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Research paper

Evolution of rifampicin treatment for tuberculosis

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ABSTRACT

Rifampicin was discovered in 1965 and remains one of the most important drugs in tuberculosis treatment that is valued for its sterilizing activity and ability to shorten treatment. Antimicrobial activity of rifampicin was initially proved in vitro; subsequently numerous in vivo studies showed the bactericidal properties and dose-dependent effect of rifampicin. Rifampicin was first during the late 1960s to treat patients suffering from chronic drug-resistant pulmonary TB. Decades later, rifampicin continues to be studied with particular emphasis on whether higher doses could shorten the duration of treatment without increasing relapse or having adverse effects. Lesion-specific drug penetration and pharmacokinetics of rifampicin are improving our understanding of effective concentration while potentially refining drug regimen designs. Another prospective aspect of high-dose rifampicin is its potential use in treating discrepant mutation thereby eliminating the need for MDR treatment. To date, several clinical trials have shown the safety, efficacy, and tolerability of high-dose rifampicin. Currently, high-dose rifampicin has been used successfully in a routine clinical setting for the treatment of high-risk patients. However, the WHO and other relevant policy makers have not committed to implementing a controlled rollout thereof. This review describes the course that rifampicin has travelled to the present-day exploration of high-dose rifampicin treatment.

1. Rifampicin

1.1. Historical experiments: evidence on the bactericidal properties of Rifampicin

The rifamycin complex derived from *Nocardia mediterranei* was first discovered in 1957 (Sensi, 1983; Sensi et al., 1959), after which rifampicin was synthesized in 1965 and its antimicrobial profile described in 1966 (Maggi et al., 1966; Sensi et al., 1966). This was followed by reports documenting the activity of rifampicin against gram-positive and gram-negative organisms in 1967 (Arioli et al., 1967; Furesz et al., 1967; Pallanza et al., 1967). Between 1967-1970, various investigators confirmed the antimycobacterial activity of rifampicin *in vitro,* by testing the susceptibility of *Mycobacterium tuberculosis* strains to rifampicin (Grumbach and Rist, 1967; Hobby et al., 1970; Hobby et al., 1969; Pallanza et al., 1967). The majority of strains (99.5%) had a minimum inhibitory concentration (MIC) ranging between 0.006 and 0.05μg/ml in liquid media and ≤1.0 μg/ml on 7H10 agar and this was independent of whether the strains were resistant to other anti-TB drugs (Hobby, 1972).

Following these *in vitro* results, early *in vivo* studies were conducted in mice, guinea pigs and rabbits (Batten, 1970; Batten, 1969; Furesz et al., 1965; Grumbach, 1969a,b; Havel et al., 1970; Hobby and Lenert, 1968; Nitti and Ninni, 1969; Rosenfeld, 1970; Verbist, 1969). Murine studies were the first to show the bactericidal properties and dose-dependent effect of rifampicin by quantifying the number of viable bacilli in the lungs and spleens of *M. tuberculosis* infected mice (Batten, 1970, 1969; Grumbach, 1969a; Grumbach and Rist, 1967; Verbist, 1969; Verbist and Gyselen, 1968). Early *in vivo* studies have been extensively reviewed by Binda et al., 1971 (Binda et al., 1971). The antimicrobial activity of rifampicin alone or in combination with isoniazid was shown by Verbist and Gyselen (Verbist and Gyselen, 1968). Mice were infected intravenously with *M. tuberculosis* var. *hominis* and treated 10 days after infection with either isoniazid (2 – 10 mg/kg) or rifampicin (10 – 20

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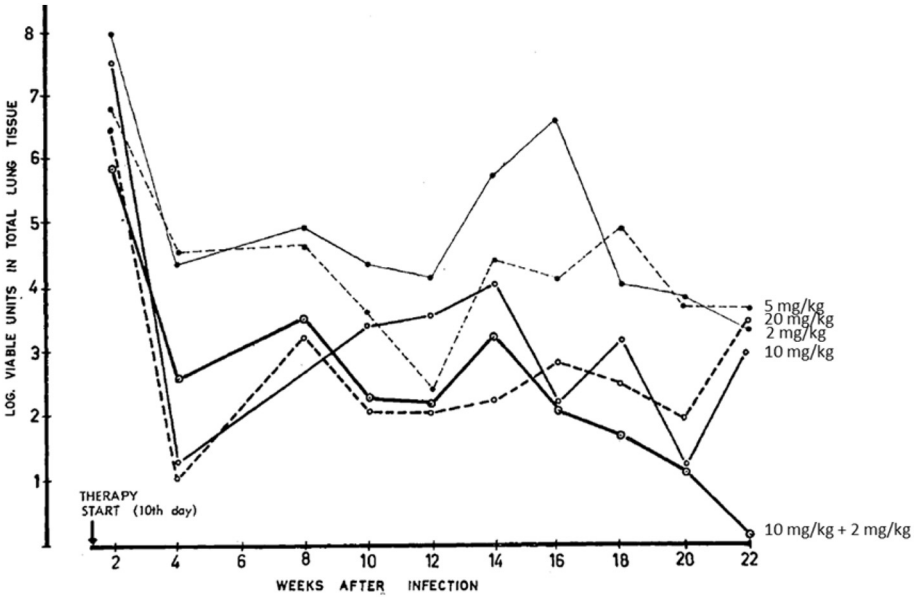

