Published in final edited form as:
Future Microbiol. 2010 June ; 5(6): 849–858. doi:10.2217/fmb.10.50.

TMC207: the first compound of a new class of potent anti-tuberculosis drugs

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Abstract

Disease caused by *Mycobacterium tuberculosis* continues as a global epidemic: over 2 billion people harbor latent TB infection, and more than 9 million new TB cases, of whom 500,000 are multidrug-resistant (MDR), and nearly 2 million deaths are estimated to occur each year. New drugs are required to shorten treatment duration of drug-sensitive TB and for the treatment of MDR-TB. TMC207 is a first-in-class diarylquinoline compound with a novel mechanism of action, the inhibition of bacterial ATP synthase, and potent activity against drug-sensitive and drug-resistant TB. It has bactericidal and sterilizing activity against *M. tuberculosis* and other mycobacterial species, but little activity against other bacteria. In a Phase II efficacy study conducted in patients with MDR-TB taking TMC207 plus a standard background regimen, the drug appeared to be safe and well tolerated, and showed significant efficacy after 2 months of treatment with conversion rates of sputum culture of 48% (vs 9% in the placebo group). Given the product development partnership between Tibotec and the TB Alliance, the strategies of using TMC207 in shorter first-line regimens or using it in second-line regimens for drug-resistant *M. tuberculosis* infections are both being pursued. No clinical data of TMC207 in TB patients with HIV coinfection have been published; drug–drug interaction studies with antiretrovirals are being conducted. Finally, the remarkable sterilizing capacity of TMC207 also makes it an attractive drug in the strategy of TB elimination. Current and future studies will determine the role of TMC207 in a shortened treatment regimen for drug-sensitive TB, a more effective and better-tolerated regimen for MDR-TB, the treatment of latent TB infection, and intermittent-TB treatment regimens.

Keywords

diarylquinolines; R207910; TMC207; tuberculosis

Disease caused by *Mycobacterium tuberculosis* continues as a global epidemic, with more than 9 million new cases each year and nearly 2 million deaths [1]. In addition, over 2 billion people harbor latent TB infection (LTBI), thus representing an enormous reservoir of *M. tuberculosis* that can subsequently progress to active disease and spread. The directly observed therapy strategy launched in 1993 (consisting of five key elements: government commitment, diagnosis through bacteriology, standardized and supervised treatment, uninterrupted drug supply and regular program monitoring) has greatly contributed to the improvement of global TB control over the last 15 years [2–4]. Standardized treatment for

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active TB consists of a 2-month intensive phase with four anti-TB drugs, namely rifampicin, isoniazid, pyrazinamide and ethambutol, followed by a 4-month continuation phase with rifampicin and isoniazid. Although capable of achieving a cure rate of 85% or more at a global level [1], this regimen is lengthy, cumbersome and requires considerable efforts to ensure patient adherence and treatment completion. Similarly, the current therapeutic standard for the treatment of LTBI is isoniazid for 6–9 months, but completion rates are unacceptably low, ranging from 20 to 70%. Of note, the majority of patients with LTBI are healthy individuals who may never experience progression to active disease, even in the absence of LTBI treatment.

The new global STOP-TB strategy, launched in 2006, reiterates the central importance of standardized TB treatment, while recognizing that the emergence of drug resistance constitutes a real threat to TB control and elimination [101]. Multidrug-resistant (MDR)-TB is defined as TB caused by *M. tuberculosis* strains that are resistant to, at least, the two most powerful first-line anti-TB drugs, isoniazid and rifampicin; extensively drug-resistant (XDR)-TB refers to a form of disease caused by strains of *M. tuberculosis* that are resistant to isoniazid and rifampicin, in addition to any fluoroquinolone, and to at least one of the three following injectable drugs: capreomycin, kanamycin or amikacin [5,6]. Over 500,000 new cases of MDR-TB occur each year, and prevalent cases are estimated at over 1 million [1]. Although their number is currently unknown, XDR cases are recognized in every setting where there has been the capacity to detect them. Mathematical models show that the MDR- and XDR-TB epidemics have the potential to further expand, thus threatening all gains in TB control over recent decades [7–9].

The future is therefore in our hands and will depend on our capacity, first, to prevent the emergence of additional drug resistance through sound TB control efforts and, second, to effectively diagnose and cure existing MDR- and XDR-TB cases [10]. Our success will depend on the development of new anti-TB agents designed to achieve four major objectives:

- □ Shorten treatment duration
- □ Increase adherence by enabling intermittent therapy
- □ Introduce agents with novel mechanisms of action to ensure activity against drug-resistant *M. tuberculosis*
- □ Decrease incidence by developing safer, shorter duration treatment regimens for LTBI

For the first time in decades, the pipeline of new anti-TB agents is growing [11–14]. TMC207 is among three new compounds in Phase II studies and is especially promising owing to its novel mechanism of action, activity against drug-sensitive and drug-resistant TB, and potential for treatment shortening in preclinical studies.

