Rifampin and Their Analogs: A Development of Antitubercular Drugs

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Abstract There has been considerable interest in various analogues of antitubercular drugs particularly against multidrug and extensively drug resistant tuberculosis because mycobacterium species has developed resistant against available drugs. The currently used antitubercular also causes some serious toxic effects and also require long period of therapy for the treatment. Therefore, various new drugs and analogues of currently used antitubercular drugs were prepared with minimum side effects or effective against multidrug and extensively drug resistant strains of tuberculosis. In present review we discussed about brief introduction of tuberculosis followed the rifampicin and their analogues which are effective against tuberculosis.

Keywords: multidrug resistance, mycobacterium, tuberculosis, rifampicin, analogues

1. Introduction

Tuberculosis (TB) is a chronic infectious disease, still remains one of the most serious problems to humans worldwide. TB is an airborne communicable disease caused by transmission of aerosolized droplets of M. tuberculosis. It is responsible for 3 million deaths per year. Moreover, nearly all drugs used for the treatment of TB and possessing different mechanisms of activity are able to cause adverse side effects on the human organism. Therefore, it is extremely important to search for new more potent with low-toxicity drugs superior to the current available drugs and also effective against resistant tubercular strains [1,2,3,4].

Tuberculosis (TB) is generally associated with “tuberculosis complex”, including primarily Mycobacterium tuberculosis. Other species M. bovis, M. africanum, M. canetti and M. microti can also cause TB, these strains do not usually infect healthy adults [5,6]. The M. bovis and M. africanum only very rarely cause disease in immuno competent people. On the other hand although M. microti is not usually pathogenic, it is possible that the prevalence of M. microti infections has been under estimated [7,8]. These species are intracellular pathogens of higher animals. Since HIV/AIDS patients have a higher probability of acquiring TB or other mycobacterial opportunistic infections, particular drug regimens have been designed for treating active TB disease in them. Also, the severity of adverse effects of anti-TB drugs due to the interactions with anti-retroviral drugs and mortality is higher among HIV-positive patients. Although, in general, HIV-positive patients respond well to a standard short-course treatment of TB, treatment failure due to malabsorption of anti-TB drugs has been reported. The WHO recommends not using streptomycin or thiacetazole in HIV-positive patients in order to prevent the adverse effects of these drugs, often enhanced by antiretroviral drugs; ethambutol can be used instead [9,10]. TB requires much longer periods of treatment to entirely eliminate mycobacterium from the body. Multidrug-resistant (MDR) TB is strictly defined as M. tuberculosis strains showing resistance simultaneously against isoniazid and rifampicin [11,12]. TB with a different drug resistant (DDR-TB) involves M. tuberculosis strains displaying resistance not including associated resistance against isoniazid and rifampicin. The M. tuberculosis strains may be sensitive or resistant. The review includes the introduction section, to reveal possible activity of rifampicine and their various analogues. In addition to this, the increase in M. tuberculosis strains resistant to front line antiTB drugs rifampin has further complicated the problem, which clearly indicates the need for more effective drugs for the efficient management of TB [13,14,15].

2. Therapy of Tuberculosis

Chemotherapy of TB are mainly depends on first-line anti-TB drugs, which include five drugs namely, streptomycin, isoniazid, rifampicin, ethambutol and pyrazinamide, they more effective and less toxic as compare to second-line anti-TB drugs. Some drugs may be classified as a second-line because of one of two possible reasons: it may be less effective than the first-line drugs or it may have toxic side-effects. These comprise of different classes namely, aminoglycosides (amikacin, kanamycin), polypeptides (capreomycin, viomycin), fluoroquinolones (ciprofloxacin, moxifloxacin, etc), thioamides (ethionamides, prothioamide), cycloserine and p-aminosalicylic acid [6,16]. The term MDR-TB is used to describe strains that are resistant to two or more of the five first-line anti-TB drugs. Treatment regimen of TB
comprises five first line antiTB drugs followed by second line antiTB drugs. Then, a drug regimen of nine months of isoniazid and rifampicin supplemented with ethambutol during the first three months has been proposed. Rifamycins (rifampicin, rifabutin, etc.) have clinically relevant interactions with some drugs used in the antiretroviral therapy, since they induce the metabolism of anti-retroviral agents such as zidovudine, non-nucleoside reverse transcriptase inhibitors, and HIV protease inhibitors, whose concentrations may fall to subtherapeutic levels. Then, rifamycin-free regimens have been suggested. However, it has also been described that the use of Rifamycins throughout anti-TB treatment improves outcome in HIV patients [17]. This is aimed at preventing the occurrence of TB. Prophylaxis is most frequently achieved by the administration of isoniazid only, at doses of 300mg daily for 6-9 months (risk of developing isoniazid resistance). When resistance to isoniazid is suspected, other regimens include rifampicin, pyrazinamide or ethambutol can be administered, although there is a greater chance of having adverse effects. In TB prophylaxis, rifampicin can be given concurrently with isoniazid, reducing the prophylaxis treatment to three months. It is of prime importance to ensure complete elimination of the bacilli, and also to prevent the emergence of drug resistance. Most drugs used in anti-TB treatment-isoniazid, rifampicin, rifampicin, rifabutin, pyrazinamide, ethambutol, and ethionamide. The three main drugs used in the standard anti-TB regimen-isoniazid, rifampicin, and pyrazinamide [18]. There are several combinations, like isoniazid, and rifampicin, isoniazid and ethambutol, isoniazid, rifampicin and pyrazinamide, and isoniazid, rifampicin, pyrazinamide and ethambutol. Most importantly, this form minimizes the possibility of monotherapy and therefore, reduces the risk of drug resistance development.