Fig. 1. Viable bacilli in the lungs of infected mice after treatment with isoniazid or rifampicin. Mice were treated with rifampicin (10 mg/kg, 20 mg/kg), isoniazid (2 mg/kg, 5 mg/kg) or the combination of rifampicin 10 mg/kg plus isoniazid 2 mg/kg (Verbist and Gyselen, 1968). (Permission under license from American Thoracic Society)

mg/kg) or in combination (10 mg/kg rifampicin plus 2 mg/kg isoniazid) (Fig. 1). The group that received rifampicin showed an earlier reduction of log10 CFU/lung ($10^8 \rightarrow 10^{1\text{-}2}$) of culturable mycobacteria compared to isoniazid ($10^8 \rightarrow 10^4$). When comparing monotherapy with combination therapy in mice, Verbist and Gyselen showed that complete sterilization was only achieved when rifampicin and isoniazid were combined (Verbist and Gyselen, 1968).

Batten *et al.*, subsequently also provided evidence of rifampicin plus isoniazid combination treatment. This study showed the advantage of combination therapy in intravenously *M. tuberculosis* infected mice treated with rifampicin (40 mg/kg) or isoniazid (25 mg/kg) either as monotherapy or in combination (Fig. 2) (Batten, 1969). Results showed, only a subset of infected mice was completely sterilized after receiving rifampicin and isoniazid monotherapy, while complete sterilization was achieved in the lungs of *M. tuberculosis* infected mice after rifampicin plus isoniazid combination treatment was administered.

The same trend was observed in guinea pigs infected intracardially with *M. tuberculosis* H37Rv and treated for 42 days with the combination of rifampicin (40 mg/kg) plus isoniazid (4 mg/kg), rifampicin plus streptomycin (40 mg/kg), rifampicin plus ethambutol (100 mg/kg) or streptomycin plus isoniazid (Nitti and Ninni, 1969). The activity of rifampicin in terms of the mean log viable bacterial units (3.1) after monotherapy was significantly higher ($p < 0.01$) that that of ethambutol (4.5) and streptomycin (4.2). However, rifampicin monotherapy was not statistically higher that of isoniazid monotherapy (3.0) or ethambutol plus rifampicin combination therapy (3.2). The combination of rifampicin plus isoniazid reduced the mean log v.b.u (1.5) significantly higher than that of rifampicin plus streptomycin (2.4) or isoniazid plus streptomycin (2.2) (Nitti and Ninni, 1969).

Verbist and Gyselen further focused on which rifampicin dose was as effective as the standard isoniazid dose of 5 mg/kg which was considered the most potent drug used against TB at the time (Verbist and Gyselen, 1968). Their results showed that the mean survival time of *M. tuberculosis* infected mice treated with 10 mg/kg rifampicin (80 days) was longer compared to mice treated with the standard dose of 5 mg/kg isoniazid (78 days) or 5 mg/kg rifampicin (58 days). In addition, 5 mg/kg rifampicin was less effective than 5 mg/kg isoniazid (Furesz et al., 1965; Hobby and Lenert, 1968; Verbist and Gyselen, 1968).

