in the mouse model and effectiveness in once-weekly treatment of latent TB infection,[22] RPT is a promising drug for shortening the duration of treatment for smear-positive, drug-susceptible pulmonary TB. Its failure to do better than RMP in the 2-month culture conversion rate raised numerous issues, including the predictive value of the mouse model, the predictive value of the 2-month culture conversion as a surrogate marker for sterilizing activity,[23] the optimal dosage of RPT, the best companion drugs for RPT and the impact of 5 days/week treatment vs. 7 days/week treatment. Numerous studies are therefore in progress to optimize the use of RPT.

Moxifloxacin

Quinolones are synthetic compounds active on the microbial DNA gyrases, enzymes needed for DNA replication. Third-generation quinolones have increased in vitro activity against *M. tuberculosis* as well as augmented pharmacokinetic parameters that result in enhanced pharmacodynamic characteristics.[24] Among these, the most promising is the 8-methoxy-fluoroquinolone, MXF, which has an MIC_{90} of 0.5 μg/ml for *M. tuberculosis*. In humans, after an oral dose of 400 mg, the maximum serum concentration (C_{max}) of MXF is 3.2–4.5 μg/ml and the $t_{1/2}$ is 9–12 h.[25]

MXF has bactericidal activity similar to that of INH against multiplying *M. tuberculosis* both in vitro and in the murine model of TB.[25–29] Furthermore, MXF also demonstrated EBA approaching that of INH in patients with pulmonary TB (Table 1).[30–32] For this reason, the substitution of MXF for EMB in the standard four-drug regimen for drug-susceptible

Table 1 Comparative early bactericidal activity* of INH and MXF[30–32]

Authors	Place of study	Days	INH 300 mg/day	MXF 400 mg/day
Pletz, 2004[30†]	Germany	0–5	0.209	0.273
Gillespie, 2005[31]	Tanzania	0–5	0.77	0.53
Johnson, 2006[32]	Brazil	0–2	0.67	0.33
		2–7	0.08	0.17

*Decline in $\log_{10}$ cfu/ml of sputum per day.
†Dose of INH was 6 mg/kg.
INH = isoniazid; MXF = moxifloxacin; cfu = colony-forming unit.

*E, EMB = ethambutol. Numbers before the letters indicate the duration in months of the phase of treatment.

cases of pulmonary TB was thought to permit shortening the treatment duration. The first phase II study to test this hypothesis was conducted among 217 patients from four clinics in KwaZulu-Natal, South Africa, admitted over a 12-month period beginning in June 2004.[33] Patients were treated 6 days a week using the serial sputum colony forming unit (cfu) counts (SSCC) method of appraisal. The substitution of MXF or gatifloxacin, but not ofloxacin (OFX), for EMB resulted in a significantly more rapid decline of cfu counts during the first 2 months and a higher culture conversion rate at the 2-month time point. A second phase II study, a randomized double-blind trial, conducted among 146 patients admitted from October 2004 to March 2007, in Rio de Janeiro, Brazil,[34] was also aimed at assessing the benefit of substituting MXF for EMB. Patients were treated by directly observed therapy (DOT) 5 days/week for 8 weeks. The proportion of 2-month sputum culture conversion to negative was 80% in the MXF-treated patients and 63% in the EMB-treated patients ($P = 0.03$). Unlike the first two studies, the third phase II study, conducted by the Tuberculosis Trials Consortium (TBTC), assessed the benefit of substituting 400 mg MXF for 300 mg INH in the standard drug regimen for pulmonary TB.[35] In this multicenter study, the 328 eligible patients were treated by DOT 5 days/week. The proportion of 2-month sputum culture conversion to negative was 60.4% in the MXF-treated patients and 54.9% in the INH-treated patients, a non-significant difference ($P = 0.37$). Unlike mice,[25] humans with TB did not appear to benefit from the substitution of MXF for INH.

Conclusion: MXF is as potent an anti-tuberculosis drug as INH, and its substitution for INH in the standard first-line drug regimen was only marginally ($P = 0.37$) beneficial.[35] On the other hand, its substitution for EMB was significantly beneficial.[33,34] Whether MXF becomes a first-line drug may depend on the outcomes of the ongoing controlled clinical trial comparing the potential of two MXF-containing regimens to shorten treatment in pulmonary TB (REMOX TB). MXF is currently recommended as the backbone of combined drug regimens for MDR-TB.

Clofazimine

CFZ, B663 or lamprene, is a fat-soluble riminophenazine dye developed by Barry et al. in the 1950s as an anti-tuberculosis drug.[36,37] Its MIC for *M. tuberculosis* is in the range of 0.6–1.2 μg/ml.[38,39] Administered in the diet of *M. tuberculosis*-infected mice, CFZ increased the median survival time over controls by more than 200 days at daily doses of 5–10 mg/kg. After treatment for 14 days with a daily dose of 119 mg/kg, mice killed 200 days later remained culture-negative.[37] On curative treatment, 20 mg/kg of daily CFZ alone was as bactericidal as 5 mg/kg of INH alone, and resulted in the selection of mutants resistant to 1.25–2.5 μg/ml CFZ. Also in mice, the combination of INH and CFZ prevented the selection of resistant mutants.[38] After some weeks of CFZ administration in mice, internal tissues were stained an orange color, and histological examination showed crystal deposits of the drug.[37] Concentrations of CFZ in the lungs of mice were estimated to be 42 μg/g after 7 days, 190 μg/g after 30 days and 567 μg/g fter 60 days of daily administration of 50 mg/kg.[38]

Despite these quite favorable findings, CFZ was not further considered for anti-tuberculosis treatment, likely due to fears related to skin discoloration and the accumulation of crystals in the tissue. Furthermore, at the time of its development, the three-drug combination of streptomycin, INH and para-aminosalicylic acid was successful in the treatment of TB. Thus, due to its activity against *M. leprae* and its anti-inflammatory properties, CFZ became a drug for leprosy.[39]

The half-life of CFZ has been estimated to be about 70 days.[40,41] At autopsy of leprosy patients on long-term treatment with 100 mg/day CFZ, concentrations of the drug in the lungs were in the range of 600–1400 μg/g,[40] indicating huge accumulation in the tissues. A short-lived renewal of interest in CFZ for treatment of infections due to mycobacteria other than *M. leprae* was triggered by its apparent experimental activity against the *M. avium* complex (MAC). However, this experimental activity could not be clinically confirmed for the treatment of MAC bacteremia in acquired immune-deficiency syndrome patients.[41,42] It is likely that tissue accumulation of CFZ resulted in drug carryover from tissue samples to culture medium, which gave an experimentally false impression of bactericidal activity.[43] With the emergence of MDR-TB, the interest in CFZ was once more renewed.[44,45] In 1995, Jagannath et al.[46] confirmed the already reported[37,38] anti-tuberculosis activity of CFZ in the mouse model. Although not scientifically proven to be active in human TB, CFZ is among the drugs being considered for treatment of MDR-/XDR-TB,[47,48] and, more recently, has been used with success in a short, 9-month combined drug regimen for the treatment of MDR-TB.[49] Newer derivatives with fewer potential side effects and improved anti-tuberculosis activity are in the process of development.[50]

Conclusion: It remains to be proven whether CFZ is an effective anti-tuberculosis drug. However, historical findings in the murine model of TB,[36–38] and encouraging evidence in MDR-/XDR-TB patient outcomes when treated with CFZ-containing regimens, are sufficient evidence to justify further laboratory and clinical studies.

