Moxifloxacin: a potential new drug for shortening treatment of pulmonary TB?

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TB requires treatment for at least 6 months with the standard regimen utilizing isoniazid, rifampicin, ethambutol and pyrazinamide. There is a pressing need for shorter regimens to improve adherence and completion rates. Moxifloxacin is highly active *in vitro* against *Mycobacterium tuberculosis*, is well absorbed with a wide volume of distribution. The drug is concentrated in lung tissue and in macrophages: important target sites for TB treatment. The excellent bactericidal activity data has been confirmed in animal models and Phase II studies. Animal experiments suggest that by using moxifloxacin to replace either ethambutol or isoniazid in the regimen, the duration of TB treatment could be shortened. This review summarizes the data that support the development of this drug into new treatment regimens.

Keywords: bacterial load, clinical trials, early bactericidal studies, pharmacokinetics, treatment regimens, TB

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TB remains a major public-health threat in both the developing and developed world. The drugs in the internationally approved regimen were developed between 1948 and 1967, and the regimen was established by a series of clinical trials completed in the 1970s [1]. For the next 30 years, there was little enthusiasm for the development of novel anti-TB agents, although ciprofloxacin was proposed for TB treatment and trialled [2]. In Cape Town, South Africa, in 2000, a meeting of funding agencies, pharmaceutical companies and researchers involved with chemotherapy studies met to plan a way forward, announcing what became known as the Cape Town declaration, an undertaking to license a new agent for the treatment of TB before 2010. This meeting and the subsequent formation of the Global Alliance for TB-drug development has seen a transformation in the interest in TB-drug development, with several promising new agents having been developed [3,4] and a strong pipeline of potential agents at different stages of development [4,5]. Moxifloxacin is only one drug that will be able to meet the ambitious target set by the Cape Town declaration. Fluroquinolones have been proposed as potential anti-TB drugs, but earlier compounds lacked the bactericidal and sterilizing activity to improve the regimens sufficiently to permit treatment shortening [2,6,7]. Moxifloxacin has enhanced activity against *Mycobacterium tuberculosis,* and there are promising data to suggest that it may be able to reduce treatment duration.

Chemistry & mode of action

The quinolones interfere with the delicate process whereby the bacterium is able to coil its long single chromosome within the cell. This requires the DNA to be supercoiled, a process governed in mycobacteria by the enzyme DNA gyrase. Quinolones interfere with this process. DNA gyrase binds to DNA and makes a break, permitting another strand of DNA that is being coiled to pass through the gap, and the enzyme then repairs the gap. When quinolones are administered, these bind to DNA gyrase and interfere with this complex process, producing double-stranded DNA breaks that are lethal to the cell [8,9].

Moxifloxacin is a fluoroquinolone that has a methoxy group at the C-8 position of the quinolone ring, and a diazabicyclononyl ring at the C-7 position. The addition of a methoxy group at the C8 position of the quinolone nucleus has widened the spectrum of antibacterial action to include Gram-positive pathogens. Compounds with a 2,4-difluorophenyl group at the N-1 position in the quinolone nucleus had the greatest bactericidal activity. This activity exceeded that found with substitution of the quinolone nucleus at the C-7 position. A 2,4-difluorophenyl group at the N-1 position in the quinolone nucleus may play an important role in the expression of bactericidal activity against *Streptococcus pneumoniae* [10]. The methoxy substitution at the C-8 position is thought to be especially important in increasing the activity against mycobacteria [11].

These new drugs, which include moxifloxacin and gatifloxacin, are all available in clinical practice. The principal advantage of the most recent quinolones is their extended spectrum against lower respiratory tract pathogens. These new compounds inhibit *S. pneumoniae* in the range

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0.06–0.12 mg/l, and are equally active against penicillin-resistant strains. Importantly, they are active against species of mycobacteria including *M. tuberculosis* [12,13].

Pharmacokinetics

A principal attraction for moxifloxacin as an anti-TB agent is the favorable pharmacokinetic profile. The drug is well absorbed, with 86% being absorbed with a mean dissolution time of 2.4 h. The bioavailability of the drug is almost complete at approximately 90%, with little variability between subjects [14]. Approximately 40% of the drug is bound to plasma proteins [15]. The C_{max} is 2.5 mg/l, and this is 31% lower than the intravenous preparation. The drug has a long half-life, with $t^{1/2}$ of 15.6 h. More than 96% of the drug is recovered from the urine or feces after oral dosing. Approximately 20% of the drug is excreted unchanged in the urine [15].