TMC207

TMC207 (also known as R207910 or the ‘J’ compound) is a diarylquinoline that inhibits the proton pump of *M. tuberculosis*'s ATP synthase, a novel mechanism of action. It was discovered by Johnson & Johnson (J&J) via a screening program of more than 70,000 compounds with activity against the saprophytic *Mycobacterium smegmatis*, a more rapidly growing and manageable mycobacterium compared with *M. tuberculosis* [15]. J&J's research subsidiary, Tibotec (Tibotec Research and Development, Mechelen, Belgium, and Yardley, PA, USA) is managing the clinical development of this compound for a drug-resistant indication, while the Global Alliance for TB Drug Development (TB Alliance), a not-for-profit public/private partnership, is guiding clinical development of TMC207 for

drug-sensitive TB [102]. This first-in-class anti-TB compound is a diarylquinoline with activity against drug-sensitive and drug-resistant TB that has the potential to shorten treatment duration [16–18]. It is administered orally and is being tested at a dose of 400 mg daily for 2 weeks, followed by 200 mg thrice weekly. TMC207 is metabolized by the cytochrome P450 iso enzyme CYP3A4, complicating its coadministration with drugs that inhibit or induce CYP3A4, such as rifampicin. TMC207 is currently being investigated in Phase II trials for the treatment of smear-positive pulmonary MDR-TB; initial safety and efficacy data show that most adverse events are mild to moderate and only nausea occurs more frequently than in placebo treated patients [19].

Chemistry

Diarylquinolines, belonging to the quinoline class of compounds, possess a quinolinic central heterocyclic nucleus and side chains of tertiary alcohol and tertiary amine groups which are responsible for their antimyco bacterial action (Figure 1) [20]. The absolute configuration of TMC207 has been determined by conformational analysis [21] and x-ray diffraction studies [22].

Mechanism of action

The initial identification of the target of TMC207 relied on sequence analysis of a single mutant of *M. tuberculosis* and two mutants of *M. smegmatis* that were resistant to the drug [15]. It was thus demonstrated that TMC207's unique and specific antimycobacterial activity derives from inhibition of the proton pump of mycobacterial ATP synthase. ATP synthase is a critical enzyme in the synthesis of ATP for *M. tuberculosis* [16,23]. Binding of TMC207 to the oligomeric and proteolipic subunit c of mycobacterial ATP synthase leads to inhibition of ATP synthesis, which subsequently results in bacterial death.

The gene encoding for the subunit c of ATP synthase is denominated *atpE*, and its amino acid sequence is highly conserved in nonrelated *M. tuberculosis* isolates [24].

The mechanism of resistance of *M. tuberculosis* to TMC207 has been elucidated: the presence of mutations at position 63 (with a proline substituting alanine) or at position 66 (with a methionine substituting a leucine) of the *atpE* gene disrupts the capacity of TMC207 to bind to the c subunit of the ATP synthase enzyme [24,25]. TMC207 is thought to have a binding pocket around amino acid residue Glu61: mutations in positions 63 and 66 interfere with the drug's access to its target at residue 61, conferring either natural (as in *M. xenopi* and other nontuberculous mycobacteria [NTM] species) or acquired (as in *M. tuberculosis* mutants) resistance [24,25].

Pharmacodynamics & microbiology

In vitro mycobacterial susceptibility experiments have shown that TMC207 potently inhibits drug-sensitive, as well as drug-resistant mycobacterial TB at a minimal inhibitory concentration (MIC) ranging from 0.002 to 0.06 μg/ml and with a MIC_{50} of 0.03 μg/ml (Table 1) [16,25]. The proportion of naturally occurring resistant mutants is low, being estimated in one strain over $10^7/10^8$ bacteria [16].

Recent studies suggest that lower ATP stores of dormant (nonreplicating) bacilli may make these bacteria exquisitely vulnerable to further ATP depletion by TMC207 [26–28]. Koul and colleagues have shown that dormant myco bacteria possess residual ATP synthase enzymatic activity, necessary for their survival, which is effectively blocked by nanomolar concentrations of TMC207 [28]. Although the genes encoding the components of the ATP synthase operon are downregulated by decreased metabolic and replication requirements,

this enzyme still represents a sensitive drug target. Moreover, the scarcity of energy resources in a nonreplicating cell may make TMC207 extremely effective as a sterilizing agent, being superior to presently used first-line anti-TB drugs, such as rifampicin [28]. If these experimental *M. tuberculosis* populations are representative of *in vivo* persisters (i.e., mycobacteria that survive in the setting of appropriate therapy and necessitate long treatment duration), then TMC207 has the capacity to become an important sterilizing agent with the potential for shortening the duration of TB treatment.