NEW MOLECULES OF POTENTIAL INTEREST FOR ANTI-TUBERCULOSIS TREATMENT

TMC207

TMC207 is the diarylquinoline R207910, which goes under the brand name of bedaquiline. This molecule[51]

Table 2 Bactericidal and sterilizing activity of TMC207-containing regimens in mice*[59]

	Bactericidal activity, mice culture-positive at month				Sterilizing activity, relapses after treatment (in months) for			
Drug regimen	2 *n/N*	3 *n/N*	4 *n/N*	6 *n/N*	2 (+3)† *n/N*	3 (+3)† *n/N*	4 (+3)† *n/N*	6 (+3)† *n/N*
2RHZ/4RH‡	No data	No data	No data	0/10	No data	No data	No data	5/30
2JRHZ/2JRH‡	0/9	0/9	0/9	No data	12/18	7/20	1/17	No data
2JRZ/2JR‡	1/6	1/7	0/7	No data	10/18	5/18	2/15	No data
2JHZ/2JH‡	0/9	0/9	0/8	0/8	13/19	13/18	5/17	No data

*On treatment initiation, the lung cfu count was 6.5 $\log_{10}$.
†Indicates that mice were killed 3 months after treatment cessation.
‡Numbers before letters indicate duration in months.
R = rifampicin 10 mg/kg; H = isoniazid 25 mg/kg; Z = pyrazinamide 150 mg/kg; J = TMC207 25 mg/kg.

belongs to a new chemical family and targets the proton pump of adenosine triphosphate (ATP) synthase, leading to inadequate synthesis of ATP.[52,53] Its MIC for *M. tuberculosis* is 0.06 μg/ml and it has no cross-resistance with existing anti-tuberculosis antibiotics.[51]

In mice, after a single dose of 30 mg/kg, the C_{max} reached 2.14 μg/ml within 3 h. TMC207 is metabolized primarily by the cytochrome P_{450} 3A4 (CYP3A4) into its major *N*-monodesmethyl metabolite, which is about five times less active than the parent compound. Both compounds are eliminated with long terminal half-lives of 50–60 h in mice, suggesting considerable tissue binding. This is confirmed by a lung/plasma ratio of about 20 for TMC207 and 100–200 for N-desmethyl TMC207.[54] The concentration of free (not bound) TMC207 in mice has been estimated to be ≤0.001 μg/ml.[54]

In humans, the C_{max} reached 1.2 ± 0.39 μg/ml within 4 h after an oral dose of 100 mg and 5.5 ± 2.96 μg/ml within 4 h after a dose of 400 mg.[55] The half-life is estimated to be ⩾24 h, also suggesting considerable tissue binding of TMC207. The steady-state plasma concentration is close to 0.5 μg/ml on average.[54]

In vitro, TMC207 has time-dependent activity driven by the time over MIC, a measure of how long the active concentration of the drug remains greater than the MIC.[51] In 7H9 broth, at concentrations 10 times and even 100 times the MIC, the drug was highly bactericidal against *M. tuberculosis*, but this was only observed after 6 days of incubation. In the experimental mouse model of TB, potent activity of TMC207 was also observed after treatment for at least 1 month,[51,56] and TMC207 displayed concentration-dependent bacterial activity.[54] Such observations might suggest that the drug needs to accumulate in *M. tuberculosis* to express its antimicrobial activity, and that the accumulation is dose-related.

From the numerous studies conducted in the mouse model of TB,[51,54,56–61] it may be concluded without any doubt that the culture conversion rate achieved by TMC207 alone and in combination with other drugs, particularly PZA, was impressive. It is debatable whether the speed of the culture conversion is related only to the potent bactericidal activity of TMC207 or, at least partly, to drug carryover from the tissues and/or drug accumulation inside the mycobacterial cells.[58] Indeed, there is limited correlation (Table 2) between the time to culture conversion and the percentage of relapse after stopping treatment, i.e., the sterilizing potency.[59,60] Whatever the reasons for the rapid culture conversion, it is remarkable that a 6-month combination of TMC207 with PZA (for the initial 2 months) and MXF, i.e., 2JZM/4JM,* a regimen containing neither RMP nor INH, was shown to have the same sterilizing effect as the 6-month standard regimen 2RHZ/4RH.[61] However, it should be noted that the absence of PZA or a rifamycin in any TMC207-containing regimen was associated with a significant decrease in sterilizing activity.[60,61]

To date, two clinical studies have been performed with TMC207 and reported in peer-reviewed journals. The first was an EBA study of 7 days' duration that showed that the decline in cfu counts in sputum samples was dose-dependent,[55] began only on day 5 of daily 400 mg treatment and then paralleled the decline observed in control patients treated with RMP or INH; no serious side effect was reported. The second was an 8-week randomized study involving a total of 47 MDR-TB patients treated with a 5-drug control regimen consisting of kanamycin, OFX, ethionamide, PZA and cycloserine, or the same regimen reinforced by TMC207 at 400 mg daily for 2 weeks, followed by 200 mg three times a week for 6 weeks;[62,63] the latter resulted in a higher proportion ($P = 0.003$) of culture conversion by the end of 8 weeks (48%, 10/21 vs. 9%, 2/23) and less acquisition of resistance to the companion drugs.