3. Toxic Effects of Antitubercular Drugs

The currently available first line drugs are show serious side effects like severe damage to the eighth cranial nerve, irreversible impairment of auditory function, hypersensitivity (streptomycin), hepatotoxicity and hepatitis (isoniazide, pyrazinamide and rifampicin (rifampicin, rifabutin, rifampicin) and thrombocytopenic purpura (rifampicin). Second line anti-TB drugs are more toxic than first line drugs, amikacin and kanamycin causes kidney damage and hearing loss, viomycin and capreomycin causes nephrotoxicity and eighth cranial nerve toxicity [19,20]. Fluoroquinolones (ciprofloxacin, moxifloxacin, ofloxacin, levofloxacin, gatifloxacin, trovafloxacin, enrofloxacin, sparfloxacin etc) are contraindicated due to growing prevalence of antibiotic resistance. Ethionamide and prothionamide causes gastrointestinal tract (g.i.t) disorders (anorexia, salivation, nausea, abdominal pain, and diarrhea), mental disturbances (depression, anxiety, psychosis, dizziness, drowsiness, and headache) and hypersensitivity [21]. Cycloserine causes CNS disorders such as headache, irritability, depression, convulsions. Para amino salicylic acid causes g.i.t. problems including anorexia, nausea, epigastric pain, abdominal distress, diarrhea, ulcers and hypersensitivity [22].

4. Drug-Resistant Tuberculosis

Drug resistance (MDR and XDR) by M. tuberculosis is an important obstacle for the treatment and control of TB. MDR-TB refers to simultaneous resistance to at least two or more of the five first-line anti-TB drugs. Treatment for MDR-TB is long lasting, less effective, costly, and poorly tolerated [4]. Extensively drug resistant (XDR) TB is resistance to at least isoniazid and rifampicin in addition to any quinolone and at least one injectable second-line agent (capreomycin, amikacin, kanamycin). The principles of treatment for MDR-TB and XDR-TB are the same. The main difference is that XDR-TB is associated with a much higher mortality rate than MDR-TB, because of reduced number of effective treatment options [23,24]. Hence there is a need for new drugs that are active against M. tuberculosis in order to shorten the duration of TB therapy [20].

5. Targets and Need of New Anti-TB Drugs

Although current drugs treatment is complex and long-lasting. This makes compliance difficult. TB treatment should improve the existing regimens by shorten the duration of treatment, reduce the number of doses, improve the treatment of MDR-TB and provide a more effective treatment of latent TB infection [25]. Effective drug candidates currently in two main categories are novel chemical entities and drug originating from existing drugs, where innovative chemistry is used to optimise the compounds.

