Drugs of the Future 2008, 33(12): 1018-1024

CCC: 0377-8282/2008
DOI: 10.1358/dof.2008.033.12.1291333

TMC-207

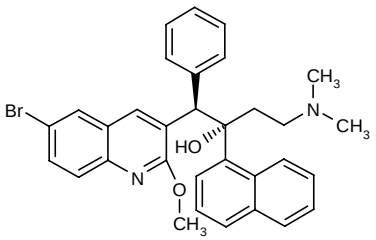
Mycobacterial ATP Synthase Inhibitor
Treatment of Tuberculosis

R-207910

(αS,βR)-6-Bromo-α-[2-(dimethylamino)ethyl]-2-methoxy-α-(1-naphthalenyl)-β-phenyl-3-quinolineethanol

1(*R*)-(6-Bromo-2-methoxyquinolin-3-yl)-4-(dimethylamino)-2(*S*)-(1-naphthyl)-1-phenylbutan-2-ol

InChI=1/C32H31BrN2O2/c1-35(2)19-18-32(36,28-15-9-13-22-10-7-8-14-26(22)28)30(23-11-5-4-6-12-23)27-21-24-20-25(33)16-17-29(24)34-31(27)37-3/h4-17,20-21,30,36H,18-19H2,1-3H3/t30-,32-/m1/s1



$C_{32}H_{31}BrN_2O_2$
Mol wt: 555.505

CAS: 843663-66-1

CAS: 654653-93-7 (racemate)

CAS: 654655-80-8 (no stereochemistry)

EN: 386239

Abstract

The tuberculosis (TB) epidemic constitutes a major global health threat. The steady emergence of *Mycobacterium tuberculosis* strains resistant to current anti-TB drugs, the therapeutic obstacles posited by coinfection with HIV and the cumbersome implementation of current treatment protocols all demand the development of new, fast-acting, effective compounds that shorten and simplify the treatment of TB. TMC-207 (R-207910) is a novel diarylquinoline with a unique biological target: the F0 subunit of mycobacterial ATP synthase. TMC-207 exhibits high in vitro activity against a wide range of mycobacterial strains, both susceptible or resistant to all of the first-line and many of the second-line anti-TB drugs available. It has also shown remarkable in vivo efficacy against *M. tuberculosis* and other mycobacterial species in several animal models. Preliminary pharmacokinetic, safety and efficacy analyses in humans have reasserted the potential of this compound for treating TB. TMC-207 is currently undergoing phase II clinical evaluation.

Synthesis*

Condensation of 4-bromoaniline (I) with 3-phenylpropionyl chloride (II) by means of triethylamine in dichloromethane gives the propionamide (III), which is cyclized with dimethylformamide by means of $POCl_3$ in hot DMF to yield 3-benzyl-6-bromo-2-chloroquinoline (IV). Reaction of compound (IV) with NaOMe in refluxing methanol affords the 2-methoxyquinoline derivative (V), which is condensed with 3-(dimethylamino)-1-(1-naphthyl)propanone (VI) by means of BuLi in THF to provide a mixture of two diastereomeric racemates (*R**,*R**/*R**,*S**) (VII) that are separated by column chromatography. Finally, the desired (*R**,*S**)-racemic mixture is submitted to chiral chromatography (1). Scheme 1.

In an improved process, 3-benzyl-6-bromo-2-methoxyquinoline (V) is condensed with 3-(dimethylamino)-1-(1-naphthyl)propanone (VI) by means of LDA in THF and then treated with AcOH to afford the tertiary alcohol (VII). Finally, alcohol (VII) is submitted to optical resolution by crystallization with chiral 4-hydroxydinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin 4-oxide (2). Scheme 1.

Background

Tuberculosis (TB), one of the leading causes of death worldwide by an identifiable pathogenic microorganism (3), is an infectious disease caused by *Mycobacterium tuberculosis* bacilli. The common route of transmission is the inhalation of airborne particles carrying viable microorganisms that are phagocytosed by alveolar macrophages. In immunocompetent adults, primary infection is generally asymptomatic and results in small