Conclusion: TMC207 is unquestionably a promising new anti-tuberculosis drug which, at present, shows great potential to be part of a more effective treatment for MDR-TB. Among the issues that remain to be addressed are 1) the impact of TMC207 accumulation on the speed of culture conversion,

*J = TMC207; Z = pyrazinamide; M = moxifloxacin. Numbers before the letters indicate the duration in months of the phase of treatment.

and 2) the bactericidal and sterilizing activity of TMC207 in combination therapy *without* any of the well-established sterilizing drugs, PZA and/or a rifamycin. Conversely, considering the promise of TMC207, further optimization studies should be conducted to develop a shortened first-line regimen with PZA and a rifamycin. Of particular interest in the face of rising drug resistance is the novel mechanism of activity of TMC207, which provides an alternative avenue for attacking *M. tuberculosis*.

The nitroimidazopyrans

The nitroimidazo-oxazine PA-824

PA-824 is a derivative of metronidazole, a drug sold under the brand name of Flagyl with potent activity against protozoa (trichomoniasis, amoebiasis) and anaerobic bacteria. PA-824 had substantial anti-tuberculosis activity, with an MIC_{90} of 0.125 μg/ml against both drug-susceptible and -resistant strains of *M. tuberculosis*.[64,65] It is bactericidal against actively replicating as well as non-replicating bacilli.[64–66] It may inhibit the synthesis of ketomycolates, an essential component of the mycobacterial cell wall,[67,68] and donate nitric oxide during enzymatic nitro-reduction within the tubercle bacillus, thereby poisoning the respiratory apparatus.[68,69]

In murine models of TB, PA-824 has bactericidal activity during both the initial and the continuation phases of treatment.[65,66,70,71] Like TMC207, PA-824 exhibited time-dependent bactericidal activity, with a maximal observed bactericidal effect of 0.1 $\log_{10}$ cfu/day over 24 days.[72] When given daily in combination with MXF and PZA, it contributes to an impressive sterilizing regimen,[73] suggesting that such a regimen has the potential to shorten the duration of treatment for drug-susceptible as well as MDR-TB in humans, similar to the effects shown by TMC207.

In humans, PA-824 was well tolerated following oral doses once daily for up to 7 days, and pharmacokinetic parameters were consistent with a once-daily regimen.[74] However, PA-824 induced an isolated and reversible increase in blood creatinine levels after 800 or 1000 mg daily.[75] An EBA study was performed to evaluate oral PA-824 at 200, 600, 1000 or 1200 mg doses per day for 14 days.[76] All doses were well tolerated, but, surprisingly, exhibited equivalent activity. This activity was significant, though limited (daily $\log_{10}$ cfu decline of 0.098 ± 0.072), similar to that observed in mice.[72] As the 200 mg daily dose was as active as higher doses, the EBA of doses < 200 mg/day is under study.[77]

Conclusion: With TMC207, PA-824 is currently among the more promising new anti-tuberculosis drugs. As is the case for TMC207, further work is needed to define its place in the TB treatment armamentarium, i.e., its best companion drugs and the patients who would best benefit from its use. In this perspective, it is rather worrisome that the anti-tuberculosis contribution of PA-824 as well as that of TMC207 is greatly dependent on its synergy with PZA, thus underscoring the importance of PZA, a drug to which an increasingly higher proportion of MDR-TB strains are likely to be resistant (Table 3).[78]

Table 3 Rate of resistance to second-line drugs in a limited set of multidrug-resistant *M. tuberculosis* strains[65]

Second-line drug	China (*n* = 40) *n* (%)	Asia (other) (*n* = 24) *n* (%)	Eastern Europe (*n* = 34) *n* (%)	South America (*n* = 10) *n* (%)	South Africa (*n* = 59) *n* (%)
Ethionamide	11 (28)	4 (17)	8 (24)	0	6 (10)
Kanamycin	12 (30)	7 (29)	15 (44)	3 (30)	8 (14)
Ofloxacin	29 (73)	14 (58)	13 (38)	1 (10)	7 (12)
Pyrazinamide	30 (75)	18 (72)	30 (88)	9 (90)	48 (76)

OPC-67683 (delamanid)

OPC-67683 (OPC) is a nitro-dihydro-imidazooxazole, a derivative of metronidazole like PA-824, with which it shares the same mechanism of action.[79] Its MIC for *M. tuberculosis* is in the range of 0.006–0.024 μg/ml, about 10 times lower than the MIC of PA-824. It also has excellent activity against intracellular *M. tuberculosis*, where its activity at a concentration of 0.1 μg/ml was equivalent to that of RMP at a concentration of 1–3 μg/ml.[79] In murine models, OPC combined with RMP and PZA caused more rapid culture conversion of lung tissue than the standard RHZE regimen.[79]

In humans, OPC was well tolerated at oral doses of 100, 200, 300 or 400 mg daily for 14 days. After an oral dose of 200 mg, its C_{max} reached 0.22 μg/ml with an area under the curve $(AUC)_{0–24}$ (μg·h/ml) of 3.551,[80] while after the same dose, the values for PA-824 were respectively 1.7 and 15.6, i.e., close to 10 times higher.[74] As similarly observed with PA-824, the EBA values were nearly equivalent for the whole range of doses, on average 0.040 ± 0.056 $\log_{10}$ cfu/ml sputum/day, about half the PA-824 values.[80]

Conclusion: Delamanid has an MIC 10 times lower than that of PA-824; however, its bioavailability might be 10 times less than that of PA-824. There is no apparent advantage of delamanid over PA-824. However, delamanid in the long term may be revealed to be more active or less toxic, in other words able to substitute for PA-824 in case of unexpected events.

The oxazolidinones: linezolid, PNU-100480 and AZD-5847

The oxazolidinones, which contain a 2-oxazolidinone-fluorobenezene backbone, are the latest class of antibiotics directed at the inhibition of translation, the third stage of protein biosynthesis.[81] The oxazolidinones function via competitive inhibition of the enzyme that binds the incoming transfer RNA with the complementary codon on the messenger RNA.[82]

A remarkable review of their activities was made

by Shaw and Barbachyn in 2011.[83] The first ever used oxazolidinone was cycloserine (4-amino-1,2-oxazolidin-3-one), a well-known second line anti-tuberculosis drug used since 1955.[84] Developed during the nineties, linezolid (Zyvox), released in 2000 by Upjohn, remains the only oxazolidinone approved by the US Food and Drug Administration for the treatment of nosocomial pneumonia and skin and soft tissue infections caused by Gram-positive bacteria.[84] At the most common dosing regimen of 600 mg twice daily, the C_{max} is 17.8 ± 6.03 μg/ml at steady state.[85] Linezolid has been used off-label against MDR-TB, as its MIC for *M. tuberculosis* is in the range of 0.125–1.0 μg/ml, with an MIC_{50} of 0.25 μg/ml and an MIC_{90} of 0.50 μg/ml.[86] However, the long-term administration required for the treatment of MDR-TB patients is hampered by major side effects such as anemia, thrombocytopenia and/or peripheral and optic neuropathy.[87,88]