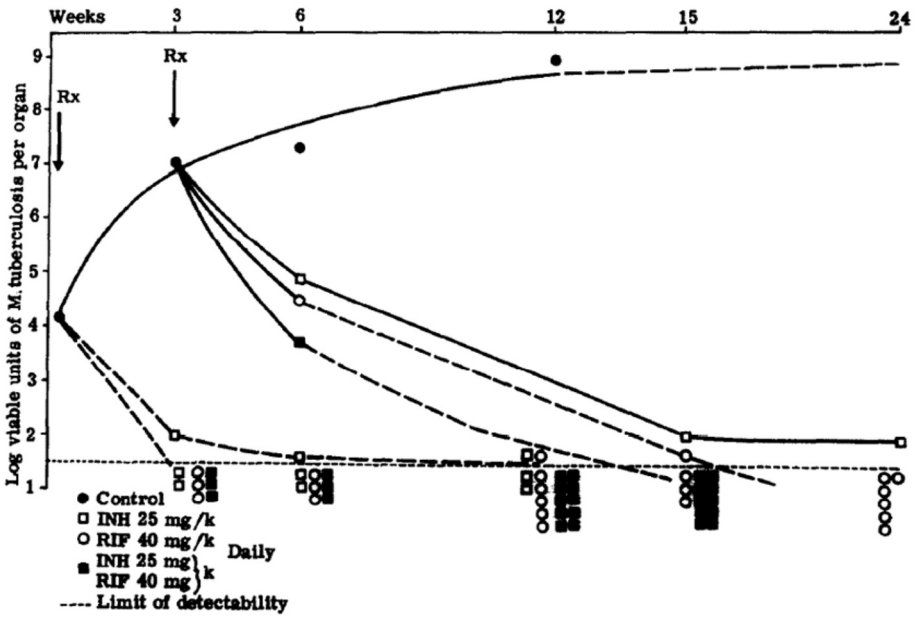

Fig. 2. Viable bacilli in the lungs of infected mice treated with either rifampicin (40 mg/kg), isoniazid (25 mg/kg) or the combination thereof. Mice were treated directly or three weeks after infection indicated by the Rx. Complete sterilization of viable *M. tuberculosis* bacilli in lungs of an individual mouse is represented by the symbols below the limit of detectability (Batten, 1969). (Permission under license 4564191256705)

1.2. Implementation of rifampicin administration in tuberculosis treatment regimen

In 1966 the desperation expressed by physicians to successfully treat TB prompted the first attempts to treat patients suffering from chronic drug-resistant pulmonary TB (Gyselen et al., 1971). Seven patients received only rifampicin (450 mg) while an additional 14 patients received ethambutol (15-25 mg/kg) in addition to the previously administered drugs. The 7 rifampicin patients were previously treated unsuccessfully with ethambutol. All 21 patients were sputum-smear positive for between 7 and 66 months prior to this study. Sputum smear and culture conversion were reported for 5 out of the 14 patients treated with ethambutol and 5 out of the 7 patients treated with rifampicin (Gyselen et al., 1968). Essentially these patients received rifampicin monotherapy as resistance was documented for all other anti-TB drugs at the time.

A second group of similar patients were treated daily between 1968 and 1970 with either ethambutol (19 patients) plus an additional second-line drug not previously used or rifampicin plus ethambutol (12 patients) (Gyselen et al., 1971; Gyselen et al., 1968). The addition second-line drugs included, viomycin, capreomycin, ethionamide and thiocarlide. Sputum smear and culture conversion was reported for 11 out of the 19 patients treated with ethambutol and an added second-line drug and 10 out of the 12 patients treated with rifampicin and ethambutol (Gyselen et al., 1971, Gyselen et al., 1968). In this study, it was observed more frequent culture conversion in groups treated with rifampicin (between 3 and 12 weeks) compared to ethambutol (between 4 and 23 weeks). In addition, patients treated with rifampicin also experienced no toxicity of adverse reaction.

The high culture conversation rates seen in previously treated TB patients when treated with rifampicin prompted a pilot study to test the efficacy of rifampicin in the treatment of new pulmonary TB patients (Gyselen et al., 1971). In this study, the culture conversion rate was compared between each of the four different drug combinations (1. Rifampicin (600 mg) plus isoniazid (300 mg), 2. Rifampicin plus ethambutol (15-25 mg/kg), 3. Isoniazid plus ethambutol and 4. Isoniazid plus streptomycin (1 g)) (Gyselen et al., 1971). Out of the four treatment groups, a bacteriological conversion was achieved after 7.2 weeks (mean) in patients treated with rifampicin plus isoniazid compared to 11.9 weeks (mean) for patients treated with isoniazid plus ethambutol. This pilot study provided additional supporting evidence that confirmed the bactericidal activity of rifampicin, especially in combination with isoniazid, as shown in animal model studies, but also indicated possible better sterilizing activity. A similar pilot study was also launched in 1968 by Baronti and Lukinovich, during which they treated 11 patients with chronic pulmonary tuberculosis with rifampicin in combination with isoniazid, para-aminosalicylic acid or ethionamide (Baronti and Lukinovich, 1968). Rifampicin (450 mg) alone was administered for the first 45 days followed thereafter by rifampicin in combination with 10 mg/kg isoniazid and 15 g para-aminosalicylic acid or 0.5 g ethionamide for the next 45 days. In contrast to the study by Gyselen *et al.*, (Gyselen et al., 1971; Gyselen et al., 1968) only 4 out of the 11 patients were smear- and culture-negative, while the remaining patients developed rifampicin resistance (Baronti and Lukinovich, 1968). The resulting resistance may be attributed to the 45 days of rifampicin monotherapy before a 4-drug regimen was used. Nonetheless, no toxicity or adverse effects were reported.