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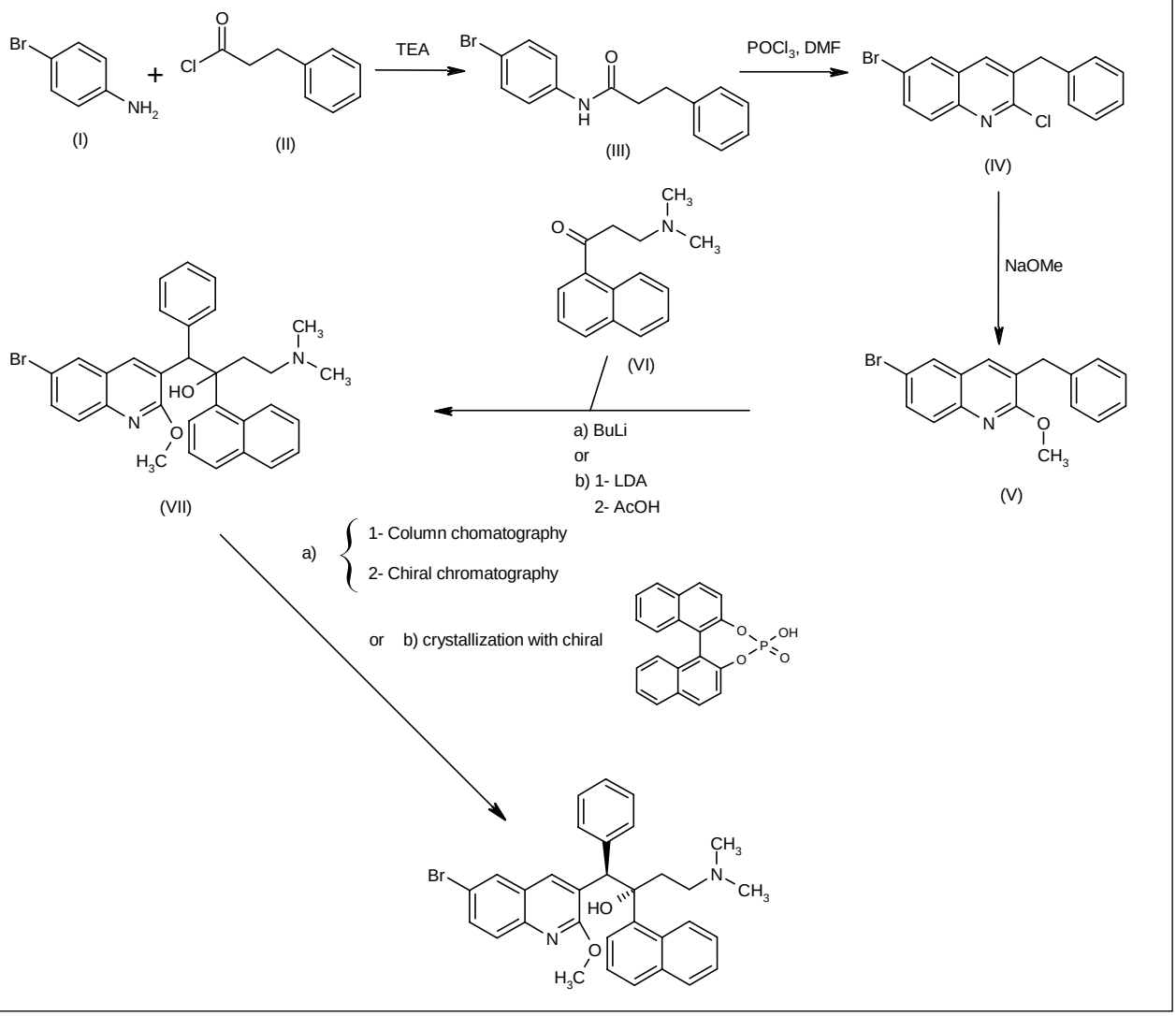
Scheme 1: Synthesis of TMC-207



lesions containing low numbers of dormant bacilli. This latent infection may be reactivated years to decades later, producing either local disease (usually affecting the lungs) or disseminated infection (4). Recent estimates indicate that there are 9 million new TB cases per year. Also, one-third of the world's population carries TB bacilli and approximately 10% of these will develop active disease, leading to 1.6 million deaths annually (5). The risk of developing TB is greatly increased by immunosuppression (including HIV infection), repeated exposure to bacilli-spreading individuals and chronic malnutrition. Indeed, 95% of all TB cases and 98% of all deaths caused by TB occur in developing countries (4).