Importantly, the new quinolones have a high volume of distribution, with moxifloxacin being 3.08 l (range: 2.37–4.51 l)[14]. Moxifloxacin penetrates well into pulmonary tissues. This is illustrated by the results of one study that showed that the concentrations after a 400 mg oral dose in the epithelial lining fluid (ELF), alveolar macrophages (AM) and bronchial mucosa (BM) at 2.2, 12 and 24 h were as follows [16]:

- 2.2 h: 20.7 mg/l, 56.7 mg/l and 5.4 mg/kg;
- 12 h: 5.9 mg/l, 54.1 mg/l and 2.0 mg/kg;
- 24 h: 3.6 mg/l, 35.9 mg/l and 1.1 mg/kg

Similar results have been obtained by other groups [17]. Evidence from mouse studies suggests that transfer across the blood–brain barrier only takes place to a small extent [18].

Moxifloxacin is metabolized by glucuronide and sulphate conjugation and does not affect CYP3A4, CYP2D6, CYP2C9, CYP2C19 or CYP1A2 [19]. The sulphate conjugate (M1) accounts for 38% of the oral dose, and is excreted in feces; approximately 14% of an oral dose is converted to the glucuronide conjugate (M2) and is excreted in urine. Peak plasma levels of M1 and M2 are less than 10% and approximately 40% of those of the parent drug, respectively. Overall, approximately 45% of an oral dose is excreted as parent drug, and approximately 51% as known metabolites [15].

Safety & tolerability

Moxifloxacin has been in clinical use for the treatment of lower respiratory and other infections. It has been shown in a number of postmarketing studies to have a good safety record [20]. Concern has been voiced about the potential cardiac toxicity of moxifloxacin given that prolongation of QTc is a class effect of quinolones. Several studies have suggested that, using the dosage and precautions recommended, moxifloxacin is well tolerated, and that all adverse events were transient and had a favorable outcome [21]. A prospective, randomized trial comparing cardiac toxicity of moxifloxacin and levofloxacin was performed in the USA among elderly patients treated for community-acquired pneumonia. Holter-monitor data were available for 387 patients (192 receiving moxifloxacin and 195 receiving levofloxacin). A total of 16 moxifloxacin-treated patients (8.3%) and ten levofloxacin-treated patients (5.1%) had a primary composite cardiac event ($p = 0.29$); most events were nonsustained ventricular tachycardia (VT) (14 patients receiving moxifloxacin: 7.3%; and ten patients receiving levofloxacin: 5.1%). One moxifloxacin-treated patient had sustained monomorphic VT (more than 30 s), and one levofloxacin-treated patient had torsade de pointes. Mean ± standard deviation QTc (Fridericia formula) change on day 3 was + 6.4 ± 23.2 ms for moxifloxacin and -2.5 ± 22.9 ms for levofloxacin ($p = 0.04$). No deaths clearly related to study drugs occurred during the observation period [22]. Safety data from 27 prospective, randomized, comparative Phase II/III trials of oral moxifloxacin included in the manufacturer's clinical trial database were pooled and analyzed by age group (age <65 years, age 65–74 years, age ≥75 years) and by treatment group (moxifloxacin vs comparator). No arrhythmias related to QTc interval prolongation were reported following oral moxifloxacin or comparator treatment in this large group of young and elderly patients. Overall, the number of deaths was similar between the treatment groups (17 moxifloxacin and 19 comparator) [23].

Moxifloxacin in TB treatment

TB therapy is considerably longer than the durations reported above; however, in reports of patients treated over an extended period with moxifloxacin for drug-resistant TB, the drug was shown to be well tolerated [24]. In study 27, which compared a moxifloxacin-containing regimen with standard anti-TB therapy, the proportion completing therapy was similar, as were the rates of serious adverse events. There

was a significant increase in the number of patients complaining of nausea, but this symptom seldom required temporary or permanent discontinuation of therapy.

Activity against *Mycobacterium TB in vitro*

The first report of the activity of moxifloxacin against *M. tuberculosis in vitro* was by Woodcock *et al.*, who tested four strains with varying degrees of susceptibility to standard anti-TB drugs and found minimum inhibitory concentrations (MICs) of between 0.12 and 0.5 mg/l [25]. This result has been confirmed by others. Testing a larger number of strains, Ji *et al.* found moxifloxacin to have activity similar to that of sparfloxacin, while clinafloxacin was less active [26]. Gillespie *et al.* found moxifloxacin to be the most active fluoroquinolone, with MIC90 values of 0.25 mg/l [13]. Based on the information currently available, moxifloxacin would appear to be one of the most active fluoroquinolones overall, comparing favorably with gatifloxacin, and having MIC values generally of 0.5 mg/l or less.