In 1970, the British Medical Research Council then conducted a trial in East Africa enrolling 610 patients with previously untreated, extensive pulmonary tuberculosis to evaluate the efficacy of rifampicin or pyrazinamide as part of a 6-month streptomycin plus isoniazid regimen (EA/BMRC, 1974; EA/BMRC, 1972). The efficacy of four daily regimens namely, streptomycin (1 g) plus isoniazid (300 mg) plus rifampicin (600 mg), streptomycin plus isoniazid plus pyrazinamide (2 g), streptomycin plus isoniazid plus thiacetazone (150 mg) and streptomycin plus isoniazid were evaluated (EA/BMRC, 1972). The 6-month regimen proved to be highly effective as only 4% of patients that received rifampicin and 6% that received pyrazinamide relapsed after therapy was stopped compared to 21% that received thiacetazone (EA/BMRC, 1972). The favourable outcome of this study paved the way for the development of the modern short-course regimen.

2. Toxicity and metabolism

Reported rifampicin-associated adverse effects included hepatitis, dermatological events, hypersensitivity, cholestasis, and gastrointestinal disturbances and most commonly a flu-like syndrome that was most often associated with intermittent rifampicin regimens (Chien et al., 2013; Grosset and Leventis, 1983; Horne et al., 2011). However, higher rifampicin doses were generally well tolerated in most historical trials, and reported adverse reactions were not significantly greater than when using the standard 10 mg/kg rifampicin (Anastasatu et al., 1973; BMRC, 1975; BMRC, 1974; Decroix et al., 1969; Larbaoui et al., 1970; Nitti, 1973). Fear of adverse reactions was one of a few reasons why 10 mg/kg was used as the standard dose. Other reasons included cost of treatment, peak serum concentration and that a higher dose might give rise to the occurrence of resistant bacilli (Boman et al., 1972; Fox and Nunn, 1979; Furesz et al., 1967; Peloquin, 1998; van Ingen et al., 2011a,b).

Toxicity may not always be due to one drug alone but can result from interaction when drugs are used in combination. One such study found that rifampicin monotherapy is less toxic than a multidrug regimen, suggesting that the increase in toxicity is attributed to drug-drug interactions (Steele et al., 1991; Ziakas and Mylonakis, 2009). It is also known that the metabolism of isoniazid is influenced by the action of cytochrome P450 enzymes (CYP450) which are induced by rifampicin, resulting in the subsequent production of toxic metabolites (Steele et al., 1991). Rifampicin drug-drug interactions are aided in particular by the induction of CYP3A4. It should be noted that 50 – 60% of all clinically relevant drugs are substrates of CYP3A4 (Chen and Raymond, 2006; Guengerich, 1999; Guengerich, 1995). The interaction of isoniazid and rifampicin is particularly relevant and one theory is that the acetylation of hydrazine during isoniazid metabolism leads to the production of toxic species while another claims that an increase in hydrazine via isoniazid hydrolase causes toxic species (Ellard and Gammon, 1976; Sarma et al., 1986). There is general agreement that rifampicin negatively affects isoniazid metabolism but there is no detailed information on the mechanism (Ellard and Gammon, 1976; Lees et al., 1970; Mitchell et al., 1975; Sarma et al., 1986).

Rifampicin assimilation can also be affected by xenobiotics in the gastrointestinal tract and liver, which is mediated by organic anion transported peptide (OATP) products of the solute carrier (SLC) transporters family of genes (Englund et al., 2006; Lau et al., 2007; Weiner et al., 2010). OATP is induced by rifampicin by means of the nuclear pregnane X receptor and may further inhibit OATP1B1 c.463 which ultimately affects the pharmacokinetics of rifampicin (Tirona et al., 2003). A study found that individuals with a SLCO1B1 c.463CA polymorphism had lower rifampicin AUC $_{0\text{-}24}$ levels (drug concentration) compared to SLCO1B1 c.463CC (Weiner et al., 2010). This polymorphism was most often associated with patients of African descent.