The HIV epidemic, which greatly expanded the TB-susceptible population, together with the common appearance of drug-resistant strains due predominantly to the inadequate therapeutic management of latent and persistent infections, have placed TB as one of the greatest current global public health emergencies (6). The standard multidrug regimen for the treatment of TB has been modified minimally in the last few decades, it takes many months to complete, and it is in many circumstances difficult to implement (7). Not surprisingly, the Global Alliance for TB Drug Development has indicated that new compounds shortening and simplifying TB treatment would substantially improve TB control programs (8). The emergence of multiple and extensively drug-resistant strains, as well as *M. tuberculosis*/HIV coinfection (which precludes the use of anti-TB agents that interact with antiretroviral agents), further stress the need for new anti-TB drugs (9). There is a consensus among health professionals that the available drug repertoire is not sufficient to control the TB epidemic, and that the treatment of both active disease and latent TB infection

needs to be reevaluated. The devastating association between TB and HIV requires new drug regimens that do not interfere with antiretroviral agents, and markedly improved therapy is needed for the treatment of multiple and extensively drug-resistant TB. In this sense, fast-acting compounds with novel mechanisms of action would be extremely useful not only to fight the emergence of resistant strains but also to reduce toxicity (10). Moreover, shortening the length of the treatment will facilitate the monitoring of patient compliance.

Here we review the current data on the pharmacology, metabolism, efficacy and safety of TMC-207, a promising investigational diarylquinoline with a novel mechanism of action and potent preclinical activity against both drug-susceptible and -resistant *M. tuberculosis* isolates.

Preclinical Pharmacology

Initial in vitro studies showed the potent activity of TMC-207 against *M. tuberculosis*. The minimal inhibitory concentration (MIC) range for the international reference *M. tuberculosis* strain H37Rv and six fully antibiotic-susceptible isolates was 0.030-0.120 μg/ml (11). The growth of an additional 10 fully antibiotic-susceptible *M. tuberculosis* strains was inhibited at similar concentrations. TMC-207 also exhibited in vitro efficacy against *M. tuberculosis* clinical isolates resistant to the first-line anti-TB drugs isoniazid, rifampicin, streptomycin, ethambutol, pyrazinamide and moxifloxacin. Moreover, TMC-207 was effective against multidrug-resistant (MDR) TB strains (0.010-0.1 μg/ml). Low MICs were also found for other mycobacterial species, including *Mycobacterium bovis*, *Mycobacterium kansasii* and *Mycobacterium ulcerans*, as well as species naturally resistant to many other anti-TB agents and involved in opportunistic infections, such as *Mycobacterium abscessus*, *Mycobacterium fortuitum*, *Mycobacterium marinum* and *Mycobacterium avium* (12). A recent mouse study, however, has shown that the in vivo efficacy of TMC-207 against *M. avium* does not match the efficacy shown by clarithromycin or amikacin treatment (13).

The activity of TMC-207 appears to be specific for mycobacteria, as it had a much higher MIC for *Corynebacterium* and *Helicobacter pylori* (4.0 μg/ml), as well as for other organisms such as Gram-positive *Nocardia*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Enterococcus faecalis*, or Gram-negative *Escherichia coli* and *Haemophilus influenzae*. Exposure of *M. tuberculosis* in log-phase growth to concentrations of TMC-207 at 10 times the MIC resulted in a reduction in bacterial load of 3 log units after 12 days, supporting the in vitro bactericidal activity of TMC-207. Additional in vitro analyses have expanded the antimycobacterial activity range of TMC-207 to 41 drug-susceptible and 44 multidrug-resistant *M. tuberculosis* clinical isolates (MIC_{50} = 0.032 μg/ml) (12). In another study, of 20 additional mycobacterial species, only 3 were found to be naturally resistant to TMC-207 and were shown to exhibit a polymorphism in the *atpE* gene (14). Collectively, these results provide strong evidence for the unique-spectrum, potent and selective antimycobacterial activity of TMC-207.