TMC207 exhibits a strong inhibitory effect against a large number of NTM, including *Mycobacterium avium* and *Mycobacterium intracellulare*, with MICs in the same range as those for *M. tuberculosis* (Table 1) [25]. In addition, the compound maintains significant activity against other nontuberculous myco-bacterial species, such as *Mycobacterium abscessus* and *Mycobacterium ulcerans*, with MICs in the range of 0.06–0.5 μg/ml [16]. The broad antimycobacterial activity of the diarylquinolines may make this drug an interesting option for the treatment of NTM, which cause diseases that are typically difficult to manage with standard medical treatment. ATP synthase inhibition is, however, not necessarily bactericidal for all mycobacterial species [29]. Among NTM species, at least three have been found to be naturally resistant to TMC207: *Mycobacterium xenopi*, *Mycobacterium novocastrense* and *Mycobacterium shimoidei*, with MICs of 4 μg/ml or more [25]. The mechanism of resistance in these species has been elucidated and is similar in all three: the presence of a methionine amino acid at position 63 of the *atpE* gene instead of an alanine [24,25].

TMC207 has only weak activity against Gram-positive and Gram-negative organisms, with MICs higher than 4 μg/ml [16].

The pharmacokinetics–pharmacodinamics parameter that best correlates with TMC207 treatment efficacy is unknown. In a study of early bactericidal activity (EBA), TMC207 showed almost no bactericidal action during the first 2–4 days of treatment; from day 4 to day 7 it was bactericidal, although the overall reduction in mycobacterial colony counts of only 0.77 $\log_{10}$ colony forming units (CFU) after 7 days of treatment (not yet steady state) was modest [30]. The delayed antimycobacterial action of TMC207 may be associated with the mechanism of action; energy depletion and disruption of intracellular pH homeostasis may require a few days to affect bacterial viability. The activity of TMC207 beyond day 7 and for up to 4 weeks in humans has been ascertained in a recently published clinical trial, in which the drug appreciably increased the capacity of a background second-line regimen to convert the sputum to negative [19]. In mouse studies, the minimal effective dose needed to prevent gross lesions (6.25 mg/kg) was similar to the bactericidal dose (dose needed to reduce lung and spleen colony counts by 3 log; 12.5 mg/kg), suggesting time-dependent killing [16].

Pharmocokinetics & metabolism

The pharmacokinetic properties of TMC207 have been investigated in single and multiple dose-ranging studies in healthy volunteers who were administered the drug at a single dose of 10, 30, 100, 300, 450 or 700 mg or daily for 14 days at doses ranging from 25 to 400 mg [16,103]. The maximum plasma concentration (C_{max}) is reached after 5 h (T_{max}) and is proportional to the administered dose: from 0.07 μg/ml after a single dose of 10 mg to 9 μg/ml for a dose of 700 mg [103]. TMC207 is characterized by an exceedingly long terminal half-life of 173 h in humans, which represents one of the most interesting characteristics of the drug, as it may allow for intermittent drug administration [16]. The area under the curve (AUC) and the C_{max} show a linear pharmacokinetic profile in both single-and multiple-dose studies, and the half-life is independent of the administered dose.

An EBA study of TMC207 showed that the pharmacokinetics in healthy volunteers and patients with pulmonary TB are comparable [30]. A TMC207 daily oral dose of 400 mg administered for a week resulted in a C_{max} of 5.5 μg/ml and an AUC of 64.75 μgh/ml. In another randomized clinical trial, TMC207 was given as part of a multidrug treatment together with an individualized background regimen of second-line TB drugs at a daily oral dose of 400 mg for 2 weeks, followed by a dose of 200 mg three times a week for 6 weeks [19]: the minimal, mean and maximal plasma concentrations after 8 weeks of treatment were 0.62 ± 0.47, 0.9 ± 0.54 and 1.66 ± 0.72 μg/ml, respectively, meeting the goal of a target average steady-state plasma concentration of 0.6 μg/ml.

TMC207 is metabolized by oxidative meta bolism via CYP3A4 to an active *N*-desmethyl metabolite, M2 [31]. Coadministration with rifampin leads to a 50% reduction in TMC207 concentrations [103]. When taken with food, TMC207 exposure increases approximately twofold.

