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Review Article

Four-Month Rifapentine Based Regimen with Moxifloxacin for Drug-Susceptible Pulmonary Tuberculosis: A Path to Tread with Caution

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Abstract

Recent evidence has shown that the efficacy of a four-month regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin is non-inferior to the standard six-month regimen in the treatment of drug-susceptible TB. The World Health Organisation has also issued interim recommendations for adopting this shorter regime by various countries. The current article discusses the various aspects of this regime that need to be considered before its wider use in the treatment of tuberculosis.

Keywords: *Tuberculosis; TB; Shorter ATT Regime; Anti Tubercular Therapy; Rifapentine; Isoniazid; Pyrazinamide; Moxifloxacin; Fluoroquinolone*

Abbreviations

TB: Tuberculosis; WHO: World Health Organization; MDR-TB: Multidrug Resistant TB; RR-TB: Rifampicin Resistant TB; Pre-XDR TB: Pre-Extensively Drug-Resistant TB; XDR-TB: Extensively Drug-Resistant TB; TPT: TB Preventive Therapy; NAAT: Nucleic Acid Amplification Test; FDC: Fixed-Dose Combination; HIV: Human Immunodeficiency Virus; ADRs: Adverse Drug Reactions; LTFU: Lost to Follow Up

Introduction

Tuberculosis (TB) is a communicable disease that is a significant cause of death worldwide and one of the top ten causes of dying from a single infectious agent. TB can afflict anybody, anywhere, although most individuals who contract the disease are adults; men are more likely than women to contract the disease. Thirty high-TB-burden nations account for about 90% of those who contract the disease each year. TB is a poverty-related disease, and persons living with the disease frequently experience economic hardship, vulnerability, marginalization, stigma, and prejudice. TB is curable and preventable. A 6-month medication regimen can successfully treat 85 percent of persons who get tuberculosis [1]. Long treatment regimens provide significant obstacles for the programmatic management of TB worldwide. The TB community has been looking for shorter and more effective therapies for TB disease since the discovery of first-line anti-TB drugs and treatment regimens. Shortened treatment has the potential to improve adherence and reduce patient and health system costs. Over the last few decades, there has been much scientific interest in reducing the length of treatment [2].

Discussion

S.E. Dorman and colleagues in their recently published research trial have shown that the efficacy of a four-month regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin is non-inferior to the standard six-month regimen in the treatment of drug-susceptible TB [3]. This is a landmark research in the field of TB chemotherapy. Also, the World Health Organization (WHO), in a recently released rapid communication on the above rifapentine based regime, remarked that "the 4-month regimen, which is shorter, effective and all-oral, would be a preference for many patients and also national TB programmes, allowing faster cure and easing the burden on both patients and the healthcare system" [2].

The composition and doses of the four-month regimen composed of rifapentine, isoniazid, pyrazinamide and moxifloxacin are given below in table 1.

Regime	Eight weeks of rifapentine, isoniazid, pyrazinamide and moxifloxacin, (intensive phase) followed by nine weeks of rifapentine, isoniazid, and moxifloxacin (continuation phase).
Daily Dose:	Rifapentine: 1200 mg od Moxifloxacin: 400 mg od INH: 300 mg od Pyrazinamide (based on patients' weight): > 55 kg: 1000 mg od 55 - 75 kg: 1500 mg od > 75 kg: 2000 mg od Tb Pyridoxine 25/50 mg od (based on local norms)

Table 1: *Regime composition and doses of four-month rifapentine based regimen with moxifloxacin.*

However, when using an effective second-line anti-TB drug like moxifloxacin to manage drug-susceptible TB, we need to carefully outweigh all associated impact such an action could have. We first need to review the current definitions of different types of drug-resistant TB need to understand this possible impact better. Currently, the updated and revised definitions of different types of drug-resistant TB, as defined by WHO, are shown in table 2 [4].

Type of drug resistant TB	Definition
MDR-TB (Multidrug Resistant TB)	TB caused by M. tuberculosis strains that are resistant to at least both rifampicin and isoniazid
RR-TB (Rifampicin Resistant TB)	TB caused by M. tuberculosis strains resistant to rifampicin
Pre-XDR TB (Pre- extensively drug-resistant TB)	TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone*.
XDR-TB (Extensively drug-resistant TB)	TB caused by Mycobacterium tuberculosis (M. tuberculosis) strains that fulfil the definition of MDR/RR-TB and which are also resistant to any fluoroquinolone and at least one additional Group A drug**.
*The fluoroquinolones include levofloxacin and moxifloxacin as they are the fluoroquinolones currently recommended by WHO to treat drug-resistant TB. **The Group A drugs are currently levofloxacin or moxifloxacin, bedaquiline and linezolid; therefore, XDR-TB is MDR/RR-TB that is resistant to a fluoroquinolone and at least one of bedaquiline or linezolid (or both).	