Mutant selection experiments have revealed that, in the case of *M. tuberculosis*, the proportion of resistant mutants that emerged under TMC-207 treatment was comparable to that resulting from rifampicin treatment. Genetic analyses demonstrated that the only gene commonly affected in all mutants encodes the atpE protein, a component of the F0 subunit of ATP synthase. This finding led investigators to postulate that TMC-207 inhibits the proton pump of *M. tuberculosis* ATP synthase, which was demonstrated by complementation studies (12). Later experiments assessing the genetic diversity of the *atpE* gene in 13 mycobacterial species revealed that the region involved in resistance to TMC-207 is highly conserved among mycobacteria. Of note, in *Mycobacterium xenopi* atpE, the highly conserved residue Ala63 is replaced by Met, a substitution that likely underlies the natural resistance of *M. xenopi* to TMC-207 (15). De Jonge et al. have recently created a homology model of the putative TMC-207 binding site, which would be located on the contact area of the a-subunit (gene *atpB*) and c-subunit (gene *atpE*) of *M. tuberculosis* ATPase. The model suggests that the activity of TMC-207 against *M. tuberculosis* relies on the interference of the compound with the escapement geometry of the proton transfer chain. Upon binding, the compound would mimic the conserved Arg186 residue of the a-subunit and would therefore interact with the conserved acidic residue Glu61 of the c-subunit. The concordance between the computed interaction energies and the observed pattern of stereospecificity in the model of the binding region further supported the proposed mechanism of action (16).

The in vivo efficacy of TMC-207 was first evaluated in a nonestablished murine TB infection model (12). A single dose of TMC-207 (50 mg/kg p.o.) resulted in a bacteriostatic effect (decrease of 0.5 log units in lung bacterial load) that lasted for 8 days and was similar to the effect of rifapentine (10 mg/kg), a second-line anti-TB drug. A single 100 mg/kg dose of TMC-207 had a bactericidal effect (decrease of up to 2.5 log units in lung bacterial load) that lasted for 8 days. The extended effect of a single TMC-207 dose provided support for a dosing regimen less frequent than 5 times per week. In mouse studies using oral administration of TMC-207 5 days per week for 4 weeks, the minimal dose that prevented mortality in a nonestablished infection model was 1.5 mg/kg, and the minimal effective dose preventing gross lung lesions was 6.5 mg/kg. In mice receiving doses of 12.5 mg/kg, the bacterial load per organ was reduced by 3 log units. At 25 mg/kg, the activity of TMC-207 improved significantly. Remarkably, at 12.5 and 25 mg/kg, TMC-207 was significantly more active than isoniazid (25 mg/kg), a drug known for its strong, early bactericidal activity. Moreover, at 12.5 mg/kg, a once-weekly dose of TMC-207 was as effective as a dose of 6.5 mg/kg given 5 times per week, which is likely a consequence of the long half-life of TMC-207 (12, 17).

When evaluated in an established murine TB infection model (treatment beginning 12-14 days after inoculation, when bacterial load was 5.94 log units), TMC-207 (25 mg/kg) alone was at least as active as the triple combination therapy rifampicin/isoniazid/pyrazinamide and more active than rifampicin alone. When added to the first-line triple TB therapy, TMC-207 (25 mg/kg) yielded a significantly larger decrease in lung bacterial load relative to the standard triple treatment regimen (2 log units after 1 month and an additional 1 log unit after 2 months of therapy). When substituting each first-line drug of the triple combination therapy with TMC-207 (25 mg/kg), the activity of each combination containing the investigational diarylquinoline was significantly improved, achieving lung culture negativity after 2 months of treatment. Of note, the bactericidal activity obtained by the standard triple-drug cocktail after 2 months of therapy was matched by TMC-207 combinations after just 1 month of therapy, indicating that the inclusion of TMC-207 in anti-TB regimens may effectively reduce the duration of treatment (12, 17).

An animal study conducted subsequently aimed to identify the optimal TMC-207-containing regimen to administer to patients who cannot be administered rifampicin and isoniazid because of MDR, the concomitant use of antiretroviral drugs or toxicity. Mice were infected i.v. with 5×10^6 colony-forming units (cfu) of the *M. tuberculosis* H37Rv strain and treated 5 times per week with TMC-207 alone or combined with second-line drugs such as amikacin. After 1 month of therapy, all regimens containing TMC-207 were significantly more active than those without TMC-207. When given for 2 months, TMC-207 alone was more active than the standard first-line regimen. When the investigational diarylquinoline was combined with second-line drugs, the combinations were more active than the currently recommended regimen for MDR TB, and culture negativity of lung and spleen was achieved after 2 months of treatment in almost every case (18). These findings were confirmed in a later study assessing the sterilizing activity of TMC-207 combined with second-line drugs in mice infected with *M. tuberculosis* H37Rv. Adding TMC-207 to amikacin/ethionamide/moxifloxacin/pyrazinamide improved the efficacy of the second-line therapeutic regimen, further supporting the theory that the addition of TMC-207 to current drug combinations containing pyrazinamide plus rifampicin or moxifloxacin may shorten the duration of MDR TB treatment (19).