Efficacy in preclinical trials

Treatment of guinea pigs with TMC207 resulted in an almost complete eradication of *M. tuberculosis* from primary and secondary lesions in lung granulomas after 6 weeks of treatment [32]. However, the great majority of preclinical information on the early bactericidal and sterilizing activity of TMC207 has been obtained in the mouse model. Andries and colleagues demonstrated that the daily administration of TMC207 (25 mg/kg) to experimentally infected mice reduced the bacillary load by approximately 2.5–3.0 $\log_{10}$ CFU per month. The drug, administered alone, was as active as the standard daily regimen of rifampicin plus isoniazid plus pyra zinamide; when substituting each first-line drug with TMC207, the activity of each combination containing TMC207 was significantly improved relative to that of the standard regimen. The addition of TMC207 to the standard triple-drug regimen resulted in accelerated clearance of bacilli [16].

Data from the mouse model suggested a synergistic interaction between TMC207 and pyrazinamide. Combinations of anti-TB drugs, including TMC207 but not pyrazinamide, were less effective than TMC207- and pyrazinamide-containing regimens in clearing bacterial counts in the lungs of mice after 2 months of treatment [33]. Although the basis of the synergism has not been formally investigated, pyrazinamide is considered to be an indirect inhibitor of ATP synthase by disrupting the membrane potential, which is required by the enzyme to generate ATP [34], and may, thus, add to the specific ATP-synthase inhibition of TMC207. The synergistic effect of TMC207- and pyrazinamide-containing regimens might contribute to further reduction of anti-TB treatment duration when used for longer than 2 months [33]. Similarly, TMC207 enhances the antibacterial activity of second-line drug combinations in the murine model of drug-sensitive TB [17].

The bactericidal activity of TMC207 appears to correlate with the total weekly dose, irrespective of the frequency of administration. In a recent trial, equivalent results were obtained using TMC207 at a dose of 100 mg/kg once per week, 50 mg/kg twice weekly, or 25 mg/kg five-times weekly [35]. A weekly dose of 100 mg/kg TMC207 was as active as a daily regimen consisting of rifampicin, isoniazid and pyrazinamide. The most remarkable finding, however, was that the triple combination of TMC207 with rifapentine and pyrazinamide given once weekly achieved outstanding bactericidal activity, reducing the bacillary load by 7 $\log_{10}$ and resulting in negative cultures in nine out of ten mice after 2 months of therapy [35]. The activity of this weekly regimen was higher than that of the standard daily triple-drug regimen of rifampicin, isoniazid and pyrazinamide. One study evaluating the impact of a 50% reduction in TMC207 exposure, as would be seen in humans

taking rifampin and TMC207 together secondary to the drug interaction, demonstrated continued significant activity of the drug in combination therapy [36].

In addition to demonstrating impressive bactericidal activity, the mouse model has provided useful information on the sterilizing capacity of TMC207, an essential characteristic for a drug that is a candidate to reduce treatment duration. In a recent experiment using the Cornell model, mice were infected by the intravenous route and treated with TMC207 plus various combinations of rifampin, isoniazid and/or pyrazinamide; a moxifloxacin-based multidrug regimen; or standard treatment with isoniazid, rifampin and pyrazinamide [18]. The mice were killed 3 months after the end of treatment to assess the relapse rate as a measure of the sterilizing activity. In this study, substitution of TMC207 for isoniazid or addition of TMC207 to the standard regimen allowed the reduction of the duration of TB treatment to 4 months. It should be noted that the statistical power of this study was low, and results were discordant from those of previous observations in the mouse model of a significant sterilizing activity of moxifloxacin [37], in line with the poor reproducibility of these experiments. Unlike the results of early bactericidal murine experiments, which suggested that TMC207 could replace both rifampicin and isoniazid [33], in this study the most powerful sterilizing activity was obtained by regimens combining TMC207 and rifampicin, suggesting that TMC207 cannot substitute for rifampicin [18]. Importantly, the sterilizing activity of TMC207 at intermittent doses has not yet been investigated in murine TB [38].

The evaluation of TMC207 for the treatment of other mycobacterial diseases is underway, with mixed results reported so far [20,39].

Efficacy in clinical trials

The ability of a single anti-TB drug to rapidly reduce the bacillary load (EBA) is an important aspect to be considered when testing a new TB drug since it is linked to the duration of infectiousness of pulmonary TB. The EBA of TMC207 was assessed in a study involving 75 treatment-naive patients with smear-positive pulmonary TB, of whom 31% were HIV infected, who were randomized to once-daily oral TMC207 (25, 100 or 400 mg) administered as monotherapy, 600 mg rifampin or 300 mg isoniazid for 7 days. The onset of bactericidal activity of 400 mg TMC207 was delayed as compared with rifampicin and isoniazid, observable beginning on day 4. From day 4 to 7400 mg TMC207 induced daily falls of CFU similar in magnitude to those with rifampicin and isoniazid during the same period [30]. The 25 mg dose did not show any bactericidal effect and the 100 mg dose had a significant EBA only on the last day (day 7) of treatment.