PNU-100480 (Sutezolid) is a linezolid analogue with similar MICs for *M. tuberculosis* that has been developed by Pfizer for better in vivo activity and hopefully less toxicity.[82,84] In the murine model of TB, compared with linezolid alone, PNU-100480 has more potent bactericidal activity, even at lower drug exposures.[89] Moreover, the incorporation of PNU-100480 dramatically improved the bactericidal activities of regimens containing some first-line drugs, suggesting that it may be capable of shortening the treatment duration for drug-susceptible TB by 1–2 months.[90]

In humans, a first study examined the safety, tolerability, pharmacokinetics and pharmacodynamics of PNU-100480 doses of 100, 300 or 600 mg twice daily or 1200 mg once daily for 14 days, or 600 mg twice daily for 28 days, to which PZA was added on days 27 and 28. A sixth cohort was given linezolid at 300 mg daily for 4 days. All doses were safe and well tolerated.[91] C_{max} was 0.94 or 2.01 μg/ml, and $t_{1/2}$ was respectively 2.92 or 3.38 h in healthy volunteers receiving twice-daily 600 mg or once-daily 1200 mg of PNU. Trough concentrations were maintained at or above the MIC. An EBA study testing daily 600 mg and 1200 mg for 14 days is scheduled.

AZD-5847 (posizolid) is a lead compound for the treatment of TB by AstraZeneca. It has an MIC similar to that of linezolid and PNU-100480 for *M. tuberculosis*, and has demonstrated efficacy in the mouse model of TB.[83] At 600 mg oral dosing, C_{max} is 2.60 μg/ml in fasting subjects and 5.66 μg/ml in fed subjects, with a $t_{1/2}$ close to 8 h. The main side effect is nausea.[83] Daily oral dosings of 800, 1600 and 2400 mg for 14 days in healthy volunteers were well tolerated, and resulted in increased C_{max} up to 10 μg/ml; however, the increase was not in proportion to the dose.[83]

Conclusion: Oxazolidinones are active molecules on *M. tuberculosis*. Their weak point is their toxicity. The hope is that sutezolid and posizolid (and other molecules such as torezolid[92] and radezolid[93]) will be at least as active as linezolid, and much less toxic.

SQ109

SQ109 is a 1,2-ethylenediamine EMB analogue developed by Sequella.[94] It has an MIC of 0.5 μg/ml for *M. tuberculosis,* while the MIC of EMB is 1.0 μg/ml,[95] and it has no cross-resistance with EMB.[96] Like EMB, it targets the cell-wall formation but by inhibition of trehalose monophosphate transferase,[97] whereas EMB inhibits the arabinosyl transferase.[98] In the mouse model, after oral dosing of 25 mg/kg, C_{max} was estimated to be about 0.14 μg/ml and the $t_{1/2}$ at 5.2 h. After 28 days of treatment with 25 mg/kg SQ109 or 100 mg/kg EMB in *M. tuberculosis*-infected mice, there was a reduction by 2-$\log_{10}$ of the lung cfu counts, compared with 3-$\log_{10}$ in control mice treated with 25 mg/kg of INH.[99] Synergy between SQ109 and INH or RMP has been observed in vitro[100] and in vivo in the murine model.[101] Similarly, there was in vitro synergy between SQ109 and TMC207,[96] and an additive effect between SQ109 and PNU-100480.[102] These findings, obtained in the absence of RMP and INH, are encouraging for the treatment of MDR-TB, and explain why SQ109 is currently undergoing safety (study NCT00866190) and efficacy studies in humans.

Conclusion: The MIC of SQ109 is above the C_{max} obtained in mice after the administration of 25 mg/kg. Despite this, SQ109 demonstrates anti-tuberculosis activity when used alone and in combination with other drugs. The damage(s) induced on the cell wall of *M. tuberculosis* by sub-inhibitory concentrations of SQ109 might be sufficient in the long term to increase the bactericidal activity of combined drug regimens.

Benzothiazinones and dinitrobenzamides

In 2009, Makarov et al. described the synthesis, anti-tuberculosis activity and mechanism of action of benzothiazinones (BTZs), a new class of antimycobacterial agents, among which BTZ043 has very potent anti-tuberculosis activity in vitro (MIC = 0.001 μg/ml) and ex vivo. However, its activity in murine models of TB was less pronounced, likely due to in vivo enzymatic inactivation.[103] Clinical isolates, both fully drug-susceptible and MDR-TB, were uniformly susceptible to BTZ043.[104] All BTZ derivatives target the enzymes responsible for the formation of arabinans, essential parts of the cell wall.

Dinitrobenzamides, DNB1 and DNB2, acting by a similar mechanism[105] and having cross-resistance with benzothiazinones,[106] are still more potent in vitro, with an MIC of 0.0002 μg/ml for *M. tuberculosis*.[105]

Conclusion: Careful consideration of how BTZ derivatives and DNB compounds can be incorporated into TB drug regimens is warranted. It is exciting that both compounds show promising in vitro

antimicrobial activity and that their mechanism of activity is novel.

CONCLUSIONS

Because of man-made multidrug resistance, successful eradication of TB requires not only new drugs and new drug regimens, but also, and just as importantly, new approaches to drug delivery and patient care management. Thus, for the above-mentioned compounds, their full potential, i.e., their hope and reality, must be carefully assessed in controlled clinical trials of combination regimens, keeping in mind that the regimens will have to be implemented in resource-limited settings, and made available to TB-HIV co-infected patients. Of the six new drugs or drug classes discussed in this review, only BTZ043 and the DNBs have not yet advanced beyond pre-clinical development; these were included because of their promising novel mechanism of activity. Those reading this review should therefore be optimistic, particularly considering how much progress has been made in recent years, but also cautious about efficacy data that are only presented in the context of monotherapy or short-term clinical trials and not yet, for the majority, in the context of combination clinical trials. Above all else, to ensure that the benefits of the recent advances in drug discovery reach those in need, rigorous organization of drug delivery and intake, supported by strong political and social commitment, is crucial.