3. Rifampicin penetration, accumulation, and distribution at the site of infection

The current rifampicin dose of 10 mg/kg has remained unchanged since the early 1970s, however, this is being re-evaluated to possibly improve bactericidal activity and shorten treatment without increasing adverse reactions or relapse rates and to evaluate eradication of persister TB to effect permanent cure. Studies assessing drug concentrations in different tissues and organ systems have reported low rifampicin concentrations in epithelial lining fluid, cerebrospinal fluid, and pleural fluid, concluding that the standard dosage of 600 mg rifampicin is

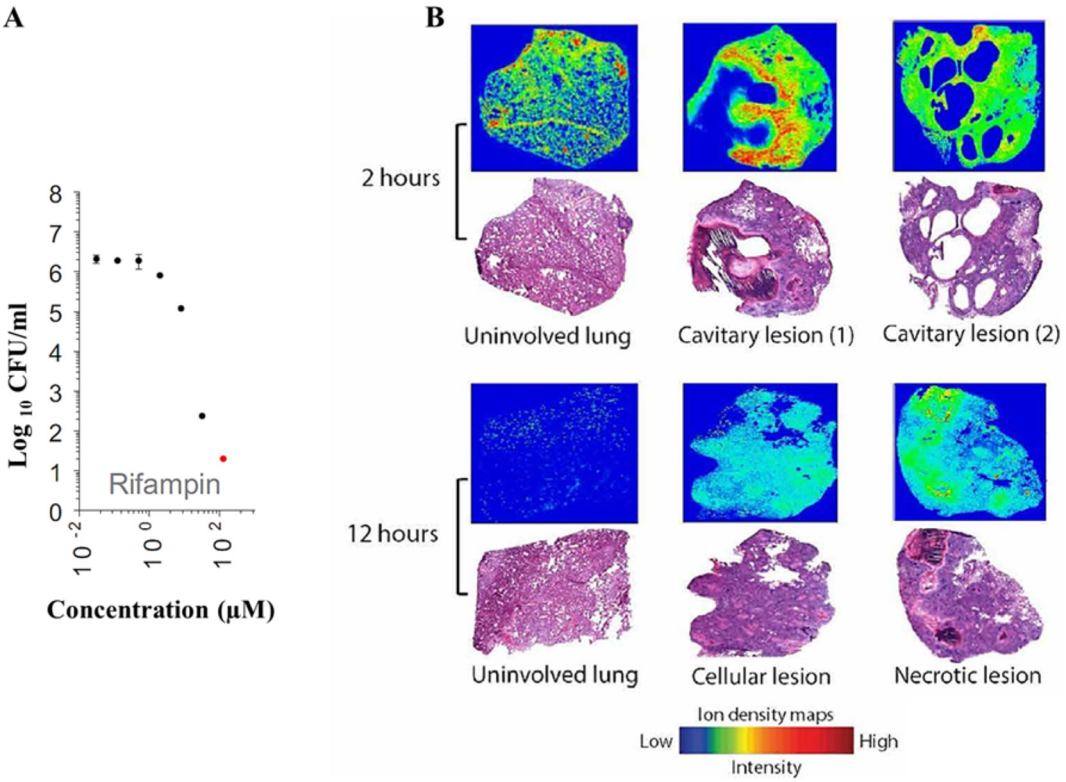

Fig. 3. Bactericidal activity and tissue-to-plasma drug concentration ratios after rifampicin treatment. A) Bactericidal activity of rifampicin in caseum expressed as $\log_{10}$ of average CFU/ml. The red dot indicates the point of sterilization as data points are below the limit of detection. B) MALDI-MS images are shown as ion density maps taken 2 and 12 hours after rifampicin treatment and shows a higher rifampicin signal in necrotic regions compared to different lung tissue. Hematoxylin and eosin stained lung lesions are shown directly below the MALDI-MS images. Modified from (Rifat et al., 2018; Sarathy et al., 2018). (Permission under license 4564200616868 and CC BY 4.0)

suboptimal, suggesting a revision of the current standard dose (Donald, 2010; Elliott et al., 1995; Goutelle et al., 2009).

Studies focusing on drug concentrations in plasma are not always predictive of the concentration at the site of infection (Dartois, 2014; Kjellsson et al., 2012). Thus, investigating drug concentrations and penetration at the site of infection may provide data which will justify increasing the current drug dosages (Goutelle et al., 2009). A group from Rutgers University started using a rabbit model that develops lung cavities similar to that of patients with pulmonary cavitary TB and studied this model with matrix-assisted laser desorption/ionization mass spectrometry imaging (MALDI-MSI) and liquid chromatography tandem mass spectrometry (LC-MS/MS) to determine the extent of drug penetration (Dartois, 2014; Kjellsson et al., 2012; Prideaux et al., 2015; Rifat et al., 2018; Sarathy et al., 2018). Two recent studies analysed rifampicin concentrations in multiple diseased lesions and measured the bactericidal activity in cavity caseum *ex vivo*, showing that rifampicin diffuses readily into the protein and lipid-rich caseum (Fig. 3) (Rifat et al., 2018; Sarathy et al., 2018). A dose-escalation simulation was performed on a 1000 simulated patient pharmacokinetic profiles by Strydom et al., to determine if high-dose rifampicin would outperform the standard dose in a hard-to-treat closed nodule caseum (Strydom et al., 2019). A 100% target attainment was predicted in the simulated patients when 900 mg or 1200 mg rifampicin was used compared to 65% when using the standard dose (Strydom et al., 2019).

