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Considerations in preparing for clinical studies of inhaled rifampicin to enhance tuberculosis treatment

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ABSTRACT

Drug delivery via the inhaled route has advantages for treating local and systemic diseases. Pulmonary drug delivery may have potential in treating tuberculosis (TB), which is mainly localised in the lung (pulmonary tuberculosis ~75%) while also affecting other organs (extra-pulmonary tuberculosis). Currently, rifampicin, a first-line anti-tubercular drug, is given orally and the maximum daily oral dose is the lesser of 10 mg/kg or 600 mg. Since only a small fraction of this dose is available in the lung, concentrations may frequently fail to reach bactericidal levels, and therefore, contribute to the development of multi-drug resistant pulmonary TB. Pulmonary delivery of rifampicin, either alone or in addition to the standard oral dose, has the potential to achieve a high concentration of rifampicin in the lung at a relatively low administered dose that is sufficient to kill bacteria and reduce the development of drug resistance. As yet, no clinical study in humans has reported the pharmacokinetics or the efficacy of pulmonary delivery of rifampicin for TB. This review discusses the opportunities and challenges of rifampicin delivery via the inhaled route and important considerations for future clinical studies on high dose inhaled rifampicin are illustrated.

1. Introduction

1.1. Brief history of rifampicin

Rifampicin, also known as rifampin, is a semi-synthetic, broad-spectrum antibiotic commonly used to treat tuberculosis (TB). It is a first line agent, along with isoniazid, pyrazinamide and ethambutol, in the treatment of pulmonary and extra-pulmonary TB and is also a primary agent for the prophylaxis of meningococcal disease (Scholar, 2007). Rifampicin was developed by Dow-Lepetit Research Laboratories (Milan, Italy) in 1965 and was introduced into therapeutic use in 1968 (Fig. 1) (Sensi, 1983).

The early clinical studies on rifampicin demonstrated its efficacy against several infections including TB, staphylococcal disease, respiratory tract infections, gonorrhoea and meningococcal diseases (Phillips, 1971; Sensi, 1983). Since then, laboratory and clinical studies on rifampicin have continued, and research has focused on its efficacy against mycobacterial infections in humans.

1.2. Pharmacology and pharmacokinetics of rifampicin

Rifampicin acts on bacterial polymerase by forming a stable drug-enzyme complex that inhibits the DNA transcription of the bacteria without affecting the mammalian enzymes (Wehrli, 1983). Rifampicin is completely absorbed after oral administration, is widely distributed throughout the body, undergoes enterohepatic circulation and deacetylation and is mostly excreted in the faeces (Scholar, 2007). The pharmacological and pharmacokinetic properties of rifampicin are summarized in Table 1.

1.3. TB as a global health problem

TB is caused by *Mycobacterium tuberculosis* and mostly affects the lungs, since the lungs are the primary site of aerosols' entry into the body (WHO, 2017). TB is one of the most common infectious diseases worldwide and is a leading cause of death: 1.8 million people died as a result of TB in 2015 (Van Crevel and Hill, 2017; WHO, 2017). In the early 20th century, therapeutic options were restricted to surgery intended to collapse or remove infected TB lung cavities, but the introduction of chemotherapeutic agents in the 1940s played a decisive

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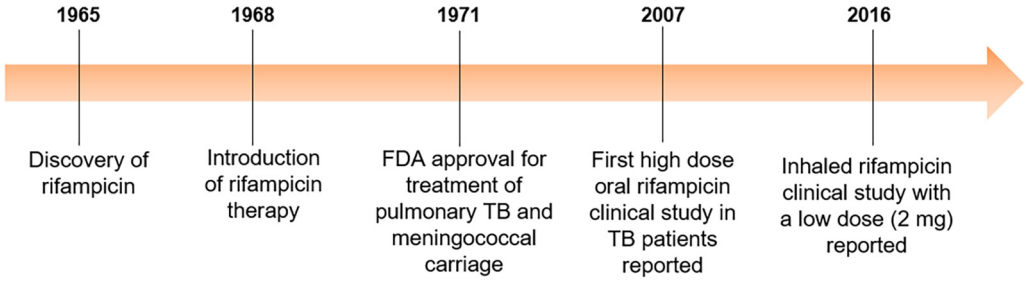

Fig. 1. Milestones in rifampicin development and its progress towards high dose rifampicin and inhaled rifampicin.

Table 1
Pharmacological and pharmacokinetic properties of rifampicin (Scholar, 2007).