References

1 O'Brien R J, Nunn P P. The need for new drugs against tuberculosis. Obstacles, opportunities, and next steps. Am J Respir Crit Care Med 2001; 163: 1055–1058.
2 Spigelman M, Woosley R, Gheuens J. New initiative speeds tuberculosis drug development: novel drug regimens become possible in years, not decades. Int J Tuberc Lung Dis 2010; 14: 663–664.
3 World Health Organization. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response 2010. WHO/HTM/TB/2010.3. Geneva, Switzerland: WHO, 2010.
4 Glickman S W, Rasiel E B, Hamilton C D, Kubataev A, Schulman K A. A portfolio model of drug development for tuberculosis. Science 2006; 311: 1246–1247.
5 Koul A, Arnoult E, Lounis N, Guillemont J, Andries K. The challenge of new drug discovery for tuberculosis. Nature 2011; 469: 483–490.
6 Ginsberg A M. Drugs in development for tuberculosis. Drugs 2010; 70: 2201–2214.
7 Arioli V, Berti M, Carniti G, Randisi E, Rossi E, Scotti R. Antibacterial activity of DL473, a new semisynthetic rifampicin derivative. J Antibiot 1981; 34: 1026–1032.
8 Heifets L, Lindholm-Levy P, Flory M. Bacterial activity in vitro of various rifamycins against *Mycobacterium avium* and *Mycobacterium tuberculosis*. Am Rev Respir Dis 1990; 141: 626–630.
9 Rosenthal I M, Zhang M, Williams K N, et al. Daily dosing of rifapentine cures tuberculosis in three months or less in the murine model. PLoS Med 2007; 4: e344.
10 Keung A, Eller M G, McKenzie K A, Weir S J. Single and multiple dose pharmacokinetics of rifapentine in man: Part II. Int J Tuberc Lung Dis 1999; 3: 437–444.
11 Tuberculosis Trials Consortium. Rifapentine and isoniazid once a week versus rifampin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomized clinical trial. Lancet 2002; 360: 528–534.
12 American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of tuberculosis. Am J Respir Crit Care Med 2003; 167: 603–662.
13 Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Lancet 1999; 353: 1843–1847.
14 Tam C, Chan S, Lam C, et al. Rifapentine and isoniazid in the continuation phase of treating pulmonary tuberculosis. Initial report. Am J Respir Crit Care Med 1998; 157: 1726–1733.
15 Mitchison D A. Development of rifapentine: the way ahead. Int J Tuberc Lung Dis 1998; 2: 612–615.
16 Burman W J, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. Clin Pharmacokinet 2001; 40: 327–341.
17 Daniel N, Lounis N, Ji B, O'Brien R, et al. Anti-tuberculosis activity of once-weekly rifapentine containing regimens in mice. Am J Respir Crit Care Med 2000; 161: 1572–1577.
18 Weiner M, Bock N, Peloquin C, et al. Pharmacokinetics of rifapentine at 600, 900 and 1200 mg during once-weekly tuberculosis therapy. Am J Respir Crit Care Med 2004; 169: 1191–1197.
19 Bock N, Sterling T, Hamilton C, et al. A prospective, randomized, double-blind study of the tolerability of rifapentine 600, 900 and 1200 mg plus isoniazid in the continuation phase of tuberculosis treatment. Am J Respir Crit Care Med 2002; 165: 1526–1530.
20 Sirgel F A, Fourie P B, Donald P R, et al. The early bactericidal activities of rifampin and rifapentine in pulmonary tuberculosis. Am J Respir Crit Care Med 2005; 172: 128–135.
21 Dorman S, Goldberg S, Feng P, et al. A Phase II study of a rifapentine-containing regimen for intensive phase treatment of pulmonary tuberculosis: preliminary results for Tuberculosis Trials Consortium Study 29. Am J Respir Crit Care Med 183; 2011: A6413.
22 Sterling T R, Villarino M E, Borisov A S, et al., for the TB Trials Consortium PREVENT TB Study Team. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med 2011; 365: 2155–2166.
23 Phillips P P J, Fielding K. Surrogate markers for poor outcome to treatment for tuberculosis: results from extensive multi-trial analysis. 38th International Union Against Tuberculosis and Lung Disease Congress, Cape Town, South Africa, 8–12 November 2007. [Poster]
24 Stein, G. E. Pharmacokinetics and pharmacodynamics of newer fluoroquinolones. Clin Infect Dis 1996; 23 (Suppl 1): S19–S24.
25 Nuermberger E L, Yoshimatsu T, Tyagi S, et al. Moxifloxacin-containing regimen greatly reduces time to culture conversion in murine tuberculosis. Am J Respir Crit Care Med 2004; 169: 421–426.
26 Ji B, Lounis N, Maslo C, Truffot-Pernot C, Bonnafous P, Grosset J. In vitro and in vivo activities of moxifloxacin and clinafloxacin against *Mycobacterium tuberculosis*. Antimicrob Agents Chemother 1998; 42: 2066–2069.
27 Yoshimatsu T, Nuermberger E, Tyagi S, Chaisson R, Bishai W, Grosset J. Bactericidal activity of increasing daily and weekly doses of moxifloxacin in murine tuberculosis. Antimicrob Agents Chemother 2002; 46: 1875–1879.

28 Miyazaki E, Miyazaki M, Chen J M, Chaisson R E, Bishai W R. Moxifloxacin (BAY12-8039), a new 8-methoxyquinolone, is active in a mouse model of tuberculosis. Antimicrob Agents Chemother 1999; 43: 85–89.

29 Lenaerts A J, Gruppo V, Brooks J V, Orme I M. Rapid in vivo screening of experimental drugs for tuberculosis using gamma interferon gene-disrupted mice. Antimicrob Agents Chemother 2003; 47: 783–785.

30 Pletz M W R, De Roux A, Roth A, Neumann K-H, Mauch H, Lode H. Early bactericidal activity of moxifloxacin in treatment of pulmonary tuberculosis: a prospective, randomized study. Antimicrob Agents Chemother 2004; 48: 780–782.

31 Gillespie S H, Gosling R D, Uiso L, Sam N E, Kanduma E G, McHugh T D. Early bactericidal activity of a moxifloxacin and isoniazid combination in smear-positive pulmonary tuberculosis. J Antimicrob Chemother 2005; 56: 1169–1171.

32 Johnson J L, Hadad D J, Boom W H, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis 2006; 10: 605–612.

33 Rustomjee R, Lienhardt C, Kanyok T, et al.; and the Gatifloxacin for TB (OFLOTUB) study team. A Phase II study of the sterilizing activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis 2008; 12: 128–138.

34 Conde M B, Efron A, Loredo C, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. Lancet 2009; 373: 1183–1189.

35 Dorman S E, Johnson J L, Goldberg S, et al., Tuberculosis Trials Consortium. Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. Am J Respir Crit Care Med 2009; 180: 273–280.

