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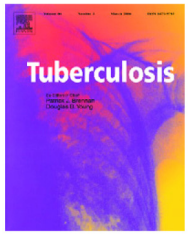

Pharmacokinetics and pharmacodynamics in the development of anti-tuberculosis drugs

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Summary
Optimization of dosing strategies and companion drugs prior to Phase III trials is currently a critical obstacle in the development of new anti-tuberculosis drugs. Pharmacokinetic-pharmacodynamic (PK-PD) methods have assumed an important role in improving the efficiency of this process across the pharmaceutical industry and in other areas of anti-infective therapy. Information gained using PK-PD methods from the earliest in vitro assessments right up to the end of Phase II development can underpin proof-of-concept and ensure that agents are fully pharmacologically optimized. Despite our limited understanding of the biology of bacillary elimination in vivo, such an approach has already provided key insights into these mechanisms and helped to identify the role of different drugs in therapy and assess their potential for progression to pivotal trials. While isoniazid appears historically to have been effectively exploited, human studies suggest that it does not play a key role in the sterilizing phase of treatment. Re-evaluation of the PK-PD of rifamycins by contrast suggests that there may be considerable scope for improving their activity by intensifying current dosing strategies. Various PK-PD analyses of the fluoroquinolone series demonstrate remarkable agreement concerning the ranking of their sterilizing activity, results which appear to be confirmed in recent human phase II studies. The pharmacological characteristics of completely new classes of drugs now entering clinical development suggest that experience with existing drugs, particularly EBA studies, should not prejudice evaluation of their pharmacodynamic activity which may differ qualitatively from that of many current agents. In conclusion, PK-PD analysis has a vital role to play in the rational development of new anti-tuberculosis drugs and combination regimens.

Introduction

For the first time in thirty years, ultra-short course chemotherapy for tuberculosis appears a feasible goal. Investment in basic mycobacteriology and drug discovery has produced an unprecedented portfolio of lead compounds. Their late pre-clinical and early clinical development presents several specific challenges however, some arising from weaknesses in our understanding of how therapy works. Modern pharmacokinetic-pharmacodynamic (PK-PD) methods provide a conceptual framework within which we can improve our knowledge of the biological basis of pharmacodynamic phenomena and enhance the methodology and causal interpretation of clinical trials. In this review we describe some obstacles facing new anti-tuberculosis drugs during development, outline the contribution that

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PK-PD methods can be expected to make to resolving them and review the current state of our knowledge of the PK-PD properties of existing and new anti-tuberculosis drugs.

Current problems in development of new anti-tuberculosis drugs

The sequence of clinical trials that resulted in modern short-course chemotherapy was completed by 1985, using a development strategy moving directly from Phase I studies of restricted scope to pivotal Phase III trials with limited prior evaluation in animal models.[1] This approach is no longer feasible. Regulatory changes in clinical drug development have formalized staging of the evaluation of efficacy and safety as well as increased scrutiny of different aspects of the pharmacology of new drugs.

Moreover, short-course regimens virtually eliminated failure during treatment and shifted attention to rates of relapse, which were consistently reduced to 5% or less. Such a strong comparator makes new Phase III trials, even non-inferiority designs, expensive and risky and since definitive proof of "sterilizing" activity relies on relapse, there is controversy as to whether a range of surrogate endpoints used in animal models and early clinical development can adequately capture this specific pharmacodynamic activity. PK-PD approaches may be key to resolving these disagreements about how best to demonstrate efficacy, while ensuring that the regimens are fully optimized at the intermediate Phase II stage.

Pharmacokinetic-pharmacodynamic methods in modern drug development

Classical PK-PD analysis focused on mechanistic representations of intensively sampled *ex vivo* and animal models[2] but PK-PD ideas have recently been applied in clinical drug development, lending statistical and causal support to the evaluation of dose-response[3,4] and are advocated as a means of improving its efficiency.[5,6] In infectious diseases therapy, PK-PD analysis is of particular clinical interest and has demonstrated its practical relevance in acute pneumonia,[7] HIV infection[8,9] and malaria.[10,11] Clinical translation of the PK-PD approach has been enabled by key advances in hierarchical or "population" approaches to pharmacokinetics capable of making effective use of sparse data collected under clinical trial conditions.[12] Therefore, tools now exist which can accrue increasingly reliable PK-PD information from the earliest in vitro assessments right through to the beginning of Phase III.

PK-PD methods in tuberculosis

In vitro methods

The simplest bacteriological pharmacodynamic measure is the Minimum Inhibitory Concentration (MIC), the drug concentration which arrests growth of 90 or 99% of colony-forming units in vitro under conditions of unrestricted growth at a standardized density employing static drug exposure. This is the measure of activity typically used in primary drug discovery screens.[13] It can be crudely related to pharmacokinetic properties by establishing breakpoints related to peak plasma concentrations (C_{max}) and can aid prediction of in vivo pharmacodynamics within series of related agents. However, it does not represent the concentration at which growth ceases[14] and does not distinguish between static and cidal activity. More importantly, static drug exposure cannot accurately represent dynamic in vivo PK-PD relationships (such as Area-under-the curve (AUC)/MIC or time > MIC) and growth conditions are unrepresentative of persisting organisms in vivo.

Liquid culture models of microbial persistence have been developed and used to assess potential "sterilizing" activity of drugs. These models enable repeated evaluation of killing under conditions of altered growth characteristics[15,16,17] and have been applied to the study of altered time-kill properties in antibiotic-tolerant *Mycobacterium tuberculosis* strains.[18] Hollow fiber systems that allow for realistic pharmacokinetic patterns of drug exposure can also be adapted to the study of *M. tuberculosis*.[19] This approach has been used to study the relationship between PK and emergence of resistance for several fluoroquinolones, isoniazid and rifampin[19,20,21,22] as well as the post-antibiotic effect of moxifloxacin.[23] Transferring the environmental conditions of persistence models to the hollow fiber system could be the ideal approach to study the pharmacodynamics of sterilizing activity in vitro but prolonged experiments in this system are prone to contamination. All of these models produce sizeable populations of non-multiplying and drug-tolerant organisms but the extent to which they reproduce in vivo conditions remains unclear.