Table 2: *Current definitions of different drug-resistant TB.*

WHO now recommends using fluoroquinolones in the upfront management of drug-sensitive TB based on the current study results by S.E. Dorman., *et al* [3]. Also, WHO has already recommended fluoroquinolones in TB preventive treatment (TPT) among contacts of drug-resistant TB patients [5]. As evident from table 2, fluoroquinolone is an integral drug in defining advanced forms of drug-resistant TB. Early and increased exposure to this drug by including it in upfront management of drug-sensitive TB and TPT may increase the proportion of fluoroquinolone resistance in the community. This is especially important in high TB burden countries like India, where the National drug-resistant survey has shown that among MDR TB patients, additional resistance to fluoroquinolones was seen in 21.82% of patients [6]. One of the studies from Mumbai, India, on 340 MDR-TB patients showed that an alarming 69.5% of these patients had additional resistance to moxifloxacin [7]. Rifapentine, a part of the current four-drug anti-TB regime, exhibits cross-resistance with rifampicin [8]. Currently, molecular-based tests for specific rifapentine resistance testing is not available, and rifampicin resistance testing may be taken as a surrogate for rifapentine sensitivity till such facilities are available. Thus, there may be a potentially high risk of developing Pre-XDR and XDR-TB among patients if they fail this four-month regime. A baseline Nucleic Acid Amplification Test (NAAT)/molecular drug sensitivity report of all first-line drugs and select second-line drugs, including fluoroquinolones, has recently been recommended in all TB patients by the WHO [9]. Baseline drug sensitivity testing of the drugs used in the regime will help increase the success of this regime. It will require rigorous antibacterial stewardship to ensure the appropriate use of this first-line regimen.

The WHO Global TB Programme has also recently submitted applications to include the rifapentine 300 mg scored tablet in the WHO Model List of Essential Medicines to make it easier for countries to employ rifapentine-based regimens. According to the WHO, this is a versatile formulation for meeting the dose needs of the rifapentine-containing 4-month regimen for drug-susceptible TB [10]. But considering the fixed dose of 1200 mg per day of rifapentine used in the trial by S.E. Dorman., *et al*. the pill burden with 300 mg rifapentine tablets may lead to challenges associated with adherence and compliance during the programmatic implementation of this rifapentine based shorter regime [3]. Fixed-dose combination (FDC) formulations of the combination therapy used in this regime will help address this challenge.

Some of the crucial exclusion criteria for enrolled TB patients in the current research trial were: 1. Pregnant or breast-feeding females, 2. known history of prolonged QT syndrome, 3. suspected or documented tuberculosis involving the central nervous system and/or bones and/or joints, and/or miliary tuberculosis and/or pericardial tuberculosis, 4.current or planned use within six months following enrollment of one or more of the following medications: HIV protease inhibitors, HIV integrase inhibitors, HIV entry and fusion inhibitors, HIV non-nucleoside reverse transcriptase inhibitors other than efavirenz; quinidine, procainamide, amiodarone, sotalol, disopyramide, ziprasidone, or terfenadine, 5. weight less than 40 kgs. and 6. M. Tuberculosis isolates being resistant to any one or more of the following: rifampin, isoniazid, pyrazinamide, ethambutol, or fluoroquinolones [3].

When implementing the above standardized regime on a programmatic mode, the above patients need to be excluded from receiving this regime till further evidence of safety and efficacy of this regime on patients of the above exclusion criteria are available. Thus, currently, the above regime may be initiated in drug-sensitive pulmonary tuberculosis patients. Patients with extensive pulmonary disease and all forms of extrapulmonary disease should not be started on this regime as they may require a prolonged course of anti-TB treatment. Currently, there is no data on safety and efficacy associated with an extension of this regime. This is especially important as the daily dose of rifapentine used in the study is 1200 mg/day. This dosing is based on recent evidence regarding the optimal dosing of rifapentine and is double the previously recommended 600 mg weekly dose [11,12]. ADRs (Adverse drug reactions) need to be closely monitored and managed at the earliest in this regime as they can be a potential cause of TB patients being lost to follow up (LTFU), which may be catastrophic and lead to poor treatment outcomes in these patients [13].

Conclusion

To conclude, the newer four-month rifapentine-based shorter regime with moxifloxacin needs to be utilized carefully in a select group of microbiologically confirmed pulmonary tuberculosis patients only. The eligibility criteria for initiation of this regime, monitoring adherence and compliance of this regime, and early recognition and management of any ADRs to this regime are crucial factors that will be paramount to the success of this regime in the future.

"This treatment plan is not the national consensus of clinical treatment, so please refer to local laws and regulations when choosing this treatment plan".

Conflict of Interest

The authors declare no conflict of interest.

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