Penetration and diffusion of anti-TB drugs into necrotic lesions and across the caseum is essential to maximize the antibacterial value of each drug. These studies can, therefore, help in optimizing drug regimens by predicting drug distribution, penetration and concentration in various lesions, thus limiting local monotherapy and chances of selecting drug resistance or relapse.

4. High-dose rifampicin

Progress has been made in the development of new drugs such as bedaquiline and delamanid and the repurposing of other drugs for MDR-TB treatment such as linezolid (Silva et al., 2018). However, thus far little has been done to change the treatment or develop new drugs for drug-sensitive TB, and we are still using the same 6-month four-drug regimen.

The use of high-dose rifampicin gained traction when results from murine model studies (de Steenwinkel et al., 2013; Hu et al., 2015; Jayaram et al., 2003; Rosenthal et al., 2012) showed early culture conversion rates and relapse-free cure with increasing rifampicin doses (Fig. 4). BALB/c mice infected with *M. tuberculosis* H37Rv were treated with 10, 15, 20, 30 and 50 mg/kg rifampicin for 14 weeks. Complete sterilization was only achieved after treatment with 20, 30 and 50 mg/kg and not with 10 and 15 mg/kg (Hu et al., 2015). This suggests that the current rifampicin dose was too low to treat TB effectively, however murine studies do not always reflect outcome or cure in humans.

Early bactericidal activity (EBA) studies and longer duration clinical trials have started to assess whether increasing the dose of rifampicin will shorten treatment without the risk of adverse reactions or increasing the relapse rate. EBA studies originating from Kenya, Hong Kong, and South Africa showed a dose-related improved bactericidal activity between 150 – 1200 mg rifampicin (Fig. 5) (Chan et al., 1992; Diacon et al., 2007; Jindani et al., 1980; Sirgel et al., 2005; Sirgel et al., 2000; Sirgel et al., 1993). This suggests that high-dose rifampicin might decrease time to sputum culture-negativity.

As shorter treatment periods ultimately increase patient compliance, emergence of drug resistance may be reduced at the same time (Hu et al., 2015). This may be particularly important in TB/HIV co-infection where studies have reported high-rates of acquired rifampicin

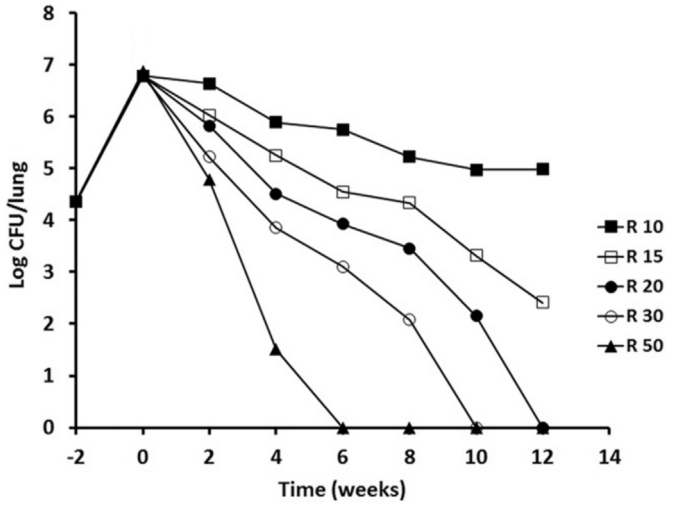

Fig. 4. Viable bacilli in the lung of infected BALB/c mice after treatment with rifampicin. Mice were treated for 12 weeks with different concentrations of rifampicin after an initial 2-week infection period (Hu et al., 2015). (Permission under licence CC BY)