6. Rifampin and Other Rifamycins

Rifampin inhibits the growth of most gram-positive bacteria as well as many gram-negative microorganisms such as Escherichia coli, Pseudomonas, indole-positive and indole-negative Proteus, and Klebsiella. Rifampin is very active against Staphylococcus aureus and coagulase-negative staphylococci. The drug also is highly active against Neisseria meningitidis and Haemophilus influenzae; minimal inhibitory concentrations range from 0.1 to 0.8µg/ml. Rifampin inhibits the growth of Legionella species in cell culture and in animal models [26,27]. Rifampin in concentrations of 0.005 to 0.2µg/ml inhibits the growth of M. tuberculosis in vitro. Among nontuberculous mycobacteria, M. kansasii is inhibited by 0.25 to 1 µg/ml. The majority of strains of M. scrofulaceum, M. intracellulare, and M. avium are suppressed by concentrations of 4µg/ml, but certain strains may be resistant to 16 µg/ml. M. fortuitum is highly resistant to the drug. Rifampin increases the in vitro activity of streptomycin and isoniazid, but not that of ethambutol, against M. tuberculosis.

The rifamycins are a group of structurally similar, complex macrocyclic antibiotics produced by Amycolatopsis mediterranei [28]; rifampin (Rifadin; Rimactane) is a semisynthetic derivative. It is active towards a number of bacteria but used almost exclusively to TB. Rifampin (Rifadin): Semisynthetic derivative of rifamycin and most potent antiTB agent. Rifapentine
(Priftin): It is Cyclopentyl derivative of rifamycin. Advantage over rifampin is less frequent dosing. Inhibits bacterial DNA-dependent RNA polymerase and binds to the β-subunit. Blocks elongation of the RNA transcript and prevents gene expression. It is strong CYP450 inducer. One unusual side effect is discoloration of body fluids. Rifampicin has been used for front-line TB therapy. A longer acting rifamycin, rifapentine [29] (T1/2 10-15 hours v 2-3 hrs for rifampicin), has approved by the FDA as an anti-TB drug. This drug can be given twice weekly initially and then once weekly during the continuation phase of treatment. However, in comparative studies with rifampicin, it appears to be slightly less effective and there is also a significant interaction with the AIDS drug indinavir [30]. Continuing interest in new rifamycins is focused on longer-acting compounds which can be given just once weekly to simplify short-course chemotherapy regimens. Rifapentine has not been approved for pediatric use.

6.1. Bacterial Resistance

Mycobacterium may develop resistance to rifampin. resistance to rifampin is due to an alteration of the target of this drug, DNA-dependent RNA polymerase, with resistance in most cases being due to mutations between codons 507 and 533 of the polymerase rpoB gene [31]; the mutations reduce binding of the drug to the polymerase. As a result, the antibiotic must not be used alone in the TB therapy. TB caused by rifampin-resistant mycobacteria has been described in patients who had not received prior chemotherapy, but this is very rare and usually less than 1% [32,33,34].

6.2. Mechanism of Action

Rifampin inhibits DNA-dependent RNA polymerase of mycobacteria and other microorganisms by forming a stable drug-enzyme complex, leading to suppression of initiation of chain formation (but not chain elongation) in RNA synthesis. More specifically, the β-subunit of this complex enzyme is the site of action of the drug, although rifampin binds only to the holoenzyme. Nuclear RNA polymerases from a variety of eukaryotic cells do not bind rifampin, and RNA synthesis is correspondingly unaffected in eukaryotic cells. High concentrations of rifamicyn antibiotics can inhibit RNA synthesis in mammalian mitochondria, viral DNA-dependent RNA polymerases, and reverse transcriptases. Rifampin is bactericidal for both intracellular and extracellular microorganisms [35,36].

6.3. Therapeutic Uses

Rifampin for oral administration is available alone and as a fixed-dose combination with isoniazid [150mg of isoniazid, 300mg of rifampin; (rifamate)] or with isoniazid and pyrazinamide [50mg of isoniazid, 120mg of rifampin, and 300mg pyrazinamide; (rifater)]. A parenteral form of rifampin is available for use when the drug cannot be taken by mouth. Rifampin and isoniazid are the most effective drugs available for the treatment of TB. The dose of rifampin for treatment of tuberculosis in adults is 600mg , given once daily, either 1 hour before or 2 hours after a meal. Children should receive 10mg /kg given in the same way. Doses of 15mg /kg or higher are associated with increased hepatotoxicity in children [27,37]. Rifampin, like isoniazid, should never be used alone for the treatment of TB because of the rapidity with which resistance may develop.