Animal models

Evaluation of in vivo efficacy of new drug regimens in animals still depends on mouse models. Simple monotherapy protection experiments using lethal inocula via the intravenous or aerosol route can provide proof of efficacy and preliminary dose selection. Short-term studies can estimate the bactericidal activity of single drugs or combinations using colony counting of organ homogenates and the ability to prevent selection of mutants resistant to companion drugs, but experiments longer than two months appear necessary to describe sterilizing activity. Negative organ cultures at completion of therapy cannot be assumed to indicate sterilization and three month follow-up to determine durable cure should be considered the most rigorous measure of sterilization. Alternative approaches based on the "Cornell" mouse model utilize intensive therapy to obtain a culture-negative state and then test the ability of individual drugs or combinations to prevent "relapse" when mice are left untreated or undergo immunosuppression, but this is a time-consuming and risky system which may not give consistent results.[24,25]

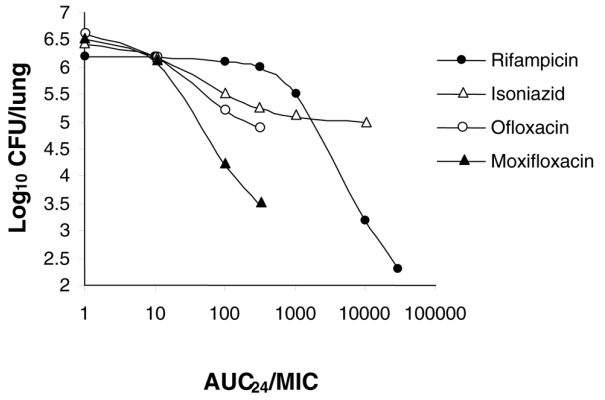

Figure 1 Mouse dose-fractionation studies (Jayaram et al 2003, 2004, 2007).

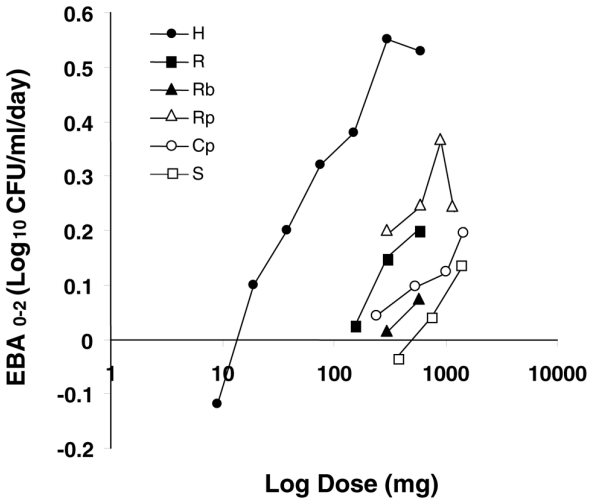

Figure 2 EBA Dose Titration Studies (from Donald 2003) H=isoniazid, R=rifampicin, Rb=rifabutin, Rp=rifapentine, Cp=ciprofloxacin, S=streptomycin.

Dose fractionation studies are also feasible in mice and can determine the strongest PK-index and its precise relationship with PD effect. Recent such studies have improved our understanding of the PK-PD of isoniazid, rifampin and the fluoroquinolones[26,27,28] (see Figure 1). These experiments may inform clinical development with regard to optimal dosing strategies and may be used to perform population-based pharmacodynamic simulations and to prioritize related compounds in a discovery program. They are labor-intensive, however, and not very amenable to long-term models including relapse.

Due to their small size, relatively low expense and extensive history, mice will likely remain the animal model of choice for tuberculosis but they do not develop caseation necrosis or cavitation, the hallmarks of pulmonary tuberculosis,[29] and great care is required when scaling doses of agents between mouse and man due to metabolic differences and unforeseen pharmacokinetic interactions.[30] Recent work with microelectrodes and the redox indicator pimonidazole in murine tuberculosis suggests that anaerobic conditions are not reproduced in these lesions in vivo[31] and that transcription profiles of recovered bacilli may be dependent on the stage of infection and species used.[32]

The histological features of guinea pig tuberculosis more closely approximate human pathology but there is little modern experience with this experimental model in chemotherapeutics. Prior studies suggest that, like the mouse, the guinea pig model is able to differentiate between the superior sterilizing activity of rifampin over that of isoniazid but pyrazinamide historically demonstrated no activity in guinea pigs.[33,34] New drugs in development provide an excellent opportunity to compare assessment of sterilizing activity across existing in vitro and animal models in hopes of ultimately referencing each model to the activity demonstrated in clinical trials.

Clinical PD measures

Though the relapse endpoint has been utilized in clinical dose-response studies,[35] this requires prohibitively large sample sizes and clinical PK-PD studies have necessarily relied on intermediate bacteriological endpoints. The simplest approach uses the proportion of negative smears or cultures at fixed timepoints during treatment, usually two or three months.[36,37] Selecting a single endpoint is arbitrary, however, and its power when expressed as a binary outcome depends strongly on the magnitude of the probability of smear/culture conversion in the comparator arm. One solution to this problem is to model the probability of conversion using logistic regression. A more informative approach is to use samples obtained at multiple timepoints which can be analyzed using a variety of survival techniques.[38,39,40] All of these techniques, however, express the bacillary load in sputum only indirectly.

Quantitation of the decline of viable *M. tuberculosis* in sputum during the first 14 days of therapy using plate-counting was first used to assess drug activity in 1977.[41] This "early bactericidal activity" (EBA), analyzed using summary statistics based on linear regression, proved a useful means of comparing agents during monotherapy, demonstrating dose-response and in the case of isoniazid, identifying the PK-PD relationship, at small sample sizes[42] (see Figure 2). However, EBA did not appear to reflect the "sterilizing activity" of drugs observed in Phase III trials. Subsequent colony-counting studies of combination therapy extended over the first four-eight weeks and analyzed using hierarchical nonlinear regression techniques suggest that bacillary elimination is biphasic and that by focusing on the later phase this approach can reproduce the results of historical clinical trials[43,44] and detect differences between novel regimens[40] (see Figure 3).

