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# A Review On The Role Of Pharmacogenomics And Pharmacotherapy For The Treatment Of Tuberculosis To Optimize Patient Care Strategies

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## ABSTRACT:

One of the main public health issues in the world is tuberculosis. With typical short-course regimes of chemotherapy containing rifampicin, isoniazid, ethambutol, and pyrazinamide, the modern treatment for tuberculosis can cure up to 95% of the patients. Drugs used to treat tuberculosis have been the focus of pharmacogenomic research, which may help explain inter-subject variability in response. The factors influencing the therapeutic efficacy of pharmacogenomics, their side effects and its importance for treatment of tuberculosis are very well examined in the research. According to studies, pharmacogenomics greatly impacts how isoniazid is metabolized and how often adverse events occur during treatment. As far as medications like pyrazinamide and ethambutol are considered, there is no particular data available. Pharmacogenomics must be incorporated into clinical studies.

Although drug susceptible TB multidrug therapy lasts for about six months, it has never been perfected. The study exhibits potential for the current medications and some advanced substances in order to accelerate the treatment for tuberculosis. Treatment shortening is sterilizing activity or the medications' capacity to continue killing mycobacteria beyond the first few days of combination therapy. Rifamycin have the best chance of shortening a course of treatment while maintaining safety, as shown in animal, vitro, and human evidence of improved sterilizing activity (at high daily dosages). Additionally, the fluoroquinolones seem to have a large sterilizing effect. Other potential advancements could come from inhaled delivery, new categories of medications with new mechanisms of action, or drugs that can't be taken orally because of toxicity or poor absorption. The difficulty with TB pharmacotherapy is coming up with well-tolerated, effective, and short-term systems that can be utilized successfully against a drug resistant TB for a diverse patient group.

**Keywords:** tuberculosis, sterilizing activity, TB, antituberculosis treatment, pharmacogenomics, polymorphism, drug metabolism

## Tuberculosis treatment and pharmacotherapy

The tuberculosis-causing organism, Mycobacterium tuberculosis, is one-third of the world's population. Isoniazid, rifampin, and pyrazinamide make up a safe and efficient standard regimen for the treatment of tuberculosis (TB). Ethambutol, isoniazid, pyrazinamide, and rifampicin are often used for about two months, followed by rifampicin and isoniazid for the next four months, respectively, to treat both pulmonary and extrapulmonary tuberculosis. This regimen is quite effective, with cure rates of nearly 95% and relapse rates of only 5%. Combination

therapy is used to treat tuberculosis since single-agent treatment causes M. tuberculosis to develop resistance quickly. Therefore, multiple medication therapies are used to treat various populations of tubercle bacilli as well as to stop the establishment of drug resistance. [1]

## PHARMACOTHERAPY OF TUBERCULOSIS

Medications used in the TB treatment, which focuses on M.tuberculosis, include isoniazid, pyrazinamide, and ethambutol. Certain TB drugs, including different indications, are rifamycin, aminoglycosides, and fluoroquinolones. Beta lactams, clarithromycin, linezolid, dapsone, clofazimine, and metronidazole have rarely been utilized for multidrug-resistant TB. [1] Combination chemotherapy is necessary for the treatment of active TB illness in order to prevent the selection of naturally occurring drug-resistant mutations. Agents working on both sub-populations and solely provide sterilizing activity without recurrence are present in effective therapy regimens. The main focus of the current research is to find certain regimens or systems which are powerful enough to kill the persisting organisms and also to stop the formation of these organisms, thereby reducing the time taken for treatment due to organism resistance and in turn boosting its simplicity [1,2].

**Rifapentine** (RPNT): With its longer half-life and sterilizing potential, RPNT has shown activity in the mouse model. This therapy may make TB therapy more effective and efficient. Additionally, RPNT may delay the development of moxifloxacin resistance when used in intermittent regimens. Increasing the dose of rifamycin in combination with moxifloxacin has hastened sterilization in mouse models. [2]

**Rifabutin (RBN):** The main benefit of RBN is that it can be helpful for TB patients who are simultaneously taking antiretroviral therapy. The choice of the appropriate dose presents a dilemma for practitioners. Its main benefit is a decreased induction of hepatic metabolism. To avoid failure of the treatment, relapse, and also the formation of a rifamycin resistance, TDM is advised for the rifabutin to limit toxicity and maximize positive outcomes. [3]

**Fluoroquinolones (**FQ): FQ is the next most potent class of medications after rifampicins. FQs are active mostly against M. tuberculosis and are bactericidal. Most of the active FQ are LEVO, GATI, and MOXI, whereas CIP and OFL have an MBC/MIC ratio between 2 and 4. The activity of FQ is concentration-dependent. The side effects are the QT interval extension, dysglycemia, severe skin problems, and tendon rupture. The resistance of FQ is alarmingly prevalent among MDR-TB isolates; a comparable activity was seen across LEVOFLOXACIN 1000 mg, MOXIFLOXACIN 400 mg, and GATIFLOXACIN 400 mg and to shorten the standard treatment. It can be used to prevent contacts with a latent infection [4].