6.4. Adverse Effects

Rifampin generally is well tolerated. When given in usual doses, less than 4% of patients with TB have significant adverse reactions, commonly are rash, fever, nausea and vomiting [38]. Rarely, hepatitis and deaths due to liver failure have been observed. Hepatitis from rifampin rarely occurs with normal hepatic function patient. The combination of isoniazid and rifampin are safe from hepatitis [39]. However, chronic liver disease, alcoholism, and old age appear to increase the incidence of severe hepatic problems. Rifampin may cause eosinophilia, interstitial nephritis, acute tubular necrosis, thrombocytopenia, hemolytic anemia, and shock. Because rifampin potently induces CYP1A2, 2C9, 2C19, and 3A4, include HIV protease and non-nucleoside reverse transcriptase inhibitors, digitoxin, digoxin, quinidine, disopyramide, mexiletine, tocainide, ketoconazole, propranolol, metoprolol, clofibrate, verapamil, methadone, cyclosporine, corticosteroids, oral anticoagulants, theophylline, barbiturates, oral contraceptives, halothane, fluconazole, and the sulfonylureas [28]. Rifabutin has less effect on the metabolism of many of the HIV protease inhibitors. Rifampin may reduce biliary excretion of contrast media used for visualization of the gallbladder [31]. Gastrointestinal disturbances produced by rifampin (epigastric distress, nausea, vomiting, abdominal cramps, diarrhea) have occasionally required discontinuation of the drug. Various CNS problems have been noted, including fatigue, drowsiness, headache, dizziness, ataxia, confusion, inability to concentrate, generalized numbness, pain in the extremities, and muscular weakness. Hypersensitivity reactions include fever, pruritus, urticaria, various types of skin eruptions, eosinophilia, and soreness of the mouth and tongue. Hemolysis, hemoglobinuria, hematuria, renal insufficiency, and acute renal failure have been observed rarely; these also are thought to be hypersensitivity reactions. Thrombocytopenia, transient leukopenia, and anemia have occurred during therapy. Since the potential teratogenicity of rifampin is unknown and the drug is known to cross the placenta, it is best to avoid the use of this agent during pregnancy [40]. Rifampin is effective for chemoprophylaxis of meningococcal disease and meningitis due to H. influenza. Combined with a β-lactam antibiotic or vancomycin, rifampin may be useful for therapy in selected cases of staphylococcal endocarditis or osteomyelitis, especially those caused by staphylococci “tolerant” to penicillin [41].

7. Compounds Originating from Existing Families of Drugs

7.1. Rifamycins Analogues: Rifampicin, Rifabutin and Rifapentine

The rifamycin and semi-synthetic rifamycins belong to a novel class of macrolide antibiotics that feature a
propionate-derived chain bridging a tricyclic naphthalene core. They inhibit prokaryotic DNA-dependent RNA polymerase, an enzyme necessary for RNA synthesis. Inhibition is due to the formation of a stable non-covalent complex between the antibiotic and the enzyme. Rifamycins cause inhibition of bacterial RNA synthesis and have no effect on mammalian enzymes. The mechanism of the action of the rifampicin/rifampin (1) is similar to that of rifamycin. Rifabutin (2) has activity spectrum similar to rifampicin, but appears to possess incomplete cross-resistance with rifampicin in vitro. Rifapentine (3) is an analogue of rifampicin in which a cyclopentyl group substitutes for a methyl group on the piperazine ring. It is more lipophilic and has a serum half life about five times longer than rifampicin [42,43,44]. Rifabutin (Mycobutin) is a rifampin derivative used in tuberculosis-infected HIV patients treated concurrently with protease inhibitors because rifabutin is a less potent inducer of CYPs. It has the same mechanism of action as rifampin and is discussed further in the section on drugs for M. avium complex. Unique side effects of rifabutin include polymyalgia, pseudojaundice, and anterior uveitis. About one-fourth of rifampin-resistant M. tuberculosis isolates are rifabutin-sensitive, so it may have a role in the treatment of multidrug-resistant tuberculosis. Rifapentine (Priftin) has a longer half-life than rifampin and rifabutin, which allows once-weekly dosing. Compared to rifabutin and rifampin, it is intermediate in its induction of CYPs. Its use in the treatment of tuberculosis in HIV-infected patients was associated with the selection of rifamycin resistance; rifabutin is therefore preferred in this situation [44].

To avoid rapid development of resistance, RMP is recommended in combination with other first-line agents either isoniazid or ethambutol. RMP is effective against M. tuberculosis with MIC ranging from 0.1-0.2μg/mL. RMP was modified with several analogs and among them one compound KRM-1648, was found to be more potent than Rifampicin [42,43,44]. In a different approach, Figueiredo et al. synthesized Rifabutin (RBT) analogues. Among them, compound 4 displayed good potency of MIC <0.013 μg/mL against M. tuberculosis H37Rv, while compound 5 showed potency of MIC 0.08 μM against non-replicating M. tuberculosis strains [45].