Liquid culture systems, especially those that are continuously monitored, are also inherently quantitative, producing a "time-to-positivity" (TTP) directly related to colony counts on a logarithmic scale. Experience with such data is limited but it may better represent that part of the bacillary population in a restricted growth

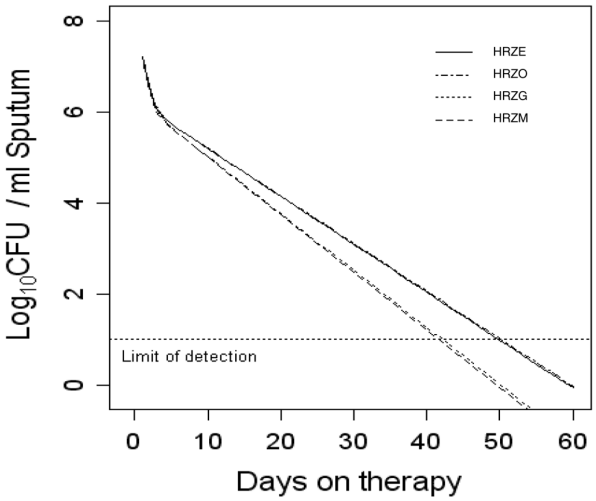

Figure 3 Oflotub IIB study. Results of mixed effects modelling of serial sputum colony counting data (Rustomjee 2008).

state while preserving the power of a hierarchical regression approach. Non-bacteriological endpoints such as whole-blood bactericidal and interferon-gamma release assays may also have a role to play in PK-PD analysis.[45,46]

PK-PD of anti-tuberculosis agents

Nicotinamide analogs

Isoniazid

Isoniazid shows very high inter-individual pharmacokinetic variability, with a multi-modal distribution of exposure.[47,48,49] This pharmacokinetic phenotype was recognized in early studies as an important determinant of neurotoxicity[50,51] and is determined by polymorphisms at the N-arylamine acetyltransferase (NAT2) locus,[52] with alleles conferring a "slow" acetylator phenotype associated with 4-fold greater exposure compared to "rapid" acetylators.[53,54] Disposition of isoniazid in pulmonary epithelial lining fluid is comparable to that in plasma.[55]

Isoniazid exhibits the highest EBA yet observed,[42] reflecting its potent action on multiplying bacilli.[37] Rapid attenuation of its effect after the first few days has been attributed to eradication of a majority subpopulation of actively dividing bacilli.[56] Though it has been argued from hollow fiber system data that the emergence of drug resistance may explain the phenomenon,[22] this has not been observed in clinical studies.[57] EBA dose titration studies have defined a complete dose response curve with maximum achievable EBA within the range of clinically tolerable doses.[58] The PK-PD relationship is well-defined in animal, hollow fiber and EBA studies, exhibiting a log-linear relationship with response over a wide range of AUC/MIC values and an independent effect of acetylator genotype.[22,27,45,59] *In vitro* pharmacodynamic studies support a prolonged post-antibiotic effect, increasing with repeated drug pulses[60,61] and consistent with dosing intervals effective in clinical trials.[62] Acetylator phenotype does not affect outcomes of short-course therapy[63] except in highly intermittent regimens in HIV-positive patients where low isoniazid exposure has been linked with relapse.[64,65]

Pyrazinamide

Pyrazinamide shows limited pharmacokinetic variability[48,66] even in HIV positive subjects[67,68] despite phenotypical variation in its metabolism (particularly xanthine oxidase).[69,70] Although the nicotinamide analog pyrazinamide acts by an entirely different mechanism than isoniazid,[71] it requires acidic conditions to inhibit *M. tuberculosis* at clinically relevant concentrations and has little or no activity in pH-neutral media or in macrophage models.[72] It has modest bactericidal activity in murine models when administered alone but displays remarkable synergy with rifamycins and several new drugs.[73,74,75,76] It shows no EBA over the first two days[41] though in extended colony counting studies it does have a detectable effect.[37,44] The PK-PD correlates of pyrazinamide's unique sterilizing activity therefore remain undefined and pragmatic dose selection has been on the basis of limiting hepatotoxicity.[77,78]

Rifamycins

Rifamycins differ chemically from other first line drugs in that they are zwitterionic rather than basic and have much higher logP values. They are inducers as well as substrates of several metabolic mechanisms including CYP3A4[79] and P-glycoprotein, the efflux protein product of the MDR1a locus,[80] and consequently prone to drug-drug interactions. All produce active 25-O-desacetyl metabolites.[81] Rifampicin autoinduces its metabolism, resulting in a 20–40% fall in exposure over the first 1-to-2 weeks of therapy[45,82,83] but this is less marked in other rifamycins. The pharmacokinetics of rifampicin show substantial inter-individual and inter-occasion variability[84] which is particularly affected by HIV co-infection,[85,86] MDR1a polymorphism[45] and possibly diabetes.[87] Exposure increases non-linearly with doses up to 10–13 mg/kg.[88,89] By contrast, rifapentine pharmacokinetics are linear over doses ranging from 300 to 1200 mg during intermittent administration.[90–93] Concentrations of both agents are lower in epithelial lining fluid compared to plasma but both are accumulated in alveolar cells[94,95] and total exposure of rifampicin in respiratory secretions may be higher than in plasma.[88]

Short-term dose fractionation mouse studies confirm that AUC/MIC of rifampicin is the PK index best correlating with activity[26] and "humanized" doses of 10 mg/kg daily (with an AUC bioequivalent to the standard 600 mg dose) are barely on the upstroke of the dose-reponse curve, with activity being lost at 5 mg/kg.[96] In mice, unlike isoniazid, these doses are far from any observed maximum effect.[97]

EBA dose-titration studies confirm a minimum effective dose at approximately 5 mg/kg[41] and continuously increasing response with rifampicin doses up

to 1200 mg at which maximum effect does not appear to be achieved.[41,93,98] In USPHS Study 19, a 450 mg dose achieved slower sputum conversion and had a higher rate of treatment failure compared to doses of 600 or 750 mg in combination regimens.[35] When released for compassionate use, rifampicin was dosed at 1,200 mg or greater[99,100] and several small trials have claimed improved results with such doses.[101] Together, these PK-PD data argue that dose selection during development of rifampicin may have been inadequate and the current 600 mg dose could be sub-optimal.

Similar EBA dose-response curves have also been observed for rifabutin and rifapentine.[93,102] Development of rifapentine focused on its pharmacokinetic potential for once weekly administration, conditions under which a 600 mg dose may be inferior to standard rifampicin-based regimens in patients at high risk of relapse.[103] Rifamycins demonstrate substantial post-antibiotic effect in vitro making them suitable for intermittent therapy,[60] but all are vulnerable to the emergence of rifamycin monoresistance under these conditions.[104,105,106,107] This is likely related to pharmacokinetic mismatching with isoniazid, ready selection of rifamycin-resistant organisms, reduced rifamycin bioavailability and poor immunity in HIV-co-infected patients.[21,64,65,107,108] Whether companion drugs with longer half-lives, such as moxifloxacin, would eliminate this problem remains an open question. From the pharmacodynamic standpoint, however, rifapentine is well tolerated at doses up to 1200 mg once weekly and 450–600 mg daily.[92,109] The marked increase in rifamycin exposure obtained with such dosing regimens enables treatment to be shortened to three months or less in the mouse model[74,110] and argues that more potent daily rifapentine-based regimens could be obtained by exploiting the PK-PD relationship.