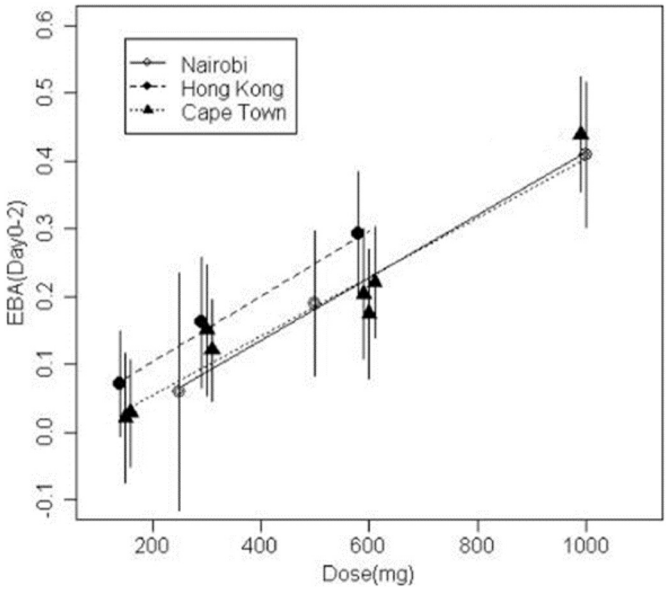

Fig. 5. Normalized EBA data from studies in Nairobi, Hong Kong, and South Africa in which the *in vivo* activity of rifampicin was assessed by measuring colony forming units. The dosage-related bactericidal activity of rifampicin from different EBA studies ranging between 150mg and 1200mg (Diacon et al., 2007). (Permission under license 4564210660302).

resistance (Hom et al., 2012; Li et al., 2005; Vidyaraj et al., 2017). Hom *et al.*, found a resistance prevalence of 10.3% in patients previously treated for TB and 52.42% in patients with no prior history of TB (Hom et al., 2012). TB/HIV patients are usually treated with rifabutin due to its low cytochrome induction as opposed to rifampicin (Blumberg et al., 2003). A subset of rifampicin conferring mutations is suspectable to rifabutin due to limited cross-resistance between the two drugs and as such, patients infected with strains harbouring these mutations can be successfully treated with rifabutin without the need for MDR treatment (Chien et al., 2014; Horne et al., 2011; Whitfield et al., 2018).

Several clinical trials have evaluated the safety and efficacy of using between 13 and 40 mg/kg high-dose rifampicin in humans (Aarnoutse et al., 2017; Boeree et al., 2017, 2015; Jindani et al., 2016; Milstein et al., 2016; Ruslami et al., 2007; Velásquez et al., 2018). Recent trials on high-dose rifampicin include the PanACEA HIGHRIF1 trial, the PanACEA HIGHRIF2 trial, the NIAID HIRIF trail and the RIFATOX and RIFASHORT (NCT02581527) studies (Boeree et al., 2015, 2017; Jindani et al., 2016; Peloquin et al., 2017; Svensson et al., 2018a,b). The latter studies focus on the risk of toxicity, adverse effects, and potential treatment shortening associated with high-dose rifampicin. The latest completed trials published in 2018 showed that high-dose rifampicin was well tolerated with shortened time to sputum culture conversion, and higher plasma concentrations (Svensson et al., 2018a,b; Velásquez et al., 2018). However, limited data is available to verify if higher concentrations of rifampicin may induce faster first-line drug metabolism or impact on antiretroviral agents, which again may compromise treatment outcome.

While the 40 mg/kg dosage was safe and well tolerated in these trials, it does not mean that a maximum tolerated dosage has been reached (Boeree et al., 2015; Svensson et al., 2018a,b). A recently completed phase IIA trial (NCT01392911) assessed the maximum tolerable dose of rifampicin in monotherapy and in combination with first-line drugs. Together with tolerability, safety, EBA and pharmacokinetics were also assessed. Patients were treated for 7-days with 10, 20, 25, 30, 35, 40, 45, 50 and 55 mg/kg followed by 7 days of combination treatment. No results have been published to date.

TRUNCATE-TB trial (NCT03474198) will evaluate the use of high-dose rifampicin in the treatment of standard drug-susceptible tuberculosis. This trail will compare the current standard regimen with 1. Rifampicin (35 mg/kg), isoniazid (5 mg/kg), pyrazinamide (25 mg/kg), ethambutol (15 mg/kg) and linezolid (600 mg), 2. Rifampicin, isoniazid, pyrazinamide, ethambutol, clofazimine (200 mg), 3. Rifapentine (1200 mg), isoniazid, pyrazinamide, linezolid, levofloxacin (1000 mg) and 4. Isoniazid, pyrazinamide, ethambutol, linezolid, bedaquiline (2 weeks, 400mg once daily then 200mg 3x a week). Patients who relapse will be retreated with the standard 6-month regimen. No results have been published to date.