7.2. CGP 7040

A number of rifamycin derivatives, exemplified by CGP 7040, have been compared in vitro to rifampicin against rifampicin-sensitive and rifampicin-resistant strains of M. tuberculosis and M. avium/intracellulare/scrofulaceum (MAIS) complex. The compounds had MICs 4 to 8 times lower than those of rifampicin against sensitive M. tuberculosis strains, but of the rifampicin-resistant strains of M. tuberculosis [46]. Overall CGP7040 was more active than rifabutin and rifampicin against M. avium and
was superior to rifampicin towards \textit{M. tuberculosis}. In addition it was found to be considerably more stable than rifampicin [46].

### 7.3. New Rifamycin Derivatives

#### 7.3.1. Rifalazil

Rifalazil, a new semisynthetic rifamycin, is characterized by a long half-life and is more active than rifampicin and rifabutin against \textit{M. tuberculosis} both in vitro and in vivo [47]. However, high level rifampicin-resistant strains present cross-resistance to all ryfamycins [48].

#### 7.3.2. Rifametane

Rifametane (SPA-S-565) is a new semi-synthetic rifamycin. It has a bactericidal spectrum and potency similar to that of rifampicin, but with much better pharmacokinetic properties. In healthy male volunteers, the pharmacokinetics and safety of a 300mg single oral dose of rifametane were compared to a 300mg dose of rifampicin. The data clearly showed the pharmacokinetic profile of rifametane to be significantly more favourable than that of rifampicin. Thus, the elimination half-life for rifametane was 10.58 hours compared with 1.89 hours for rifampicin. In a trial carried out, a single oral dose of 150mg was administered and the half-life and area under curve (AUC) were some 6 or 7-fold that of rifampicin [47,48]. Encouragingly, serum drug levels above the MIC for \textit{M. tuberculosis} were maintained for up to 48 hours after drug administration.

#### 7.3.3. Rifalazil

Rifalazil (KRM 1648) shown to have superior activity to rifampicin against \textit{M. tuberculosis} in vitro and in vivo. The compound was progressed clinically in association with Pathogenesis, and using pulmonary TB patients [49]. However, due to severe side-effects during trial, the development of rifalazil has been terminated.

### 8. Discussion

In view of the persistent drug-resistant TB problem of currently used anti-TB agents, it is important that new anti-TB drugs should address different targets, as those of currently used drugs including the shortening of TB therapy [50,51,52]. New molecules could provide a effective chemotherapeutic agents against TB. Although one possible long term solution to the problem, the major reliance will be on chemotherapy requiring the development of novel, effective and non-toxic anti-TB agents. The identification of novel target sites will also be needed to circumvent the problems associated with the increasing occurrence of MDR-TB and XDR-TB strains. To do this, biochemical pathways specific to the mycobacteria and related organisms disease cycle must be better understood. One of these attractive targets for the rational design of new anti-TB agents are the mycolic acids, the major components of the cell wall of \textit{M. tuberculosis} [53,54,55]. From the chemotherapeutic point of view, there are two sources of new chemical entities. Development of new drugs is the need to control TB. However, in recent years there is an enhanced activity in the research and development of new drugs for TB. Some compounds are presently in development, while others are being investigated in an attempt to explore new molecules for the target based treatment of TB. Simultaneously some new targets are being identified and validated for their practical usefulness [55-61]. The present review provides an overview of the newer drugs and analogues of currently used drugs against pathogenic mycobacterium.

### 9. Conclusion

Inspite of some effective chemotherapeutic agents, TB remains a leading infectious killer worldwide. This is mainly due to the lack of new drugs in the market, particularly for effective treatment against the spread of MDR and XDR, and patients co-infected with HIV/AIDS. Therefore, there is an urgent need for the development of new anti-TB drugs with lesser side-effects, improved pharmacokinetic properties to be effective against MDR and XDR resistant bacterial strains with reduce the overall duration of treatment. Precisely, because of this observed drug-resistance by the bacterium, it is imperative to develop smart new drugs that inhibit novel targets that are structurally and functionally different from those currently known. Medicinal chemists will be interested to working on new compounds. In view of above facts and inspired by the research going on new derivatives, particularly in relation to microbial infections specially against mycobacterium, different new drugs will be synthesized in the future for development of new effective molecule.

### References