Fluoroquinolones

Development of the fluoroquinolones has resulted in enhanced anti-tuberculosis activity.[111] The 8-methoxyquinolones moxifloxacin and gatifloxacin are most potent in vitro, with MICs ranging from 0.125 to 0.5 μg/mL[112] and perform well in an in vitro persistence model.[113] Experience with fluoroquinolones in non-mycobacterial respiratory infections identified AUC/MIC as the best PK index[7] and mouse data support the applicability of this concept to tuberculosis.[28] Comparison of expected AUC/MIC values in humans at standard doses range from 12 for ciprofloxacin and ofloxacin, 45 for levofloxacin, and 60–80 for moxi and gatifloxacin[114] while doubling the levofloxacin dose to 1000 mg achieves AUC/MIC parity with the 8-methoxyquinolones. Because moxifloxacin undergoes extensive hepatic metabolism, which is induced by rifampicin,[115,116] and there are toxicity concerns with gatifloxacin, high-dose levofloxacin could become the preferred fluoroquinolone in rifamycin-containing regimens.

A recent EBA study comparing high-dose levofloxacin, moxifloxacin, gatifloxacin and isoniazid[117] confirmed this pharmacodynamic ranking demonstrating similarly potent activity across these agents greater than that previously observed for ciprofloxacin.[118]Their activity approached that of isoniazid during the first two days and exceeded it over the remaining five. A retrospective study also suggested the superiority of levofloxacin over ofloxacin for MDR-TB patients.[119]

A recent extended colony counting study demonstrated faster bacillary clearance from sputum when 8-methoxyquinolone, but not ofloxacin, was substituted for ethambutol during the intensive phase of therapy[40] (Figure 3). Two other Phase II trials have examined similar regimens using culture conversion as an outcome and both suggested clearance of sputum with moxifloxacin[120,121] although there was no advantage at 2 months in one study.[120]

Emergence of fluoroquinolone-resistant mutants occurs rapidly with exposure in vitro in mice and in humans.[19,23,122] Although theory predicts that resistance under monotherapy can be prevented, the drug exposures required cannot be achieved in vivo.[19,123] While combination therapy remains necessary to prevent selection of drug-resistance, each agent should be administered in a way that minimizes the risk of resistance to the drug itself or its companions. This may prove to be particularly important in the choice of fluoroquinolone and dose selection in the treatment of MDR-TB to prevent the emergence of extensively drug-resistant (XDR) tuberculosis.

New agents

The most advanced of the novel anti-tuberculosis agents, the nitroimidazole derivatives PA-824 and OPC-67683 and the diarylquinoline TMC207 (aka R-207910), each have logP values similar to the rifamycins (3.69–6.41), are highly protein-bound and eliminated slowly with half-lives of 17–24 hours.[76,124] Among the nitroimidazole derivatives, OPC-67683 has a 10-to-20-fold lower MIC than PA-824 but the PK-PD relationship for this new class of drugs remains unknown and human PK data are not yet available. In mice, both agents demonstrate bactericidal activity when administered alone and accelerated bacillary clearance when substituted for isoniazid in a three drug regimen.[76,125]

TMC207 has potent in vitro activity against *M. tuberculosis* with a typical MIC of 0.06 μg/mL and impressive bactericidal activity in the mouse model. At doses applicable to humans, TMC207 alone is at least as active as the standard first-line regimen of rifampicin, isoniazid and pyrazinamide. A strong synergistic effect is observed with pyrazinamide, making regimens based on this couple capable of rendering mice culture-negative in two months.[75,124] As with the nitroimidazoles, the PK-PD parameter that correlates best with TMC207 activity remains unknown but in vitro studies reveal unusual time dependence. Even with concentrations up to 100× the MIC, activity is not evident until the second week of incubation. These unusual pharmacodynamic properties and the pharmacokinetic accumulation of the drug may explain the slow onset of effect observed in a recent 7-day EBA study.[126] In either event, data from mouse models suggest that these results should not discourage

further evaluation of this promising compound. The sponsor has now embarked on a Phase II study in MDR-TB patients comparing the addition of TMC207 or placebo to an optimized background regimen. For the time being, TMC207 is not under investigation for treatment of drug-susceptible tuberculosis because its metabolism is induced by rifampicin, resulting in a 50% reduction in AUC, and dosing strategies to overcome the drug-drug interaction have yet to be explored.

Conclusion

Interpretation of the pharmacodynamic activity of anti-tuberculosis drugs is complicated by an incomplete understanding of the pathophysiology of the disease. PK-PD relationships are not clearly defined for some important agents and experience is to date based on only a few classes of drugs. However, the PK-PD approach has demonstrated its relevance in contributing to the understanding of many important phenomena in the treatment of tuberculosis such as the role of isoniazid, dose size of rifamycins and potency in fluoroquinolones and promises to become a key component of the rational development of new agents.