Another study employing the proportional bactericidal technique in mouse footpads found that the bactericidal activity of TMC-207 against *Mycobacterium leprae* was equal to that of rifapentine, rifampicin or moxifloxacin, and significantly greater than that of minocycline, PA-824 and linezolid. These data suggest that TMC-207 could also be useful for the treatment of leprosy (20). In addition, when compared in vitro to 7 antimicrobials against 29 clinical isolates of *M. ulcerans*, TMC-207 demonstrated the lowest MIC_{50} and MIC_{90} values. Although TMC-207 also demonstrated some degree of in vivo bactericidal activity against *M. ulcerans* when administered as monotherapy to mice, it failed to outperform the efficacy of currently available drug regimens (21).

As described above, TMC-207 exhibited high bactericidal activity against *M. tuberculosis* when combined with first- or second-line anti-TB drugs. Ibrahim et al. extended the evaluation of TMC-207 in the curative model of murine tuberculosis by assessing the activities of one-, two- and three-drug combinations containing TMC-207 and isoniazid, rifampicin, pyrazinamide or moxifloxacin in the setting of a high initial bacillary load (7.2 log cfu). The research team found that 2 months of treatment with TMC-207 combined with pyrazinamide, pyrazinamide/isoniazid, pyrazinamide/rifampicin or pyrazinamide/moxifloxacin resulted in culture-negative lung homogenates in 70-100% of the mice, while mice treated with the standard regimen (isoniazid/rifampicin/pyrazinamide) or rifampicin/moxifloxacin/pyrazinamide remained culture-positive. Combinations including TMC-207 without pyrazinamide were less active than TMC-207/pyrazinamide-containing regimens administered either alone or combined with isoniazid, rifampicin or moxifloxacin, revealing a synergistic interaction between TMC-207 and pyrazinamide (22). These results provided further evidence supporting the notion that three-drug combinations containing TMC-207 and pyrazinamide (plus isoniazid, rifampicin or moxifloxacin) have the potential to significantly shorten the treatment duration in TB patients.

TMC-207 has also proven effective in a guinea pig model in which lung lesions produced by *M. tuberculosis* resemble those caused by natural infections in humans. After aerosol inoculation, guinea pigs develop necrotic primary lesions that are morphologically different from the secondary lesions resulting from hematogenous dissemination. Conventional 6-week anti-TB therapy reduced the bacterial load by 1.7 log in the lungs, and although it completely reversed lung inflammation associated with secondary lesions, the primary granulomas remained largely unaffected. On the other hand, when animals were treated with TMC-207 for 6 weeks, the investigators found an almost complete eradication of the bacteria in both the primary and secondary lesions (23).

The impact of reducing the dose of TMC-207 on its efficacy when combined with a background regimen of isoniazid, rifampin and pyrazinamide has been assessed in mice. Addition of TMC-207 (12.5-25 mg/kg) to the background regimen resulted in faster bacterial clearance and culture negativity. The minimal bactericidal dose of TMC-207 in combination with the mentioned drugs was identical to that obtained when it was administered as monotherapy (24). Importantly, these data showed that TMC-207 retains significant activity when its exposure is reduced and when it is added to a strong background regimen of isoniazid, rifampicin and pyrazinamide.

The long half-life for TMC-207 seen in pharmacokinetic analyses prompted investigators to evaluate the activity of once-weekly TMC-207 monotherapy and its combinations with other anti-TB agents (isoniazid, rifapentine, moxifloxacin and pyrazinamide) in an estab-

lished murine TB infection model. Veziris et al. found that 8 weeks of rifapentine monotherapy reduced the lung bacillary load by 3-4 log units, while 8 weeks of TMC-207 monotherapy reduced the lung bacillary load by 5-6 log units. The addition of rifapentine and isoniazid/moxifloxacin did not improve the bactericidal activity of TMC-207 monotherapy. In contrast, the triple combination TMC-207/rifapentine/pyrazinamide given once a week during 2 months (8 administrations) was significantly more active than TMC-207 alone or in other combinations. This triple TMC-207-containing combination led to lung culture negativity in 9 of 10 mice, while all lungs remained culture-positive in the groups treated with other drug combinations. Moreover, TMC-207/rifapentine/pyrazinamide given once a week was more active than the current standard regimen (rifampicin/isoniazid/pyrazinamide) given 5 times a week. The striking efficacy of the triple combination TMC-207/rifapentine/pyrazinamide pointed towards the feasibility of developing a fully intermittent once-a-week regimen (25).