Subsequent studies have shown useful synergy with isoniazid and lower concentrations of rifampicin [27]. Importantly, ethambutol was shown to interfere with the lethal activity of moxifloxacin. Using *Mycobacterium smegmatis* the use of ethambutol was associated with an increase in the recovery of fluoroquinolone mutants [27]. Several *in vitro* models of latency have been used to study the activity of moxifloxacin. Against rifampicin-tolerant 100-day cultures, moxifloxacin was able to exert a bactericidal effect in contrast to isoniazid, which had no similar activity [28]. The addition of moxifloxacin to combinations of standard anti-TB drugs increased the killing of 30-day stationary-phase cultures and others growing at low pH (5.9) [29].

Activity in mouse models of TB

Several fluoroquinolones have been evaluated in a mouse model using strains of human TB as the infecting organism, although results in these *in vivo* models are available for fewer of the new compounds than are *in vitro* tests. Early studies of different quinolones in mice have supported the excellent *in vitro* activity and are summarized in Gillespie *et al.* [12] and Gillespie and Kennedy [6].

Recent studies have shown that moxifloxacin is highly effective in mouse models of TB. When compared with sparfloxacin, at doses of 25–100 mg/kg six-times weekly, moxifloxacin had a similar protective effect, but produced a significantly better bactericidal effect in the spleens on a weight-for-weight basis, although activity of the two compounds was similar *in vitro* [26]. A particularly significant result from this study, in view of the importance of early bactericidal activity (see below), was the bactericidal activity produced by moxifloxacin: a dose of 100 mg/kg was as bactericidal as isoniazid at 25 mg/kg. The good activity of moxifloxacin in mouse TB has been confirmed by Miyazaki *et al.* who used a low dose of 100 mg/kg daily [30]. The authors also showed that a combination of isoniazid and moxifloxacin was synergistic. Several mouse studies have demonstrated that combinations of moxifloxacin, rifapentene and isoniazid given once-weekly are as effective as the standard regimen, although a higher relapse rate was found with lower moxifloxacin dose [31,32].

TB cannot be treated with a single drug, but must be managed with multidrug regimens where there is a potential for antagonism and pharmacological interference. Evidence from a mouse study showed that there was a significant improvement in the response with moxifloxacin, rifampicin and pyrazinamide (MRZ) compared with moxifloxacin, isoniazid, rifampicin and pyrazinamide (MHRZ), suggesting that rifampicin and isoniazid may be antagonistic [33]. Such an antagonism is plausible and has been demonstrated between antibiotics that inhibit protein synthesis and those that interfere with cell-wall metabolism [34]. In a second murine study, MRZ proved to be the optimum regimen tested (none of them contained ethambutol) in producing a stable cure using a shortened regimen [35]. Other moxifloxacin-containing combinations that have shown promise in the mouse model include those with third-line agents and against multiple drug-resistant strains [36,37]. A combination with the novel diarylquinoline TMC207 also resulted in enhanced killing *in vivo* [38].

Although the studies reported here are interesting and encouraging, the results obtained in animal studies need to be tested in properly conducted clinical trials.

Clinical studies

Phase II studies

Early bactericidal activity (EBA) studies are the cornerstone of the initial stages of TB-drug trials, as they allow comparison between individual TB drugs, where sequential viable counts (colony forming units [cfu]) of *M. tuberculosis* in 12-h overnight sputum collections are counted out for

5 days and the data evaluated by nonlinear regression analysis [39,40]. Our group has evaluated moxifloxacin using the EBA methodology, and the data from these studies show that moxifloxacin has bactericidal activity in patients with smear-positive pulmonary TB [41,42]. The time taken to reduce the sputum viable count by 50% was 0.88 days (95% confidence interval [CI]: 0.43–1.33) for moxifloxacin, 0.46 days (CI: 0.31–0.61) for isoniazid and 0.77 days (CI: 0.54–1.0) for rifampicin [42]. In a subsequent study, we showed that there was no evidence of antagonism between moxifloxacin and isoniazid *in vivo*, with the suggestion that this combination is more active, although the difference was small and did not achieve statistical significance [41]. These data have been confirmed by other groups that additionally showed similar activity for gatifloxacin and high-dose levofloxacin [43,44].