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References

1. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units 1946–1986, with subsequent relevant publications. *International Journal of Tuberculosis and Lung Disease* 1999;**3**:S231–S279.
2. Csajka C, Verotta D. Pharmacokinetic-pharmacodynamic modelling: history and perspectives. *Journal of Pharmacokinetics and Pharmacodynamics* 2006;**33**:227–279.
3. International Conference on Harmonisation. *Tripartite guideline E4 : Dose-response information to support drug registration*, 1994.
4. Food and Drug Administration. *Exposure-response relationships - study design, data analysis and regulatory applications*, 2003.
5. Sheiner L, Steimer J. Pharmacokinetic/pharmacodynamic modeling in drug development. *Annual Review of Pharmacology and Toxicology* 2000;**40**:67–95.
6. Miller R, Ewy W, Corrigan B, et al. How modeling and simulation have enhanced decision making in new drug development. *Journal of Pharmacokinetics and Pharmacodynamics* 2005;**32**:185–197.
7. Schentag J, Meagher A, Forrest A. Fluoroquinolone AUIC breakpoints and the link to bacterial killing rates Part 2: human trials. *Annals of pharmacotherapy* 2003;**37**:1478–1488.
8. Winston A, Hales G, Amin J, et al. The normalized inhibitory quotient of boosted protease inhibitors is predictive of viral load response in treatment-experienced HIV-1-infected individuals. *AIDS* 2005;**19**:1393–1399.
9. Rosario M, Poland B, Sullivan J, Westby M, Ryst Evd. A pharmacokinetic-pharmacodynamic model to optimize the phase IIa development program of maraviroc. *Journal of Acquired Immune Deficiency Syndromes* 2005;**42**:183–191.
10. Svensson U, Alin H, Karlsson M, Bergqvist Y, Ashton M. Population pharmacokinetic and pharmacodynamic modelling of artemisinin and mefloquine enantiomers in patients with falciparum malaria. *European Journal of Clinical Pharmacology* 2002;**58**:339–351.
11. Simpson J, Hughes D, Manyando C, et al. Population pharmacokinetic and pharmacodynamic modelling of the antimalarial chemotherapy chlorproguanil/dapsone. *British Journal of Clinical Pharmacology* 2006;**61**:289–300.
12. Pillai G, Mentre F, Steimer J. Non-linear mixed effects modeling — from methodology and software development to driving implementation in drug development science. *Journal of Pharmacokinetics and Pharmacodynamics* 2005;**32**:161–183.
13. Goldman R, Laughon B, Reynolds R, et al. Programs to facilitate tuberculosis drug discovery: the tuberculosis antimicrobial acquisition and coordinating facility. *Infectious Disorders and Drug Targets* 2007;7:**92**–104.
14. Mouton J, Links A. Pharmacokinetic/pharmacodynamic modelling of antibacterials in vitro and in vivo using bacterial growth and kill kinetics : the minimun inhibitory concentration versus stationary concentration. *Clinical Pharmacokinetics* 2005;**44**:201–210.
15. Hu Y, Mangan J, Dhillon J, et al. Detection of mRNA transcripts and active transcription in persistent *Mycobacterium tuberculosis* induced by exposure to rifampicin or pyrazinamide. *Journal of Bacteriology* 2000;**182**:6358–6365.
16. Wayne L, Hayes L. An in vitro model for sequential study of shiftdown of *Mycobacterium tuberculosis* through two stages of nonreplicating persistence. *Infection and Immunity* 1996;**64**:2062–2069.
17. Betts J, Lukey P, Robb L, McAdam R, Duncan K. Evaluation of a nutrient starvation model of *Mycobacterium tuberculosis* persistence by gene and protein expression profiling. *Molecular Microbiology* 2002;**43**:717–731.
18. Wallis R, Patil S, Cheon S, et al. Drug tolerance in *Mycobacterium tuberculosis*. *Antimicrobial Agents and Chemotherapy* 1999;**43**:2600–2606.
19. Gumbo T, Louie A, Deziel M, Parsons L, Salfinger M, Drusano G. Selection of a moxifloxacin dose that supresses drug resistance in *Mycobacterium tuberculosis* by use of an in vitro pharmacodynamic infection model and mathematical modelling. *Journal of Infectious Diseases* 2004;**190**:1642–1651.
20. Gumbo T, Louie A, Deziel M, Drusano G. Pharmacodynamic evidence that ciprofloxacin failure against tuberculosis is not due to poor microbial kill but to rapid emergence of resistance. *Antimicrobial Agents and Chemotherapy* 2005;**49**:3178–3181.
21. Gumbo T, Louie A, Delziel M, et al. Concentration-dependent *Mycobacterium tuberculosis* killing and prevention of resistance by rifampin. *Antimicrobial Agents and Chemotherapy* 2007;**51**:3781–3788.
22. Gumbo T, Louie A, Liu W, et al. Isoniazid's bactericidal activity ceases because of the emergence of resistance, not depletion of *Mycobacterium tuberculosis* in the log phase of growth. *Journal of Infectious Diseases* 2007;**195**:194–201.