The evaluation of a new antimycobacterial drug in combination therapy is complicated by the potency of first-line anti-TB drugs on drug-susceptible mycobacteria. The addition of a new candidate drug to second-line agents in the treatment of MDR-TB, a regimen that is far less efficient and effective, is an alternative strategy for demonstrating the activity of a new compound [15,40]. This approach has been adopted in a two-stage, randomized controlled trial whose initial results have been recently published [19].

In June 2009, Diacon *et al.* reported the first results of an 8-week, Phase II, multicenter, placebo-controlled trial of TMC207 in adult patients with newly diagnosed, smear-positive pulmonary TB caused by MDR-TB strains [19]. Investigators evaluated the safety, adverse event profile, pharmacokinetics and antibacterial activity of TMC207 during prolonged administration in combination with at least five anti-TB drugs to which the *M. tuberculosis* strain was sensitive. The clinical trial, conducted in South Africa, involved 47 patients (most of whom were HIV negative). A total of 20 out of 23 subjects in the TMC207 arm and 21 out of 24 patients in the placebo arm completed the 8-week course of therapy. All patients in

the TMC207 group received an initial daily dose of 400 mg TMC207 for 2 weeks, followed by 200 mg three times a week for 6 weeks. TMC207 was available as a 100-mg tablet and was taken with water after breakfast under direct supervision. The primary efficacy end point (available for 44 patients with positive liquid broth cultures at baseline) was the time to the conversion of sputum cultures from positive to negative in the MGIT culture system. The time to conversion to a negative sputum culture was shorter in the TMC207-treated group as compared with placebo (hazard ratio: 11.8; 95% CI: 2.3–61.3; p = 0.003 by Cox regression analysis). After 8 weeks of therapy the conversion rates of sputum culture were 48% in the TMC207 group (ten of 21 patients) and 9% in the placebo group (two of 23 patients).

Safety, tolerability & drug interactions

An important factor to consider for a new antibacterial drug is the lack of a eukaryotic homolog of the target, which could lead to toxicity and safety concerns in humans. The enzyme ATP synthase is evolutionary strongly conserved across prokaryote and eukaryote cells. In eukaryote cells, the enzyme promotes the flow of protons from the intercristae region within the mitochondria and the periplasmic space. The selectivity index of TMC207 for mycobacterial ATP synthase compared with mito chondrial ATP synthase is greater than 20,000 [41]. Selectivity indices above 1000 are regarded in drug development as a prerequisite for promising candidate drugs. The same diversity in the *atpE* gene which explains natural and acquired resistance to TMC207 seems to justify the low affinity of the drug to mitochondrial ATP synthase; a methionine at position 63 as opposed to an alanine in mycobacterial ATP synthase is characteristic of ATP synthase from human, mouse and bovine mitochondria [41]. Thus, despite the existence of a human analog of the bacterial target, TMC207 potentially has a very promising safety and tolerability profile.

In the Phase IIa EBA study reported by Rustomjee and coworkers, TMC207 at a dose of 400 mg daily was associated with a low rate of adverse events [30]. The most frequent events reported were rash (7%) in the 100 mg TMC207 group, and diarrhea (7%) and somnolence (7%) in the 400 mg TMC207 group. Two patients treated with 400 mg TMC207 died 14 and 34 days after the end of TMC207 treatment; however, neither death (one due to hemoptysis and the other from complications of TB and AIDS) was considered to be related to TMC207. In this trial the systematic electrocardiogram assessments showed increases in the QT interval in all treatment arms, including those receiving isoniazid and rifampicin, but no pathologically prolonged QT or corrected QT values were observed in any treatment group.

Among patients with MDR-TB treated with TMC207 for 2 months [19], the completion rate was the same as in the placebo group (87%) and there was no case of premature discontinuation of the drug due to adverse events. The majority of adverse events were of mild or moderate intensity; nausea, diarrhea, arthralgia, dizziness, hyper uricemia and eye disorders were more frequently reported by patients treated with TMC207, but only nausea occurred in a significantly higher proportion of patients in the TMC207 group than in the placebo group (26 vs 4%; p = 0.04). Increased QT interval corrected by the Fredericia method was observed in patients receiving both TMC207 and placebo administered with a five-drug regimen of second-line drugs. Although increases in the mean corrected QT interval were more pronounced in the TMC207 group, none of the absolute values for corrected QT interval were greater than 500 ms, and no adverse events were associated with electrocardiographic changes. Despite these encouraging data, much more data on the safety and tolerability of TMC207 need to be gathered in order to have a comprehensive understanding of the clinical potential of the drug.