36 Barry V C, Conalty M L, Gaffney E E. Anti-tuberculosis activity in the phenazine series. Isomeric pigments obtained by oxidation of *O*-phenylenediamine derivatives. J Pharm Pharmacol 1956; 8: 1089–1096.

37 Barry V C, Belton J G, Conalty M L, et al. A new series of phenazines (rimino-compounds) with high anti-tuberculosis activity. Nature 1957; 179: 1013–1015.

38 Grumbach F. Activité antituberculeuse expérimentale de deux dérivés de phénazine pigmentée (B663 et 720) seuls et associés à d'autres antituberculeux (isoniazide et éthioniamide). Ann Inst Pasteur 1960; 99: 567–585.

39 Yawalkar S J, Vischer W. Lamprene (clofazimine) in leprosy. Basic information. Lepr Rev 1979; 50: 135–144.

40 Mansfield R E. Tissue concentrations of clofazimine (B663) in man. Am J Trop Med Hyg 1974; 23: 1116–1119.

41 Shafran S D, Singer J, Zarowny D P, et al. A comparison of two regimens for the treatment of *Mycobacterium avium* complex bacteremia in AIDS: rifabutin, ethambutol and clarithromycin versus rifampin, ethambutol, clofazimine and ciprofloxacin. N Engl J Med 1996; 335: 377–383.

42 Chaisson R E, Keiser P, Pierce M, et al. Clarithromycin and ethambutol with or without clofazimine for the treatment of bacteremic *Mycobacterium avium* complex disease in patients with HIV infection. AIDS 1997; 11: 311–317.

43 Ji B, Lounis N, Truffot-Pernot C, Grosset J. Effectiveness of various antimicrobial agents against *Mycobacterium avium* complex in the beige mouse model. Antimicrob Agents Chemother 1994; 38: 2521–2529.

44 Reddy V M, Nadadhur G, Daneluzzi D, O'Sullivan J F, Gangadharam P R J. Anti-tuberculosis activities of clofazimine and its new analogs B4154 and B4157. Antimicrob Agents Chemother 1996; 40: 633–636.

45 Reddy V M, O'Sullivan J F, Gangadharam P R J. Antimycobacterial activities of riminophenazines. J Antimicrob Chemother 1999; 43: 615–623.

46 Jagannath C, Reddy M V, Kailasam S, O'Sullivan J F, Gangadharam P R J. Chemotherapeutic activity of clofazimine and its analogues against *Mycobacterium tuberculosis*. In vitro, intracellular and in vivo studies. Am J Respir Crit Care Med 1995; 151: 1083–1086.

47 Global Alliance for TB Drug Development. Handbook of anti-tuberculosis agents: clofazimine. Tuberculosis (Edinb) 2008; 88: 96–99.

48 World Health Organization. Treatment of tuberculosis: guidelines for national programmes. 4th ed. WHO/HTM/TB/2009. 420. Geneva, Switzerland: WHO, 2009.

49 Van Deun A, Maug A K M, Salim M A H, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2010; 182: 684–692.

50 Lu Y, Zheng M, Wang B, et al. Clofazimine analogs with efficacy against experimental tuberculosis and reduced potential for accumulation. Antimicrob Agents Chemother 2011; 55: 5185–5193.

51 Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. Science 2005; 307: 223–227.

52 Cole S T, Alzari P M. TB: a new target, a new drug. Science 2005; 307: 214–215.

53 Koul A, Dendouga N, Vergauwen K, et al. Diarylquinolines target subunit c of mycobacterial ATP synthase. Nat Chem Biol 2007; 3: 323–324.

54 Rouan M-C, Lounis N, Gevers T, et al. Pharmacokinetics and pharmacodynamics of TMC207 and its *N*-desmethyl metabolite in a murine model of tuberculosis. Antimicrob Agents Chemother 2012; 56: 1444–1451.

55 Rustomjee R, Diacon A H, Allen J, et al. Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. Antimicrob Agents Chemother 2008; 52: 2831–2835.

56 Ibrahim M, Andries K, Lounis N, et al. Synergistic activity of R207910 combined with pyrazinamide against murine tuberculosis. Antimicrob Agents Chemother 2007; 51: 1011–1015.

57 Lounis N, Veziris N, Chauffour A, Truffot-Pernot C, Andries K, Jarlier V. Combinations of R207910 with drugs used to treat multidrug-resistant tuberculosis have the potential to shorten treatment duration. Antimicrob Agents Chemother 2006; 50: 3543–3547.

58 Lounis N, Gevers T, Van Den Berg J, Verhaeghe T, van Heeswijk R, Andries K. Prevention of drug carry-over effects in studies assessing the antimycobacterial efficacy of TMC207. J Clin Microbiol 2008; 46: 2212–2215.

59 Ibrahim M, Truffot-Pernot C, Andries K, Jarlier V, Veziris N. Sterilizing activity of R207910 (TMC207)-containing regimens in the murine model of tuberculosis. Am J Respir Crit Care Med 2009; 180: 553–557.

60 Andries K, Gevers T, Lounis N. Bactericidal potencies of new regimens are not predictive of their sterilizing potencies in a murine model of tuberculosis. Antimicrob Agents Chemother 2010; 54: 4540–4544.

61 Veziris N, Ibrahim M, Lounis N, Andries K, Jarlier V. Sterilizing activity of second-line regimens containing TMC207 in a murine model of tuberculosis. PLoS One 2011; 6: e17556.

62 Diacon A H, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009; 360: 2397–2405.

63 Diacon A H, Donald P R, Pym A, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) for multidrug-resistant tuberculosis: long-term outcome, tolerability and effect on emergence of drug resistance. Antimicrob Agents Chemother 2012; 56: 3271–3276.

64 Stover C K, Warrener P, van Devanter D R, et al. A small-molecule nitroimidazopyran drug candidate for the treatment of tuberculosis. Nature 2000; 405: 962–966.