23. Ginsburg A, Sun R, Calamita H, Scott C, Bishai W, Grosset J. Emergence of fluoroquinolone resistance in Mycobacterium tuberculosis during continuously dosed moxifloxacin monotherapy in a mouse model. *Antimicrobial Agents and Chemotherapy* 2005;**49**:3977–3979.
24. McCune R, Tompsett R, McDermott W. The fate of Mycobacterium tuberculosis in mouse tissues as determined by the microbial enumeration technique. *Journal of Experimental Medicine* 1956;**104**:763–803.
25. Scanga C, Mohan V, Joseph H, Yu K, Chan J, Flynn J. Reactivation of latent tuberculosis: variations on the Cornell murine model. *Infection and Immunity* 1999;**67**: 4531–4538.
26. Jayaram R, Gaonkar S, Kaur P, et al. Pharmacokinetics-Pharmacodynamics of rifampin in an aerosol infection model of tuberculosis. *Antimicrobial Agents and Chemotherapy* 2003;**47**:2118–2124.
27. Jayaram R, Shandil R, Gaonkar S, et al. Isoniazid pharmacokinetics-pharmacodynamics in an aerosol infection model of tuberculosis. *Antimicrobial Agents and Chemotherapy* 2004;**48**:2951–2957.
28. Shandil R, Jayaram R, Kaur P, et al. Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against *Mycobacterium tuberculosis*: evaluation of in vitro and pharmacodynamic indices that best predict in vivo efficacy. *Antimicrobial Agents and Chemotherapy* 2007; **51**:576–582.
29. Rhoades E, Frank A, Orme I. Progression of chronic pulmonary tuberculosis in mice aerogenically infected with virulent *Mycobacterium tuberculosis*. *Tubercle and Lung Disease* 1997;**78**:57–66.
30. Grosset J, Truffot-Pernot C, Lacroix C, Ji B. Antagonism between isoniazid and the combination pyrazinamide-rifampin against tuberculosis infection in mice. *Antimicrobial Agents and Chemotherapy* 1992;**36**:548–551.
31. Aly S, Wagner K, Keller C, et al. Oxygen status of lung granulomas in *Mycobacterium tuberculosis*-infected mice. *Journal of Pathology* 2006;**210**:298–305.
32. Talaat A, Lyons R, Howard S, Johnson S. The temporal expression profile of *Mycobacterium tuberculosis* infection in mice. *Proceedings of the National Academy of Sciences USA* 2004;**101**:4602–4607.
33. Dickinson J, Mitchison D. Observations in vitro on the suitability of pyrazinamide for intermittent chemotherapy of tuberculosis. *Tubercle* 1970;**51**:389–396.
34. Steenken W, Wolinsky E. The antituberculous activity of pyrazinamide in vitro and in the guinea pig. *American Review of Tuberculosis* 1954;**70**:367.
35. Long M, Snider D, Farer L. US Public Health Service cooperative trial of three rifampicin-isoniazid regimens in treatment of pulmonary tuberculosis. *American Review of Respiratory Disease* 1979;**119**:879–894.
36. Aber V, Nunn A. Factors affecting relapse following short-course chemotherapy. *Bulletin of the International Union against Tuberculosis* 1978;**53**:260–264.
37. Mitchison D. Modern methods for assessing the drugs used in the chemotherapy of mycobacterial disease. *Journal of Applied Bacteriology* 1996;**81**:72S–80S.
38. Schwander S, Rusch-Gerdes S, Mateega A, et al. A pilot study of antituberculosis combinations comparing rifabutin with rifampicin in the treatment of HIV-1 associated tuberculosis. *Tubercle and Lung Disease* 1995;**76**:210–218.
39. Holtz T, Sternberg M, Kammerer S, et al. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to outcome. *Annals of Internal Medicine* 2006;**144**:650–659.
40. Rustomjee R, Lienhardt C, Kanyok T et al A phase II study of the sterilizing activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease* 2008;**12**: 128–138.
41. Jindani A, Aber V, Edwards E, Mitchison D. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *American Review of Respiratory Diseases* 1980;**121**:939–949.
42. Donald P, Sirgel F, Venter A, et al. Early bactericidal activity of antituberculosis agents. *Expert Reviews in Anti-Infective Therapy* 2003;**1**:141–155.
43. Brindle R, Odhiambo J, Mitchison D. Serial counts of Mycobacterium tuberculosis in sputum as surrogate markers of the sterilizing activity of rifampicin and pyrazinamide in treating pulmonary tuberculosis. *BMC Pulmonary Medicine* 2001;**1**:2.
44. Davies G, Khoo S, Aarons L. Use of nonlinear mixed effects analysis for improved precision of early pharmacodynamic measures in tuberculosis treatment. *Antimicrobial Agents and Chemotherapy* 2006;**50**:3154–3156.
45. Davies G, Chierakul N, Saguenwong N et al. A factorial study of the effect of HIV, tuberculosis and pharmacogenetics on the pharmacokinetics, pharmacodynamics of anti-tuberculosis drugs. Abstract 0-106 *Conference on Human Retroviruses and Opportunistics Infections* Boston 2008.
46. McIlleron H, Watkins ML, Folb PI, SR Ress, Wilkinson RJ. Rifampin levels, interferon gamma release and outcome in complicated pulmonary tuberculosis *Tuberculosis (Edinburgh)* 2007 ;**87**:557–564.
47. Ellard G, Gammon P. Pharmacokinetics of isoniazid metabolism in man. *Journal of Pharmacokinetics and Biopharmaceutics* 1976;**4**:83–113.
48 Peloquin C, Jaresko G, Yong C, Keung A, Bulpitt A, Jeliffe R. Population pharmacokinetic modeling of isoniazid, rifampin and pyrazinamide. *Antimicrobial Agents and Chemotherapy* 1997;**41**:2670–2679.
49. Seifart H, Parkin D, Botha F, Donald P, Walt Bvd. Population screening for isoniazid acetylator phenotype. *Pharmacoepidemiology and Drug Safety* 2001;**10**:127–134.
50. Hughes H, Biehl J, Jones A, Schmidt L. Metabolism of isoniazid in man as related to the occurrence of peripheral neuritis. *American Review of Respiratory Disease* 1954;**70**:266–273.
51. Johnson W. Biological acetylation of isoniazid. *Nature* 1954;**174**:744–745.
52. Hein D, Doll M, Fretland A, et al. Molecular genetics and epidemiology of the NAT1 and NAT2 acetylation polymorphisms. *Cancer Epidemiology Biomarkers and Prevention* 2000;**9**:29–42.
53. Parkin D, Vandenplas S, Botha F, et al. Trimodality of isoniazid elimination: phenotype and genotype in patients with tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 1997;**155**:1717–1722.
54. Chen B, Li J, Xu Y, Wang J, Cao X. T he influence of NAT2 genotypes on the plasma concentration of isoniazid and acetylisoniazid in Chinese pulmonary tuberculosis patients. *Clinica Chimica Acta* 2005;**365**:104–108.
55. Conte JE, Golden JA, McQuitty M, et al. Effects of gender, AIDS, acetylator status on intrapulmonary concentrations of isoniazid. *Antimicrobial Agents and Chemotherapy* 2002;**46**:2358–2364.
56. Mitchison D. Role of individual drugs in the chemotherapy of tuberculosis. *International Journal of Tuberculosis and Lung Disease* 2000;**4**:262–267.
57. Mitchison D, Jindani A, Davies G, Sirgel F. Isoniazid activity is terminated by bacterial persistence. *Journal of Infectious Diseases* 2007;**195**:1871–1872.