The interaction between TMC207 and rifampicin is a matter of concern. In a drug–drug interaction study, 16 healthy volunteers received 300 mg TMC207 single-dose with rifampicin 600 mg for seven daily doses: the AUC of TMC207 from time 0 to 336 h was approximately half, compared with that when the drug was dosed alone (unpublished data, reported by Lounis and colleagues in [36]). The clinical significance of this interaction is currently unknown. In the mouse model, TMC207 maintains high EBA activity when administered with rifampicin even when the dose of TMC207 was halved (mimicking the reduction of the AUC observed in humans) [36]. However, clinical trials involving coadministration of the two drugs have not yet been performed.

Regulatory affairs

Registration of a drug for the treatment of TB is tricky for several reasons: the difficulty of distinguishing the effect of a candidate drug from the effect of the other agents in a multidrug combination; the paucity of good surro gate markers for treatment efficacy; and for drug-sensitive TB, the need to compare a new regimen to the existing, highly efficacious regimen of isoniazid, rifampicin, pyrazinamide and ethambutol. Showing a treatment effect in MDR-TB, however, is more efficient, given that second-line agents have poor potency and high toxicity, and trials in MDR-TB may pave the way for larger scale trials of first-line anti-TB combination therapy for patients with drug-susceptible TB [42].

An investigational new drug for TMC207 was filed in 2006 by Tibotec. Phase I pharmacokinetic studies of TMC207 are complete, and drug–drug interaction studies, most notably with antiretrovirals, continue. Interim data on the first 47 patients from the first stage of a Phase II efficacy trial have been published [19], and the second stage of that trial has completed enrollment in South Africa, Peru, Latvia, India, Brazil, Thailand, The Philippines and Russia. In stage 2 of the same randomized, placebo-controlled clinical trial, 150 patients with smear-positive pulmonary TB received an individualized background regimen in addition to either TMC207 at 400 mg daily for 2 weeks then 200 mg thrice weekly for 22 weeks or placebo. Patients will then continue with standard therapy for 18 months. After a total of 24 months of follow-up after the last dose of TMC207 or placebo is given, time to culture conversion and relapse will be evaluated, with results of an interim ana lysis when all patients have completed the 6 months of study drug intake expected in 2010. An open-label confirmatory trial is currently recruiting patients in South Africa, China, The Republic of South Korea, Latvia, Estonia and The Ukraine, with other countries planned to begin enrollment soon [104].

In a landmark product development partnership with the TB Alliance, J&J's subsidiary, Tibotec, agreed to develop TMC207 for registration for an MDR-TB indication and will elaborate an access program for developing countries [105]. Tibotec has granted the TB Alliance a royalty-free licence to develop TMC207 for drug-sensitive TB. Trials of TMC207 for drug-sensitive TB and for children with MDR-TB infection are in the planning stages.

Conclusion

No new classes of drugs for TB have come to market for over 30 years despite the urgent need for new agents that can either shorten the period needed for TB treatment or treat MDR-TB. TMC207 is a first-in-class diarylquinolone compound with a novel mechanism of action and potent activity against drug-sensitive and drug-resistant TB. TMC207 has bactericidal and sterilizing activity against *M. tuberculosis* and other mycobacterial species but little activity against other bacteria. An EBA study in treatment-naive patients with pulmonary TB showed delayed, modest activity of the drug after 7 days, and a Phase II efficacy study conducted in patients with MDR-TB taking TMC207 plus an individualized

background regimen showed impressive results after 2 months of treatment, with the results of a longer TMC207-based treatment course to follow. The drug appears to be safe and well tolerated, and development plans with the goal of an MDR-TB indication are well underway.

Future perspective

The optimal development pathway for TMC207 faces the same strategic dilemma that is currently complicating the development of fluoroquinolone-containing TB regimens. From a programmatic perspective, the discovery of a TB regimen of shorter duration (4 months or less) for treatment of patients with newly diagnosed TB (~9 million incident cases per year) would be beneficial for TB programs that need to ensure optimal patient adherence throughout the entire treatment course. As seen in preclinical studies, TMC207 has the potential to allow the shortening of treatment duration due to its marked sterilizing activity. On the other hand, the management of the over 500,000 cases of MDR-TB and XDR-TB would greatly benefit from availability of a new drug like TMC207, which is potent, well tolerated and structurally and mechanistically unrelated to current first-line TB drugs. Fortunately, given the product development partnership between Tibotec and the TB Alliance, both strategies (using TMC207 in shorter first-line regimens or using it in second-line regimens for drug-resistant *M. tuberculosis* infections) are being pursued.

Compared with fluoroquinolones, TMC207 has the remarkable advantage of being quite ineffective against bacterial infections: the limited drug pressure exerted by a drug that is selective for mycobacterial species and would be prescribed only for mycobacterial disease would likely extend the durability of the drug itself by minimizing the emergence of drug resistance.