Comparative trials of fluoroquinolones

There are relatively few controlled trials of fluoroquinolone-containing regimens in open pulmonary TB, despite the widespread use of this class of agent. The first of these trialled an isoniazid, rifampicin regimen with 750 mg of ciprofloxacin for 4 months, followed by a further 2 months of isoniazid and rifampicin (HR) in comparison with the standard isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE2)/HR4 regimen in 200 patients [2]. All patients achieved a bacteriological cure at 6 months, but the time in months from admission to the first negative result (for both smear and culture) was longer for patients in the isoniazid, rifampicin and the isoniazid, rifampicin, ciprofloxacin (HRC) group ($p = 0.02$). When patients were stratified by HIV status it emerged that patients without HIV infection had a similar response to both therapies, suggesting that the difference was largely due to poor response of HIV-infected individuals. There was an increase in the relapse rate in the HRC arm, predominantly in the patients with HIV infection, although this difference failed to achieve statistical significance [2]. This pyrazinamide-substitution regimen had poorer sterilizing activity than the standard regimen, and this may have been due to the relatively low dose of ciprofloxacin used.

There has been one large-scale study of levofloxacin that compared the two arms HRZE and isoniazid, rifampicin, pyrazinamide, ethambutol and HRZEL in the intensive phase of treatment in 101 HIV-positive individuals. The end point used was treatment response during the first 8 weeks. Although the quinolone-containing regimen was well tolerated, it did not appear to provide any additional benefit [45]. A study from Chennai, India, has investigated four regimens containing ofloxacin: ofloxacin, isoniazid, rifampicin and pyrazinamide (OHRZ) for 3 months, OHRZ3/twice-weekly HR1, OHRZ3/twice-weekly HR2 and OHRZ2/twice-weekly HR2. This was a large study with a total of 529 patients admitted, of which 416 were evaluable. Bacteriological cure was achieved at the end of regimen in all but 1% of patients. The relapse rate was 8, 4, 2 and 13%, respectively, although among patients with initial isoniazid resistance, 19% suffered relapse. This study suggested that an ethambutol substitution regimen may provide effective treatment shortening, but no unequivocal conclusion could be drawn because there was no standard treatment arm for comparison. These data did stimulate further studies with more bactericidal quinolones: moxifloxain and gatifloxacin.

Another, as yet unpublished study, OFLOTUB, has compared three different quinolone-containing regimens (isoniazid, rifampicin, pyrazunamide and moxifloxacin [HRZM], isoniazid, rifampicin, pyrazinamide and gatifloxacin [HRZG] and isoniazid, rifampicin, pyrazinamide and ofloxacin [HRZO]) over the intensive phase, with the standard regimen using the proportion that are culture positive as the end point [46]. The results indicate that HRZM killed significantly faster than HRZE in both early and late phases of therapy. This effect suggests that a reduction in the duration of therapy of 1 or possibly 2 months was achievable. HRZG also increased the rate of sputum clearance, but this effect was smaller than the moxifloxacin-containing regimens and was not statistically significant at the sample size employed in the trial. The HRZO arm did not appear significantly different from HRZE control, and these encouraging results are being evaluated in a Phase III study.

The recent TBTC study 27 showed that there were a significantly greater proportion of patients treated with an ethambutol substitution regimen who are culture-negative after 4 and 6 weeks, indicating that this regimen provides more rapid bacterial killing than the control arm. This opens the possibility that such a regimen may be effective if only given for 4 months, providing a substantial advantage in patient adherence and treatment completion rates. A series of mouse studies have indicated that substituting a quinolone for isoniazid in the regimen may bring

Box 1. Overview of the REMoxTB Phase III trial.

Design: randomized, placebo-controlled, double-blind trial comparing:

- 2MHRZ/2MHR
- 2EMRZ/2MR
- 2EHRZ/4HR

End-points for both comparisons

- Primary efficacy end point
  - Combined failure of bacteriological cure and relapse within 1 year of completion of therapy
- Primary safety end point
  - Proportion of patients with grade 3 or 4 adverse events
- Secondary efficacy end points
  - Culture negativity at 2 months
  - Time to first culture-negative sputum sample
  - Speed of decline of sputum viable count
  - Time to unfavorable bacterial outcome

Trial design

- Noninferiority trial
- Failure/relapse rate in control regimen of 4%
- Total of 10% of patients in study arms predicted to have an unfavorable response due to classification of all defaulters and deaths during treatment, and participants dying from respiratory or unknown cause after treatment, as failures
- Inferiority margin (δ) of 6%
- Statistical justification: based on previous studies, where difference between 4- and 6-months regimens was approximately 9–10%
- One-sided significance level of 0.025
- Study size = 2000 (400 patients per arm)

Schedule of study visits

- Intensive phase (week 1–8): weekly review
- Continuation phase (week 8–26): monthly review

E: Ethambutol; H: Isoniazid; M: Moxifloxacin; R: Rifampicin; Z: Pyrazinamide.