58. Donald P, Sirgel F, Botha F, Seifart H, Parkin D, Vandenplas M. The early bactericidal activity of isoniazid related to it's dose size in pulmonary tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 1997;**156**: 895–900.
59. Donald P, Sirgel F, Venter A, et al. The influence of human N-acetyltransferase genotype on the Early Bactericidal Activity of isoniazid. *Clinical Infectious Diseases* 2004**;39:** 1425–1430.
60. Dickinson J, Aber V, Mitchison D. Bactericidal activity of streptomycin, isoniazid, rifampin, ethambutol, and pyrazinamide alone and in combination against *Mycobacterium tuberculosis*. *American Review of Respiratory Disease* 1977;**116**:627–635.
61. Mitchison D, Dickinson J. Laboratory aspects of intermittent drug therapy. *Postgraduate Medical Journal* 1998; **47**:737–741.
62. Tuberculosis Chemotherapy Centre M. Controlled comparison of oral twice-weekly and oral daily isoniazid plus PAS in newly diagnosed pulmonary tuberculosis. *British Medical Journal* 1973;**2**:7–11.
63. Ellard G. The potential clinical significance of the isoniazid acetylator phenotype in the treatment of pulmonary tuberculosis. *Tubercle* 1984;**65**:211–227.
64. Weiner M, Burman W, Vernon A, et al. Low isoniazid concentrations and outcome of tuberculosis treatment with once-weekly isoniazid and rifapentine. *American Journal of Respiratory and Critical Care Medicine* 2003; **167**:1341–1347.
65. Weiner M, Benator D, Burman W, et al. Association between acquired rifamycin resistance and the pharmacokinetics of rifabutin and isoniazid among patients with HIV and tuberculosis. *Clinical Infectious Diseases* 2005;**40**: 1481–1491.
66. Lacroix C, Houng TP, Nouveau J, et al. Pharmacokinetics of pyrazinamide and its metabolites in healthy subjects. *European Journal of Clinical Pharmacology* 1989;**36**:395–400.
67. Perlman D, Segal Y, Rosenkranz S, et al. The clinical pharmacokinetics of pyrazinamide in HIV-infected persons with tuberculosis. *Clinical Infectious Diseases* 2004;**38**: 556–564.
68. Wilkins J, Langdon G, McIlleron H, Pillai C, Smith P, Simonsson U. Variability in the population pharmacokinetics of pyrazinamide in South African tuberculosis patients. *European Journal of Clinical Pharmacology* 2006;**62**:727–735.
69. Aklillu E, Carrillo J, Makonnen E, Bertilsson L, Ingelman-Sundberg M. Xanthine oxidase activity is influenced by environmental factors in Ethiopians. *European Journal of Clinical Pharmacology* 2003;**59**:533–536.
70. Wang L, Weinshilboum R. Thiopurine S-methyltransferase pharmacogenetics: insights, challenges and future directions. *Oncogene* 2006;**25**:1629–1638.
71. Zhang Y, Mitchison D. The curious characteristics of pyrazinamide: a review. *International Journal of Tuberculosis and Lung Disease* 2003;**7**:6–21.
72. Heifets L, Higgins M, Simon B. Pyrazinamide is not active against *Mycobacterium tuberculosis* residing in cultured human monocyte-derived macrophages. *International Journal of Tuberculosis and Lung Disease* 2000;**4**:491–495
73. Lecouer H, Truffot-Pernot C, Grosset J. Experimental short-course preventive therapy of tuberculosis with rifampicin and pyrazinamide. *American Review of Respiratory Disease* 1989;**140**:1189–1193.
74. Rosenthal I, Williams K, Tyagi S, et al. Potent twice-weekly rifapentine containing regimens in murine tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 2006;**174**:94–101.
75. Ibrahim M, Andries K, Lounis N, et al. Synergistic activity of R207910 combined with pyrazinamide against murine tuberculosis. *Antimicrobial Agents and Chemotherapy* 2007;**51**:1011–1015.
76. Matsumoto M, Hashizume H, Tomishige T, et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. *PLOS Medicine* 2006;**3**:e466.
77. Ramakrishnan C, Janardhanam B, Krishnamurthy D, Stott H, Subbammal S, Tripathy S. Toxicity of pyrazinamide, administered once weekly in high dosage, in tuberculous patients. *Bulletin of the World Health Organisation* 1968; **39**:775–779.
78. Allison S. Pyrazinamide in low dosage in combination with isoniazid or paraamainosalicylic acid in the treatment of pulmonary tuberculosis. *American Review of Tuberculosis* 1959;**79**:102–104.
79. Combalbert J, Fabre I, Fabre G. Metabolism of cyclosporin A: IV. purification of the rifampicin-inducible human liver cytochrome P-450 (cyclosporin A oxidase) as a product of the P450IIIA gene subfamily. *Drug Metabolism and Disposition* 1989;**17**:197–207.
80. Hartkoorn R, Chandler B, Owen A, et al. Differential drug susceptibility of intracellular and extracellular tuberculosis and the impact of p-glycoprotein. *Tuberculosis (Edinburgh)* 2007;**87**:248–255.
81. Burman W, Gallicano K, Peloquin C. Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. *Clinical Pharmacokinetics* 2001;**40**:327–341.
82. Acocella G, Pagani V, Marchetti M, Baroni G, Nicolis F. Kinetic studies on rifampicin. I. Serum concentration analysis in subjects treated with different oral doses over a period of two weeks. *Chemotherapy* 1971;**16**:356–370.
83. Iwainsky H, Winsel K, Werner E, Eule H. On the pharmacokinetics of rifampicin I: Influence of dosage and duration of treatment with intermittent administration. *Scandinavian Journal of Respiratory Diseases* 1974;**55**: 229–236.
84. McIlleron H, Wash P, Burger A, Norman J, Folb P, Smith P. Determinants of rifampicin,isoniazid, pyrazinamide and ethambutol pharmacokinetics in a cohort of tuberculosis patients. *Antimicrobial Agents and Chemotherapy* 2006; **50**:1170–1177.
85. Sahai J, Gallicano K, Swick L, et al. Reduced plasma concentrations of antituberculosis drugs in patients with HIV infection. *Annals of Internal Medicine* 1997;**127**:289–293.
86. Perlman D, Segel Y, Rosenkranz S, et al. The clinical pharmacokinetics of rifampin and ethambutol in HIV-infected persons with tuberculosis. *Clinical Infectious Diseases* 2005;**41**:1638–1647.
87. Njiland H, Ruslami R, Stalenhoef J, et al. Exposure to rifampicin is strongly reduced in patients with tuberculosis and type 2 diabetes. *Clinical Infectious Diseases* 2006;**43**:848–854.
88. Acocella G. Clinical pharmacokinetics of rifampicin. *Clinical Pharmacokinetics* 1978**;3:**108–127.
89. Ruslami R, Njiland H, Alisjahbana B, Parwati I, van Crevel R, Aarnoutse R. Pharmacokinetics and tolerability of a higher rifampicin dose versus the standard dose in pulmonary tuberculosis patients. *Antimicrobial Agents and Chemotherapy* 2007;**51**:2546–2551.
90. Langdon G, Wilkins J, Smith P, McIlleron H. Consecutive dose pharmacokinetics of rifapentine in patients diagnosed with pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease* 2004;**8**:862–867.