Of special consideration are the recent findings demonstrating that TMC-207 kills dormant *M. tuberculosis* bacilli as effectively as aerobically grown bacilli with the same target specificity. In vitro experiments have shown that the residual ATP synthase enzymatic activity in dormant mycobacteria is blocked by nanomolar concentrations of TMC-207, further reducing ATP levels and ultimately causing a pronounced bactericidal effect. The authors interpreted that this residual ATP synthase activity is indispensable for the survival of dormant mycobacteria. Thus, the unique mechanism of action of TMC-207 not only distinguishes this investigational diarylquinoline from currently available anti-TB drugs, but also makes TMC-207 a promising treatment option to fight latent TB infections (26). Along this line, TMC-207 late bactericidal activity was recently evaluated in mice by assessing its ability to kill *M. tuberculosis* H37Rv bacilli persisting after initial intensive 1-month therapy with the standard regimen (rifampicin/isoniazid/pyrazinamide, treatment beginning 14 days after infection). This initial treatment phase was followed by 2 months of monotherapy with isoniazid, rifampicin, moxifloxacin or TMC-207. The study showed that 2 months of TMC-207 monotherapy was able to achieve 100% culture negativity, compared to 50% for rifampicin, 38% for moxifloxacin and 12% for isoniazid. These data demonstrated that during the continuation phase of treatment, TMC-207 has bactericidal activity superior to that of existing anti-TB drugs (27).

Finally, the activity of TMC-207 has been studied jointly with another investigational anti-TB drug (SQ-109) that inhibits mycobacterial cell wall synthesis. Similarly to TMC-207, SQ-109 has potent activity against susceptible and MDR TB bacilli in vitro and is active in *M. tuberculosis*-infected mice. In vitro experiments indicated that the combination SQ-109/TMC-207 is synergistic, while the combination TMC-207/rifampicin is additive (28). In time-to-kill studies, the combination SQ-109/TMC-207 was superior to TMC-207/rifampicin and SQ-109/rifampicin. The SQ-109/TMC-207 combination also showed superior intracellular killing activity compared to TMC-207/rifampicin and SQ-109/rifampicin. The MIC of SQ-109 in the presence of TMC-207 was 50% less than that of SQ-109 alone, and the MIC of TMC-207 in the presence of SQ-109 was 75% less than that of TMC-207 alone. Hence, SQ-109 and TMC-207 in combination synergistically enhance their individual activities against *M. tuberculosis*. It is worth remarking that in three-drug combinations that included rifampicin at 0.1-0.5 x MIC, the synergy displayed by SQ-109/TMC-207 was unaltered.

Pharmacokinetics and Metabolism

The first pharmacokinetic study of TMC-207 in mice showed that it is rapidly absorbed after either single or multiple oral doses. For example, after a single dose of 6.25 mg/kg, a C_{max} of 0.40-0.54 μg/ml was reached within 1 h. After a dose of 25 mg/kg, a C_{max} of 1.1-1.3 μg/ml was reached within 2-4 h. AUCs were 5.0-5.9 and 18.5-19.4 μg.h/ml, respectively, following doses of 6.25 and 25 mg/kg. TMC-207 was well distributed to tissues, including lung and spleen. Half-lives ranged from 43.7 to 64 h in plasma and from 28.1 to 92 h in tissues. No accumulation of TMC-207 was observed after five daily oral doses, indicating that slow redistribution from tissues contributed to its relatively long half-life in plasma (12). It was concluded that the long half-life and resulting prolonged exposure of TMC-207 were important factors determining the duration of its activity in vivo, warranting the assessment of less frequent dosing regimens.