Rifampicin pharmacology and pharmacokinetics	
Human pharmacokinetics after oral administration	• Almost completely absorbed after oral administration. • Widely distributed throughout the body including the central nervous system. • Undergoes enterohepatic recirculation, and is progressively deacetylated. The deacetylated metabolite retains almost full antibacterial activity. • Mostly excreted in the faeces as the metabolite, with the rest eliminated in urine. • Half-life is progressively shortened due to microsomal enzyme induction. • In healthy individuals, 600 mg dose of rifampicin results in maximum serum concentration (C_{max}) of 10 mg/L at 2 h (T_{max}) and the area under the curve from time zero to infinity ($AUC_{0-\infty}$) value of about 57 h·mg/L (Acocella, 1978; Peloquin et al., 1999).
Mechanism of action	Inhibits bacterial and mycobacterial RNA *polymerase*, an enzyme responsible for DNA transcription.
Indications and dosage	• Brucellosis (600–900 mg) • Leprosy-Hansen's disease (600 mg) • Tuberculosis (10 mg/kg with a maximum of 600 mg per day) • Osteoarthritis (300–600 mg) • Osteomyelitis (600 mg) • Staphylococcal infections (900–1200 mg) • Other bacterial infections (300–600 mg)
Adverse effects	Generally well tolerated and rare serious toxicity such as hepatotoxicity and nephrotoxicity.
Approved routes of administration	Oral and intravenous

role in controlling endemic TB in western countries (Riva, 2014). However, TB remains a problem: firstly, there is a high disease burden in low and middle income countries; secondly, treatment requires adherence to a long, multi-drug treatment regimen with a significant side-effect profile; and thirdly, current treatment regimens are sometimes unsuccessful, resulting in relapse and the emergence of multi-drug-resistant (MDR) TB, which is resistant to rifampicin and isoniazid.

1.4. Dose limitation of oral rifampicin in TB treatment

The recommended oral dose of rifampicin for TB treatment is 10 mg per kg body weight or a daily maximum of 600 mg, based on safety, cost and efficacy grounds (van Ingen et al., 2011). The 600 mg dose of rifampicin may be suboptimal, and there are reports of higher doses with potential to reduce the overall duration of TB treatment without an increase in adverse effects (Dutta and Karakousis, 2015). Moreover, higher doses of rifampicin (900–1200 mg) are sometimes used for other infections such as brucellosis, legionnaires disease, and leishmaniasis (van Ingen et al., 2011). Nevertheless 600 mg (or 10 mg/kg body weight) of rifampicin is currently the maximum recommended daily oral dose in humans for the treatment of TB.

1.5. Ineffective concentration of drug at target sites after oral delivery

Currently available first-line anti-TB drugs (rifampicin, isoniazid, pyrazinamide and ethambutol) may have suboptimal efficacy against mycobacteria when given orally to patients. This is because the mycobacteria are shielded within caseating lung lesions devoid of vasculature, preventing orally administered drug penetrating such sites at an effective concentration. Even though it is difficult to accurately measure the amount of drug that reaches the target alveolar sites after oral administration in humans, there have been suggestions of drug concentrations being inadequate in caseating tissues in TB when administered via the oral route because the bacteria at those sites are highly protected by fibrous tissues (Dartois, 2014; Lenaerts et al., 2007; Muttil et al., 2009). This makes it difficult to deliver the desired amount of drug for consistent bactericidal effects in the lesions when reliant on oral bioavailability. Inadequate concentration of rifampicin at bacterial sites may well be a reason behind ineffective bacterial killing, bacterial mutation, and emergence of drug resistant bacterial strains. The bacteria are likely to become resistant to rifampicin when they are able to change the structure of polymerase β subunit by undergoing mutation (Campbell et al., 2001).

1.6. Strategies to improve TB treatment

To overcome the issues described above, improved treatment regimens are necessary which would fulfil the following criteria: inexpensive, more effective at killing TB, of shorter duration, and a more benign side-effect profile. New anti-TB drugs are in development (AlMatar et al., 2017), but their introduction alone is unlikely to provide a complete solution to the problems with current therapy.

High dose delivery of rifampicin is a promising approach to improve therapeutic outcome and prevent emergence of resistance towards the drug. High dose rifampicin through the oral route has progressed to improve treatment efficacy but this approach requires administration of large doses. An alternative strategy might be to deliver the drug directly to the lungs via the inhaled route. This has the potential to increase the concentration of drugs in the lung and target TB directly in alveolar macrophages and tubercles with the aim of fulfilling the criteria described above.

In this review, we discuss the importance of high dose rifampicin, progress of clinical studies on high dose rifampicin through the oral route, potential of inhaled rifampicin for high dose delivery, current