91. Langdon G, Wilkins J, McFadyen L, McIlleron H, Smith P, Simonsson U. Population pharmacokinetics of rifapentine and its primary desacetyl metabolite in South African tuberculosis patients. *Antimicrobial Agents and Chemotherapy* 2005;**49**:4429–4436.
92. Keung A, Owens R, Eller M, Weir S, Nicolau D, Nightingale C. Pharmacokinetics of rifapentine in subjects seropositive for the human immunodeficiency virus:a phase I study. *Antimicrobial Agents and Chemotherapy* 1999;**43**: 1230–1233.
93. Sirgel F, Fourie P, Donald P, et al. The early bactericidal activities of rifampin and rifapentine in pulmonary tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 2005;**171**:1–8.
94. Conte J, Golden J, McQuitty M, Kipps J, Lin E, Zurlinden E. Single dose intrapulmonary pharmacokinetics of rifapentine in normal subjects. *Antimicrobial Agents and Chemotherapy* 2000;**44**:985–990.
95. Conte JE, Golden JA, Kipps J, Lin ET, Zurlinden E. Effect of sex and AIDS status on the plasma and intrapulmonary pharmacokinetics of rifampicin. *Clinical Pharmacokinetics* 2004;**43**:395–404.
96. Ji B, Truffot-Pernot C, Lacroix C, et al. Effectiveness of rifampin, rifabutin and rifapentine for preventive therapy of tuberculosis in mice. *American Review of Respiratory Disease* 1993;**148**:1541–1546.
97. Verbist L, Gyselen A. Antituberculous activity of rifampicin in vitro and in vivo and the concentrations attained in human blood. *American Review of Respiratory Disease* 1968;**98**:923–932.
98. Diacon A, Patientia R, Venter A, et al. Early bactericidal activity of high-dose rifampin in patients with pulmonary tuberculosis evidenced by positive sputum smears. *Antimicrobial Agents and Chemotherapy* 2007;**51**:2994–2996.
99. Aquinas M, Citron K. Rifampicin,Ethambutol and Capreomycin in pulmonary tuberculosis, previously treated with first and second line drugs:results of two years treatment. *Tubercle* 1972;**53**;153–65.
100. Aquinas SM, Allan W, Horsfall P, et al. Adverse reactions to daily and intermittent rifampicin regimens for pulmonary tuberculosis in Hong Kong. *British Medical Journal* 1972; **1**:765–771.
101. Gelband H. Regimens of less than six months for treating tuberculosis. *Cochrane Database of Systematic Reviews* 1999(4).
102. Chan S, Yew W, Ma W, Girling D, Aber V, Felmingham D. The early bactericidal activity of rifabutin measured by sputum viable counts in Hong Kong patients with pulmonary tuberculosis. *Tubercle and Lung Disease* 1992;**73**: 33–38.
103. Munsiff S, Kambili C, Ahuja S. Rifapentine for the treatment of pulmonary tuberculosis. *Clinical Infectious Diseases* 2006;**43**:1468–1475.
104. Burman W, Benator D, Vernon A, et al. Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 2005;**173**:350–356.
105. Nettles R, Mazo D, Alwood K, et al. Risk factors for relapse and acquired rifamycin resistance after directly observed tuberculosis treatment:a comparison by HIV serostatus and rifamycin use. *Clinical Infectious Diseases* 2004;**38**: 731–736.
106. Li J, Munsiff S, Driver C, Sackoff J. Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin- or rifbutin- based regimens in New York City, 1997–2000. *Clinical Infectious Diseases* 2005;**41**:83–91.
107. Vernon A, Burman W, Benator D, Khan A, Bozeman L. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Lancet* 1999;**353**:1843–1847.
108. Rodriguez J, Cebrian L, Ruiz M, Lopez M, Royo G. Mutant prevention concentration of isoniazid, rifampicin and rifabutin against *Mycobacterium tuberculosis*. *Chemotherapy* 2005;**51**:76–79.
109. Bock N, Sterling T, Hamilton C, et al. A prospective randomized double blind study of the tolerability of rifapentine 600, 900 and 1200 mg plus isoniazid in the continuaiton phase of tuberculosis treatment. *American Journal of Respiratory and Critical Care Medicine* 2002; **165**:1526–1530.
110. Rosenthal I, Zhang M, Williams KM et al Daily dosing of rifapentine cures tuberculosis in three months or less in the murine model *PLOS Medicine* 2007;**4**:e344.
111. Bryskier A, Lowther J. Fluoroquinolones and tuberculosis. *Expert Opinion in Investigational Drugs* 2002;**11**:233–258.
112. Ginsburg A, Grosset J, Bishai W. Fluoroquinolones, tuberculosis and resistance. *Lancet* 2003;**3**:432–42.
113. Hu Y, Coates A, Mitchison D. Sterilizing activities of fluoroquinolones against rifampin-tolerant populations of mycobacterium tuberculosis. *Antimicrobial Agents and Chemotherapy* 2003;**47**:653–657.
114. Nuermberger E, Grosset J. Pharmacokinetic and pharmacodynamic issues in the treatment of mycobacterial infections. *European Journal of Clinical Microbiology and Infectious Diseases* 2004;**23**:243–255.
115. Weiner M, Burman W, Luo C, et al. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. *Antimicrobial Agents and Chemotherapy* 2007;**51**:2861–2866.
116. Njiland H, Ruslami R, Suroto A, et al. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. *Clinical Infectious Diseases* 2007;**45**:1001–1007.
117. Johnson J, Hadad D, Boom W, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease* 2006;**10**: 605–612.
118. Kennedy N, Fox R, Kisyombe G. Early bactericidal and sterilizing activities of ciprofloxacin in pulmonary tuberculosis. *American Review of Respiratory Diseases* 1993;**148**:1547–1551.
119. Yew W, Chan C, Leung C, et al. Comparative roles of levofloxacin and ofloxacin in the treatment of multidrug-resistant tuberculosis: preliminary results of a retrospective study from Hong Kong. *Chest* 2003;**124**:1476–1481.
120. Burman WJ, Goldberg S, Johnson JL et al . Moxifloxacin versus ethambutol in the first two months of treatment for tuberculosis *American Journal of Respiratory and Critical Care Medicine* 2006;**174**:331–338.
121 Chaisson R, Conde M, Efron A, et al. A randomized, placebo-controlled trial of moxifloxacin vs ethambutol in the initial phase of tuberculosis therapy in Brazil. 2007 *ICAAC*, Abstract L-736a.
122. Ginsburg A, Woolwine S, Hooper N, et al. The rapid development of fluoroquinolone resistance in *M. tuberculosis*. *New England Journal of Medicine* 2003;**349**: 1977–1978.
123. Almeida D, Nuermberger E, Tyagi S, Bishai W, Grosset J. In vivo validation of the mutant selection window hypothesis with moxifloxacin in a murine model of tuberculosis. *Antimicrobial Agents and Chemotherapy* 2007;**51**:4261–4266.
124. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of

Mycobacterium tuberculosis. *Science* 2005;**307**:223–227
125. Nuermberger E, Rosenthal I, Tyagi S, et al. Combination chemotherapy with the nitroimidazopyran PA-824 and first-line drugs in a murine model of tuberculosis. *Antimicrobial Agents and Chemotherapy* 2006;**50**:2621–2625.
126. Diacon A, Rustomjee R, McNeely D, Kerstens R, Marez TD, Andries K. Early bactericidal activity, tolerability, and pharmacokinetics of the investigational diarylquinoline TMC207. *International Journal of Tuberculosis and Lung Disease* 2006;**10(Supplement 1):**S165.