65 Tyagi S, Nuermberger E, Yoshimatsu T, et al. Bactericidal activity of the nitroimidazopyran PA-824 in a murine model of tuberculosis. Antimicrob Agents Chemother 2005; 49: 2289–2293.
66 Lenaerts A J, Gruppo V, Marietta H S, et al. Preclinical testing of the nitroimidazopyran PA-824 for activity against *Mycobacterium tuberculosis* in a series of in vitro and in vivo models. Antimicrob Agents Chemother 2005; 49: 2294–2301.
67 Hu Y, Coates A R M, Mitchison D A. Comparison of the sterilising activities of the nitroimidazopyran PA-824 and moxifloxacin against persisting *Mycobacterium tuberculosis*. Int J Tuberc Lung Dis 2008; 12: 69–73.
68 Manjunatha U, Boshoff H I, Barry C E. The mechanism of action of PA-824: novel insights from transcriptional profiling. Commun Integr Biol 2009; 2: 215–218.
69 Singh R, Manjunatha U, Boshoff H I, et al. PA-824 kills nonreplicating *Mycobacterium tuberculosis* by intracellular NO release. Science 2008; 322: 1392–1395.
70 Nuermberger E, Rosenthal I, Tyagi S, et al. Combination chemotherapy with the nitroimidazopyran PA-824 and first-line drugs in a murine model of tuberculosis. Antimicrob Agents Chemother 2006; 50: 2621–2625.
71 Tasneen R, Tyagi S, Williams K, Grosset J H, Nuermberger E. Enhanced bactericidal activity of rifampin and/or pyrazinamide when combined with PA-824 in a murine model of tuberculosis. Antimicrob Agents Chemother 2008; 52: 3664–3668.
72 Ahmad Z, Peloquin C A, Singh R P, et al. PA-824 exhibits time-dependent activity in a murine model of tuberculosis. Antimicrob Agents Chemother 2011; 55: 239–245.
73 Nuermberger E, Tyagi S, Tasneen R, et al. Powerful bactericidal and sterilizing activity of a regimen containing PA-824, moxifloxacin and pyrazinamide in a murine model of tuberculosis. Antimicrob Agents Chemother 2008; 52: 1522–1524.
74 Ginsberg A M, Laurenzi M W, Rouse D J, Whitney K D, Spigelman M K. Safety, tolerability and pharmacokinetics of PA-824 in healthy subjects. Antimicrob Agents Chemother 2009; 53: 3720–3725.
75 Ginsberg A M, Laurenzi M W, Rouse D J, Whitney K D, Spigelman M K. Assessment of the effects of the nitroimidazo-oxazine PA-824 on renal function in healthy subjects. Antimicrob Agents Chemother 2009; 53: 3726–3733.
76 Diacon A H, Dawson R, Hanekom M, et al. Early bactericidal activity and pharmacokinetics of PA-824 in smear-positive tuberculosis patients. Antimicrob Agents Chemother 2010; 54: 3402–3407.
77 Diacon A H, Dawson R, du Bois J, et al. Phase II dose-ranging trial of the early bactericidal activity of PA-824. Antimicrob Agents Chemother 2012; 56: 3027–3031.
78 Haxaire M, Diacon A H, Pym A, et al. Phase 2 open-label trial of TMC207 in an MDR-TB treatment regimen [Abstract]. Int J Tuberc Lung Dis 2011; 15 (Suppl 3): S58.
79 Matsumoto M, Hiroyuki H H, Tomishige T, et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med 2006; 3: e466.
80 Diacon A H, Dawson R, Hanekom M, et al. Early bactericidal activity of delamanid (OPC-67683) in smear-positive pulmonary tuberculosis patients. Int J Tuberc Lung Dis 2011; 15: 949–954.
81 Barbachyn M R, Hutchinson D K, Brickner S J, et al. Identification of a novel oxazolidinone (U-100480) with potent antimycobacterial activity. J Med Chem 1996; 39: 680–685.
82 Leach K L, Swaney S M, Colca J R. The site of action of oxazolidinone antibiotics in living bacteria and in human mitochondria. Mol Cell 2007; 26: 393–402.
83 Shaw K J, Barbachyn M R. The oxazolidinones: past, present, and future. Ann NY Acad Sci 2011; 1241: 48–70.
84 Barclay W R, Russe H. The in vitro action of cycloserine on *M. tuberculosis*. Am Rev Tuberc 1955; 72: 236–241.
85 MacGowan A P. Pharmacokinetic and pharmacodynamic profile of linezolid in healthy volunteers and patients with Gram-positive infections. J Antimicrob Chemother 2003; 51 (Suppl S2): ii17–ii25.
86 Huang T S, Liu Y C, Sy C L, Chen Y S, Tu H Z, Chen B C. In vitro activities of linezolid against clinical isolates of *Mycobacterium tuberculosis* complex isolated in Taiwan over 10 years. Antimicrob Agents Chemother 2008; 52: 2226–2227.
87 Yew W W, Chau C H, Wen K H. Linezolid in the treatment of 'difficult' multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2008; 12: 345–346.
88 Migliori G B, Eker B, Richardson M D, et al. A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. Eur Respir J 2009; 34: 387–393.
89 Williams K N, Stover C K, Zhu T, et al. Promising antituberculosis activity of the oxazolidinone PNU-100480 relative to that of linezolid in a murine model. Antimicrob Agents Chemother 2009; 53: 1314–1319.
90 Williams K N, Brickner S J, Stover C K, et al. Addition of PNU-100480 to first-line drugs shortens the time needed to cure murine tuberculosis. Am J Respir Crit Care Med 2009; 180: 371–376.
91 Wallis R S, Jakubiec W M, Kumar V, et al. Biomarker-assisted dose selection for safety and efficacy in early development of PNU-100480 for tuberculosis. Antimicrob Agents Chemother 2011; 55: 567–574.
92 Prokocimer P, Bien P J, Surber J, et al. Phase 2, randomized, double-blind, dose-ranging study evaluating the safety, tolerability, population pharmacokinetics, and efficacy of oral tedizolid phosphate in patients with complicated skin and skin structure infections. Antimicrob Agents Chemother 2011; 55: 583–592.
93 Schaadt R, Sweeney D, Shinabarger D, Zurenko G. In vitro activity of TR-700, the active ingredient of the antibacterial prodrug TR-701, a novel oxazolidinone antibacterial agent. Antimicrob Agents Chemother 2009; 53: 3236–3239.
94 Protopopova M, Hanrahan C, Nikonenko B, et al. Identification of a new antitubercular drug candidate, SQ109, from a combinatorial library of 1,2-ethylenediamines. J Antimicrob Chemother 2005; 56: 968–974.
95 Heifets L B, Iseman M D, Lindholm-Levy P J. Ethambutol MICs and MBCs for *Mycobacterium avium* complex and *Mycobacterium tuberculosis*. Antimicrob Agents Chemother 1986; 30: 927–932.
96 Reddy V, Einck L, Andries K, Nacy C A. In vitro interactions between new antitubercular drug candidates SQ109 and TMC207. Antimicrob Agents Chemother 2010; 54: 2840–2846.
97 Tahlan K, Wilson R, Kastrinsky D B, et al. SQ109 targets Mmpl3, a membrane transporter of trehalose monomycolate involved in mycolic acid donation to the cell wall core of *Mycobacterium tuberculosis*. Antimicrob Agents Chemother 2012; 56: 1797–1809.
98 Takayama K, Kilburn J O. Inhibition of synthesis of arabinogalactan by ethambutol in *Mycobacterium smegmatis*. Antimicrob Agents Chemother 1989; 33: 1493–1499.
99 Jia L, Noker P E, Coward L, Gorman G S, Protopopova M, Tomaszewski J E. Interspecies pharmacokinetics and in vitro metabolism of SQ109. Br J Pharmacol 2006; 147: 476–485.
100 Chen P, Gearhart J, Protopopova M, Einck L, Nacy C A. Synergistic interactions of SQ109, a new ethylene diamine, with front-line antitubercular drugs in vitro. J Antimicrob Chemother 2006; 58: 332–337.
101 Nikonenko B V, Protopopova M, Samala R, Einck L, Nacy C A. Drug therapy of experimental tuberculosis (TB): improved outcome by combining SQ109, a new diamine antibiotic, with existing TB drugs. Antimicrob Agents Chemother 2007; 51: 1563–1565.