All high-dose rifampicin clinical trials have shown favourable outcomes thus far, yet no progress has been made in rolling out high-dose rifampicin. Magis-Escurra et al., directly challenges the WHO and other relevant parties to endorse implementation of high-dose rifampicin in the same manner as bedaquiline and delamanid if we are to reduce the incidence of global TB by 90% before 2035 (Magis-Escurra et al., 2018; WHO, 2014). The first report on the use of daily high-dose rifampicin was recently published by a Dutch TB reference centre (Seijger et al., 2019). TB patients received between 900 mg and 2400 mg rifampicin daily. High-dose rifampicin was safe and well tolerated by all patients for the duration of treatment. The authors recommend the use of high-dose rifampicin in a clinical setting to treat high risk patients who are severely ill or have low drug concentrations or poor treatment outcome (Seijger et al., 2019). Higher dosages were guided by therapeutic drug monitoring (TDM) in patients with delayed culture conversion and/or clinical response, relapse, HIV co-infection, Diabetes Mellitus and other health related problems treated at the TB centre. TDM may be used to personalize drug concentration in a low incidence, high income setting, however, limited data support TDM as a practice in a high incident, low income setting were phlebotomy skills, cold chain shipping or biohazard precautions may be limited or non-existent (Metcalfe et al., 2019). The use of dry blood spots may circumvent some of these issues as well as the use of hair samples to monitor drug concentrations (Harahap, 2018; Metcalfe et al., 2019; Zuur et al., 2016).

Increasing the drug concentration may not be the only way in which the treatment duration can be shortened. Recent studies have shown that the use of alternative delivery systems may be successful in enhancing efficacy of drug treatment (Hirota et al., 2013; Pai et al., 2016; Parikh et al., 2014; Qiao et al., 2019; Rawal et al., 2017a,b; Srichana et al., 2016). The use of carrier-mediated dry-powder inhalers, micro- and nanoparticles may change how we treat patients in the future. Preliminary results using rats and guinea pigs have shown that inhalation of rifampicin is safe to use without increasing toxicity while retaining the same pharmacokinetic responses as an oral dose but using

only half the required standard dose (Garcia Contreras et al., 2015; Singh et al., 2015; Sung et al., 2009). Several pre-clinical and clinical studies are still needed to evaluate the usability of such alternative systems before they can be safely used in routine treatment settings.

4.1. High-dose rifampicin – an answer for disputed rpoB mutations?

High-dose rifampicin may not only support treatment shortening or reduce relapse-rates but may also treat disputed *rpoB* mutations which cause low-level rifampicin resistance. These mutations are detected by Xpert MTB/RIF as rifampicin resistant and MDR-TB treatment is initiated (Ho et al., 2013; WHO, 2016). However, these patients can potentially be treated with high-dose rifampicin as part of first-line treatment, thereby avoiding the lengthy and toxic MDR treatment. Discrepant susceptibility (low-level MICs around the critical concentration) between genotype and phenotype also leads to poor treatment outcome as several studies have found that 25-70% of these disputed cases failed treatment (Ho et al., 2013; Pang et al., 2014; Williamson et al., 2012). These mutations are defined as resistant on a phenotypic level defined by critical concentration guidelines and confer slight MIC increases which overlap with the distribution of resistant strains. There is an increasing need to precisely define the MICs of strains with these and other mutations by implementing the epidemiological cutoff value together with clinical, pharmacokinetic and pharmacodynamic data (Ängeby et al., 2012; Heyckendorf et al., 2018) as disputed mutations have been reported by several studies in different settings globally (Andres et al., 2014; Ho et al., 2013; Jo et al., 2017; Somoskovi et al., 2013; Van Deun et al., 2015; Van Deun et al., 2013). The feasibility of high-dose rifampicin to treat patients with disputed *rpoB* mutations has been reported by Van Ingen *et al.*, which found that 20 mg/kg rifampicin is likely to treat mutations with a MIC of 1 μg/ml (van Ingen et al., 2011a,b). Jeong et al., reported the successful treatment of patients with disputed mutations using 20 mg/kg and 1200 mg/day rifampicin (Jeong et al., 2018).

More studies are needed to explore the use of high-dose rifampicin to overcome disputed *rpoB* mutations and strengthen treatment outcome.

5. Conclusion

In conclusion, rifampicin remains the backbone of present multidrug TB therapy. For 40 years recommended rifampicin doses have remained the same due to cost constraints and the fear of increased toxicity. Recent developments in testing the efficacy and safety of high-dose rifampicin have offered the prospect of not only shortened treatment but also reduced relapse rates. However, questions remain: To what extent does rifampicin affect the metabolism of other standard anti-TB and anti-HIV drugs; are toxic metabolites formed during this process? Will increasing the dosage of rifampicin exacerbate this process? Will increasing rifampicin be the gateway for re-evaluating other anti-TB drug concentrations or combinations as the TRUNCATE-TB trial? As more studies are suggesting that the current dose is sub-optimal, will high dose rifampicin limit the emergence of rifampicin mono-resistance? Will high dose rifampicin overcome reduced susceptibility conferred by disputed *rpoB* mutations? Lastly, should more research be focused on using alternative systems to optimise our current dosages. More than 50 years after its synthesis, rifampicin is still being developed and evaluated not only in the quest to combat TB but also to ultimately understand the effect of rifampicin on other drugs, individuals and the tubercle bacillus itself.

Declarations of Competing Interests

None.

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