an even greater reduction in the proportion of patients culture-negative at 2 months, and this is the subject of further clinical trials organized by the TBTC under the name study 28. The preliminary results from this study provide evidence of a small advantage for a moxifloxacin substitution for isoniazid in the standard regimen. To take these encouraging initial results forward towards inclusion in TB treatment program, it will be necessary to perform a Phase III pivotal study. Such as study is the objective of the REMoxTB study, which is a key component of a global program to evaluate the role of moxifloxacin under the aegis of the Global Alliance for TB Drug Development [5] and sponsored by University College (London, UK). This study, supported by the Global Alliance and the European Developing Country Clinical Trials Partnership, has a placebo-controlled, double-blind design that will compare the standard regimen HRZE2/HR4 with HRZM for 4 months and ethambutol, moxifloxacin, rifampicin and pyrazinamide (EMRZ) for 4 months, using bacteriological cure and relapse as the primary end points (**Box 1**) [5].

Quinolones have not previously been part of any recommended regimen for the treatment of TB, but have found a role in the management of disease where there has been resistance to first-line agents or the patient has been unable to tolerate these drugs [6]. There are anecdotal reports of the use of moxifloxacin in similar circumstances, which are encouraging that it may also find a similar role [47]. The difficulties of performing clinical trials among patients infected with multiple drug-resistant strains make it difficult to provide evidence-based recommendations on the use of moxifloxacin in these circumstances. Thus, each case must be approached on an individual basis, and the regimen fitted to its particular circumstances.

Conclusion

Moxifloxacin is a fluoroquinolone that has been shown to be active against *M. tuberculosis in vitro*. Studies in mouse models indicate that novel combinations of moxifloxacin and other anti-TB drugs may result in effective treatment with shorter regimens. These data have been

Executive summary

Mechanism of action

- Fluoroquinolones interfere with bacterial DNA gyrase, producing double-stranded breaks in bacterial DNA that are lethal to the cells.
- Moxifloxacin has a methoxy group at the C-8 position of the quinolone ring, and a diazabicyclononyl ring at the C-7 position has activity against mycobacteria *in vitro*.
- Moxifloxacin has been found to be the most active fluoroquinolone, with MIC90 values of 0.25 mg/l.

Pharmacokinetic properties

- The drug is well absorbed, with 86% being absorbed with a mean dissolution time of 2.4 h.
- The bioavailability of the drug is almost complete at approximately 90%, and approximately 40% bound to plasma proteins.
- After oral administration, the C_{max} is 2.5 mg/l and this is 31% lower than the intravenous preparation.
- The drug has a long half-life, with $t^{1/2}$ of 15.6 h, with more than 96% of the drug being recovered from the urine or feces after oral dosing.
- Moxifloxacin is concentrated in pulmonary tissues and macrophages.

Clinical efficacy

- The activity of moxifloxacin against *Mycobacterium tuberculosis* has been confirmed in early bactericidal studies.
- Phase II studies provide some evidence that moxifloxacin-containing regimens may be used in treatment-shortening regimens.
- Phase III pivotal studies are underway.

Safety & tolerability

- Moxifloxacin has an excellent safety record in postmarketing studies.
- Safety data from 27 prospective, randomized, comparative Phase II/III trials of oral moxifloxacin were compared and no excess of deaths attributed to QTc problems were shown.
- In TB treatment studies of 2 months and longer, moxifloxacin has been shown to be safe and well tolerated.
- Nausea was reported more frequently in control regimens, but this symptom was not sufficient to cause temporary or permanent cessation of therapy.

Drug interaction

- Moxifloxacin is metabolized by glucuronide and sulphate conjugation.
- Cytochrome enzymes are not induced by moxifloxacin.

Dosage & administration

- Moxifloxacin is administered orally in 400-mg daily doses in TB.

supported by data from Phase II studies, and Phase III studies are currently underway to provide data for registration of moxifloxacin for the treatment of TB in shortened regimens.

Future perspective

The development of new drugs in TB is a slow process because the number of patients required to perform an adequate clinical trial is very large, and patients must be followed-up for at least 1 year after treatment is completed to confirm cure. Moreover, treatment is always given as part of a regimen, with the effect that there are several potential possibilities that need to be tested. In 5 years' time, we would expect that the development program for moxifloxacin will have come to a conclusion that would, if it demonstrates similar outcomes for treatment in 4 months in comparison to 6 months, permit this new regimen to be recommended for treatment internationally. This development would make important cost savings in the treatment of TB and would be an important weapon against this disease, which has caused so much unnecessary death in developing countries.

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