Given the strong interactions between the TB and HIV epidemics, TMC207 will likely play an important role in the treatment of coinfected patients. However, drug–drug interaction studies with antiretrovirals have not yet been completed and no clinical data have been published on the treatment of coinfected patients. The intriguing sterilizing capacity of TMC207 also makes it an attractive drug in the strategy of TB elimination, as a TMC207-based regimen could be shorter and, possibly, better tolerated compared with the current standard of treatment of LTBI, a 6-month course of isoniazid. Critics may argue, though, that LTBI treatment is less of a priority than the successful treatment of active disease, and that use of a new drug for LTBI could put the durability of the drug at risk.

Executive summary

Mechanism of action

□ TMC207 is a first-in-class anti-TB diarylquinoline (also named R207910 or the ‘J’ compound) with activity against drug-sensitive and drug-resistant TB.

□ TMC207 inhibits the proton pump of mycobacterial ATP synthase, a critical enzyme in the synthesis of ATP for *Mycobacterium tuberculosis*.

Pharmacokinetic properties

□ The maximum plasma concentration (C_{max}) is reached after 5 h (T_{max}).

□ TMC207 has an exceedingly long terminal half-life of 173 h in humans.

□ It is metabolized by oxidative metabolism via cytochrome P450 isoenzyme CYP3A4.

Mechanism of resistance of *M. tuberculosis* to TMC207

□ Resistance is achieved through mutations at position 63 or at position 66 of the gene encoding for the subunit c of ATP synthase (*atpE*).

Clinical efficacy

□ Onset of bactericidal activity of 400 mg TMC207 on day 4 was found in a Phase IIa monotherapy study; induced daily falls of colony forming units from day 4 to 7 are similar to those with rifampicin and isoniazid during the same period.

□ Conversion rates of sputum culture were 48% (vs 9% in the placebo group) at 8 weeks' treatment with TMC207 on top of a standard backbone in a Phase II randomized study of multidrug-resistant (MDR)-TB pulmonary cases.

Safety & tolerability

□ There was a low rate of adverse events at a dose of 400 mg daily in the Phase IIa study.

□ The majority of adverse events are of mild or moderate intensity.

□ Nausea is significantly more frequently reported by patients treated with TMC207 in the MDR-TB trial. Diarrhea, arthralgia, dizziness, hyperuricemia and eye disorders are more frequent, but not of statistical significance.

□ TMC207 produces increases in the QT interval, but no pathologically prolonged QT or corrected-QT values are observed.

Drug interactions

□ The area under the curve of TMC207 halved when used with rifampicin, but early bactericidal activity is probably preserved.

□ Mouse model studies suggest a synergistic relationship between TMC207 and pyrazinamide.

Dosage & administration

□ Recommended dosage is 400 mg orally daily for 2 weeks, followed by 200 mg thrice weekly.

Given its long half-life, TMC207 may be amenable to intermittent therapy, a mode of administration that, coupled with shorter overall duration of treatment, could strikingly diminish the logistical burden shouldered by TB programs charged with providing directly observed therapy. The possibility of using TMC207 on an intermittent schedule is supported by studies in the murine model in which once-weekly regimens in combination with rifapentine and pyrazinamide were very effective [35]. Currently, the development of intermittent regimens with once-weekly administration has focused on rifapentine, the registered drug with the longest half-life. However, problems have arisen when searching for a companion drug with similar pharmacokinetic properties; the combination of rifapentine and isoniazid given once weekly in the continuation phase resulted in an excess of treatment relapse or failure in those with cavitary lung disease [43] and relapse with rifamycin monoresistance in HIV-infected patients with low $CD4^+$ cell counts [44], potentially owing to intermittent rifapentine monotherapy related to the differences in half-lives [45]. TMC207, due to its pharmacokinetic properties, may be a good companion drug for rifapentine.

Current and future studies will determine the role of TMC207 in a shortened treatment regimen for drug-sensitive TB, a more effective and better-tolerated regimen for MDR-TB, the treatment of LTBI and intermittent TB-treatment regimens.