102 Reddy V R, Dubuisson T, Einck L, et al. SQ109 and PNU-100480 interact to kill *Mycobacterium tuberculosis* in vitro. J Antimicrob Chemother 2012; 67: 1163–1166.
103 Makarov V, Manina G, Mikusova K, et al. Benzothiazinones kill *Mycobacterium tuberculosis* by blocking arabinan synthesis. Science 2009; 324: 801–804.
104 Pasca M R, Degiacomi G, Ribeiro A L, et al. Clinical isolates of *Mycobacterium tuberculosis* in four European hospitals are uniformly susceptible to benzothiazinones. Antimicrob Agents Chemother 2010; 54: 1616–1618.
105 Christophe T, Jackson M, Jeon H K, et al. High-content screening identifies decaprenyl-phosphoribose 2′ epimerase as a target for intracellular antimycobacterial inhibitors. PLoS Pathog 2009; 5: e1000645.
106 Ribeiro A L, Degiacomi G, Ewann F, et al. Analogous mechanisms of resistance to benzothiazinones and dinitrobenzamides in *Mycobacterium smegmatis*. PLoS ONE 2011; 6: e26675.

RÉSUMÉ

L'objectif de cette revue est de faire le point sur l'efficacité et les potentialités pour l'amélioration de la chimiothérapie de la tuberculose (TB) des antibiotiques ayant déjà obtenu l'autorisation de mise sur le marché et des nouvelles molécules ayant déjà dépassé le stade de développement préclinique. La rifapentine, une rifamycine dont la concentration minimale inhibitrice est basse, la demi-vie longue et l'activité stérilisante puissante chez la souris n'a pas confirmé ses promesses dans un récent essai clinique à court terme et fait l'objet d'une réévaluation approfondie. La moxifloxacine, une fluoroquinolone, améliore l'activité du régime antituberculeux standard lorsqu'elle est substituée à l'éthambutol (EMB). Son potentiel pour raccourcir la durée du traitement chez les patients atteints de TB à bacilles sensibles aux antibiotiques est actuellement à l'étude (étude REMOX). La clofazimine, un colorant lipido-soluble dont l'activité expérimentale contre la TB est connue depuis longtemps mais utilisé seulement pour la lèpre durant les dernières 50 années, mérite de faire l'objet d'études complémentaires, car elle a fait partie d'un régime de 9 mois qui s'est montré efficace pour le traitement de la TB multirésistante. La diarylquinoline TMC207 est une nouvelle molécule anti-tuberculeuse très prometteuse en raison de la rapidité avec laquelle elle négative les cultures chez la souris et chez l'homme. ll est très intéressant que des doses quotidiennes de 200 mg du nitroimidazo-oxazine PA-824 et du nitro-dihydro-imidazooxazole OPC-67683 soient bien tolérées chez l'homme et induisent un effet bactéricide de respectivement 0,098 ± 0,072 $\log_{10}$ et de 0,040 ± 0,056 $\log_{10}$ par jour. Les nouvelles oxazolidinones PNU-100480 et ADZ-5487 pourraient être au moins aussi actives que le linézolide et beaucoup moins toxiques. SQ109 est un analogue de l'EMB sans résistance croisée avec lui et pourrait avoir une activité synergique en association avec d'autres antibiotiques. L'activité antibactérienne in vitro des benzothiazinones et des dinitrobenzamides est remarquable et mérite une attention particulière.

RESUMEN

El objetivo del presente análisis es comunicar los datos científicos sobre la eficacia y las posibilidades de los medicamentos ya autorizados y de las nuevas moléculas que han superado la fase preclínica de desarrollo y que pueden mejorar el tratamiento de la tuberculosis (TB). La rifapentina es una rifamicina con una baja concentración mínima inhibitoria, una vida media prolongada y una fuerte actividad esterilizante en ratones, cuyas expectativas no se confirmaron en un reciente ensayo clínico a corto plazo y es actualmente objeto de una reevaluación exhaustiva. El moxifloxacino es una fluoroquinolona que mejoró la actividad de la pauta corriente al substituir al etambutol (EMB) y en la actualidad se estudia con el fin de acortar la duración del tratamiento de pacientes con TB normosensible (estudio Remox). La clofazimina es un colorante liposoluble con actividad experimental contra la TB que se ha utilizado solo contra la lepra durante los últimos 50 años y precisa mayores estudios, pues formó parte de una pauta terapéutica corta combinada de 9 meses, que demostró eficacia en el tratamiento de la TB multidrogorresistente. La diarilquinolina TMC207 es el nuevo medicamento antituberculoso más promisorio, dados sus efectos experimentales y clínicos sobre la tasa de conversión de los cultivos. Otros resultados muy interesantes se refieren a las dosis de 200 mg diarios de nitroimidazo-oxazina PA-824 y de nitro-dihidro-imidazooxazol OPC-67683 que fueron seguras en el hombre e indujeron un efecto bactericida de 0,098 ± 0,072 $\log_{10}$ y 0,040 ± 0,056 $\log_{10}$ por día respectivamente. Las nuevas oxazolidinonas PNU-100480 y ADZ-5487 podrían ser, como mínimo, tan activas como el linezolid y mucho menos tóxicas. El SQ109 es un análogo del EMB, con el cual no presenta resistencia cruzada y podría por lo tanto ofrecer una actividad sinérgica en las pautas terapéuticas combinadas. El 1,3-benzothiazin-4-ones y las dinitrobenzamidas exhiben actividad antimicrobiana interesante in vitro y merecen una atención cuidadosa.