The combination of data from in vivo efficacy and separate pharmacokinetic studies in mice has shed light on the dose–response and exposure–response relationships between TMC-207 and TB infection. A single-dose pharmacokinetic study comparing C_{max} values and AUCs after doses of 6.25, 25 and 100 mg/kg confirmed that AUC showed a better dose correlation than C_{max} values. This phenomenon would be indicative of limitations in the rate of absorption at higher doses. Dose linearity was improved in tissues in terms of both C_{max} and AUC. The results from these comparative analyses led to the conclusion that maintaining average plasma levels of 0.3 μg/ml throughout a dosing interval of 24 h (which is obtained with a dose of 100 mg/kg/week) is necessary to achieve the optimal effect of monotherapy in mice infected with *M. tuberculosis* strain H37Rv (12).

As part of the first TMC-207 clinical study, investigators explored the pharmacokinetics in healthy male subjects receiving escalating oral doses (10-700 mg). The results from this single-ascending-dose study showed that the drug was well absorbed after a single oral dose, with peak concentrations reached at 5 h (median value) after the dose. The pharmacokinetic profile of TMC-207 was linear even at the highest dose tested, with both C_{max} and AUC increasing proportionally with the dose. There was no dose-dependent change in the terminal half-life. Data from a parallel multiple-ascending-dose study (once-daily doses of TMC-207 at 50, 150 and 400 mg) indicated a 2-fold increase in the AUC_{0-24} between day 1

and day 14, with no substantial variation among subjects. These findings suggest an effective half-life of 24 h, which is significantly higher than the half-life of available anti-TB drugs. The mean AUC_{0-24} values were 7.91, 24 and 52 μg.h/ml, respectively, at steady state (corresponding to average concentrations of 0.33, 1.0 and 2.2 μg/ml, respectively, across the dosing interval) with 50, 150 and 400 mg/day doses. Of note, these average concentrations were greater than those associated with optimal activity in established infection models in mice (12).

Safety

Preclinical safety studies that included 28-day toxicology assays in rats and dogs, genetic toxicology and safety pharmacology indicated that the evaluation of TMC-207 in humans was warranted. In the first single-dose clinical study in healthy patients, adverse events were mild to moderate and were experienced by 56% of the subjects receiving TMC-207 and by 39% of those receiving placebo. The majority of adverse events reported were considered unrelated to the study interventions. In a second safety assessment, good tolerability was maintained and only 1 subject withdrew from the study due to an unrelated urinary tract infection. The study team also reported that there were no significant changes in vital signs, electrocardiogram or laboratory tests in any of the cohorts (12).

Clinical Studies

In an open-label phase II trial assessing the early bactericidal activity of TMC-207 (29), 75 treatment-naïve patients with smear-positive pulmonary TB were randomized to once-daily oral TMC-207 (25, 100 or 400 mg), 600 mg rifampicin or 300 mg isoniazid for 7 days. The mean decreases in log cfu counts in sputum from baseline to day 7 were 0.04 ± 0.46 for 25 mg TMC-207, 0.26 ± 0.64 for 100 mg TMC-207, 0.77 ± 0.58 for 400 mg TMC-207, 1.88 ± 0.74 for isoniazid and 1.70 ± 0.71 for rifampicin. Significant bactericidal activity for the highest dose of TMC-207 was observed from day 4 onward and was similar in magnitude to that of isoniazid and rifampicin over the same period. The pharmacokinetic profile of TMC-207, as assessed up to 24 h on day 7 of administration, was linear across the dose range. In conclusion, TMC-207 demonstrated bactericidal activity with a delayed onset and was well tolerated, with no serious adverse events reported.

Tibotec, a Johnson & Johnson subsidiary, is currently conducting a second placebo-controlled, double-blind, randomized phase II trial to evaluate the antimycobacterial activity, safety and tolerability of TMC-207 in subjects with newly diagnosed sputum smear-positive pulmonary infection with MDR TB (30). An interim analysis on the first stage of this trial was recently released, and comprised patients who were randomized to receive a five-drug MDR regimen plus either placebo (n = 24) or TMC-207 (n = 23) for 8 weeks (31). There were no differences in biometrics, adherence or resistance to second-line agents. This initial assessment showed that TMC-207 administered for 8 weeks with a standardized five-drug MDR regimen was generally well tolerated and significantly increased the proportion of subjects who became culture-negative (47.5%) compared to placebo (8.7%). These data serve as an early clinical validation of mycobacterial ATP synthase as a promising new target for TB treatment and confirm the results obtained with TMC-207 in animal models.

Source

Tibotec Pharmaceuticals (a subsidiary of Johnson & Johnson).

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