Acknowledgments

Financial & competing interests disclosure

Kelly Dooley is supported by K23AI080842 (a NIH grant). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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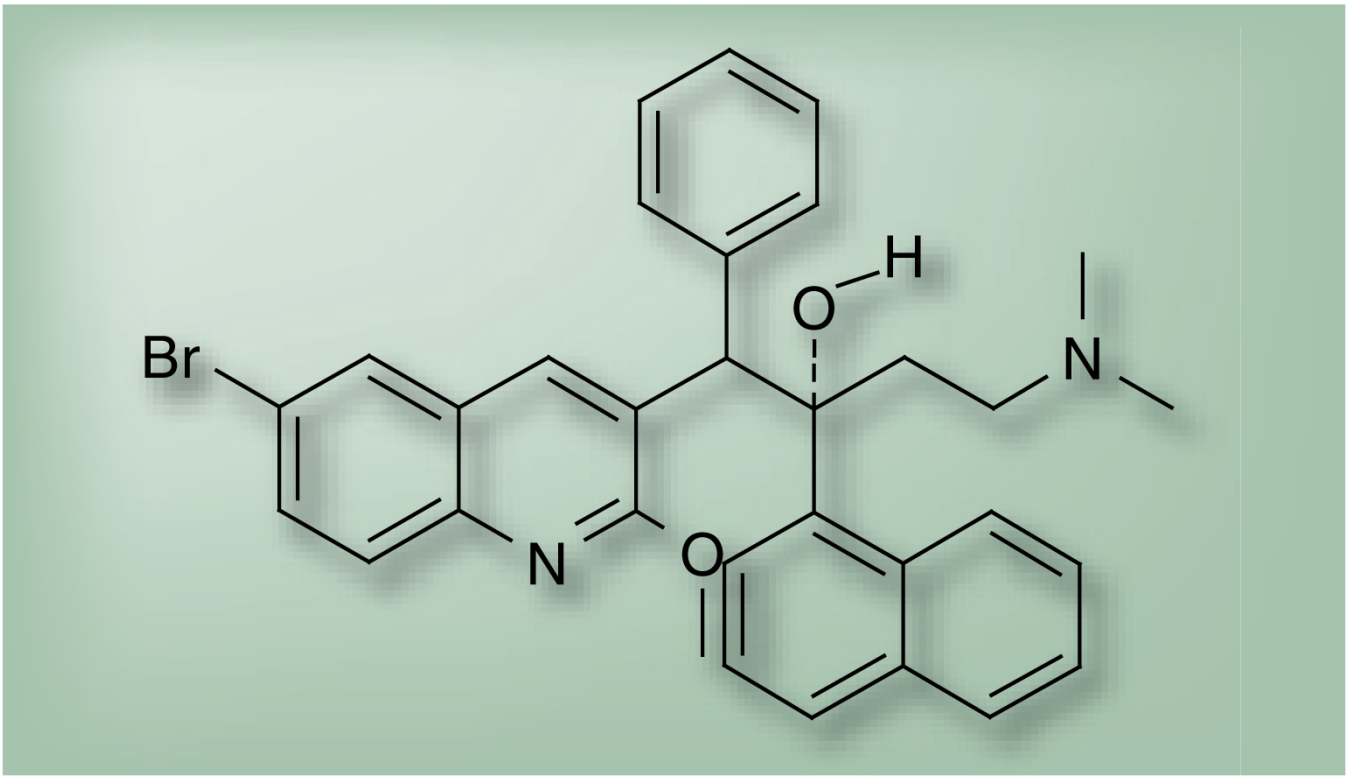

Figure 1.
TMC207 (R207910).

Table 1

Range and median minimal inhibitory concentration of TMC207 for *Mycobacterium tuberculosis*, nontuberculous mycobacteria and relevant Gram-positive and Gram-negative bacteria.

TMC207-sensitive species	MIC range (μg/ml)	Median MIC_{99} (μg/ml)
Mycobacterium tuberculosis		
Drug-sensitive *M. tuberculosis*	0.030–0.120/0.002–0.06	0.060
Multidrug-resistant *M. tuberculosis*	0.030–0.030/0.004–0.13	0.030
Nontuberculous mycobacteria		
Mycobacterium avium	0.007–0.010/0.03–0.13	0.010
Mycobacterium intracellulare	0.007–0.010/0.03–0.25	0.010
Mycobacterium chelonae	0.06–0.5	–
Mycobacterium fortuitum	0.007–0.010/0.13–0.25	–
Mycobacterium kansasii	0.003/0.03	–
Mycobacterium malmoense	0.50	–
Mycobacterium gordonae	0.03	–
Mycobacterium scrofulaceum	0.03	–
Mycobacterium marinum	0.003	–
Mycobacterium xenopi	4.0–8.0	–
Mycobacterium shimoidei	8.0	–
Mycobacterium novocastrense	8.0	–
Bacterial species		
Helicobacter pylori	2 to >4	4
Nocardia asteroides	–	>16
Nocardia farcinica	–	>16
Escherichia coli	–	>32
Haemophilus influenzae	–	>32
Streptococcus pneumoniae	16–24	>32
Staphylococcus aureus	–	>32

MIC: Minimal inhibitory concentration.

Adapted from [14,22]. *MIC range showed when more than one isolate was studied; for species with two MIC ranges the first values are from* [14] *and the second from* [22].