**Linezolid:** This oxazolidinone antibiotic is used to treat infections caused by Gram-positive bacteria. There is a significant in-vitro activity of linezolid against M. tuberculosis. Its side effects include myelosuppression, anemia, leucopenia, pancytopenia, and thrombocytopenia. A study of linezolid by Pfizer for Multi drug resistant TB treatment is at preclinical stage [2,4]

**Drug delivery:** Inhaled therapy for pulmonary TB may not only lessen toxicity from oral delivery but also cut down on dose intervals, reduce drug interactions, and optimize treatment using formulated drugs. An inhaled capreomycin will help with adherence, improve results, and perhaps even decrease the treatment time. [5]

### Pharmacogenomics and tuberculosis

Pharmacogenomics studies the molecular genetic underpinnings of efficacy and toxicity, the two main categories of medication treatment results. [6] Interindividual differences are greater when comparing people within the same group than when comparing the same person throughout time. The

existence of significant population variances with little within-subject variation can be used to explain inheritance in terms of the determinant of medication response. Sequence differences in the coding of genes for drug metabolizing enzymes, Transporters of a drug, or the drug targets may be the origin of variation in the drug pharmacokinetics and its effects, which account for 20–95% of variances. The effect of drugs can also be influenced by non-genetic factors such as organ function, age, concurrent therapy, drug interactions, nutritional state, and illness type. However, genetic factors are constant throughout a person's lifespan. [6,7,8]

The development of logical methods to optimize medication therapy, assuring maximal efficacy with minimal toxicity, is a key goal of pharmacogenomics. [9] The idea of "personalized medicine" has potential because medications and drug combinations are tailored to a person's genetic profile. Numerous disorders, including cancer, heart disease, depression, asthma, deficit disorder of attention, HIV, bipolar disorders, TB, and diabetes, are affected by pharmacogenomics. [10,11]

There are a few publications on rifampicin, that pharmacogenomics is playing a significant impact in the metabolism of first-line medication isoniazid for treating tuberculosis. This may have significant clinical ramifications for the Effectiveness of therapy and the occurrence of side events, but for second-line drugs, not much difference is observed. [12-15]

## Isoniazid

Isoniazid has been a key medication in the fight against tuberculosis. It has a low level of toxicity, is inexpensive, and works very specifically against tubercle bacilli. [13]

The acetylation of isoniazid in the liver and gut mucosa produces acetyl isoniazid, which can then create hydrazones and be hydrolyzed to produce monoacetyl hydrazine and isonicotinic acid. Isonicotinyl glycine and diacetyl hydrazine are possible products of these metabolites. None of these metabolites have any antituberculous properties. The acetylation rate for isoniazid differs from individual to individual since each person's acetylator status is genetically regulated and dependent on cytosolic NAT2 enzyme quantities. Isoniazid has been a key medication in the fight against tuberculosis. It has a low level of toxicity, is inexpensive, and works very specifically against tubercle bacilli. [13] The acetylation of isoniazid in the liver and gut mucosa produces acetyl isoniazid, which can then create hydrazones and be hydrolyzed to produce monoacetyl hydrazine and isonicotinic acid. Isonicotinyl glycine and diacetyl hydrazine are possible products of these metabolites. None of these metabolites have any antituberculous properties. The acetylation rate of isoniazid differs from one individual to another since each person's acetylator status is genetically regulated and dependent on cytosolic NAT2 enzyme quantities. Drugs, and substrates of the NAT2 enzyme can be given to the rapid acetylators in accordance with standard dosages. [13,14] Those with both an active and an inactive NAT2 allele are considered intermediate acetylators (heterozygous). For a positive therapeutic response, they might need lesser dosages of the drugs than the norm. The majority of genotypes of slow acetylator in the human population (NAT2*5A, NAT2*5B, and NAT2*6A) are caused due to different kinds of mutations in the NAT2 gene. [16] Due to decreased medication clearance, these people are more susceptible to drug-induced adverse effects.

NAT2 genotypes account for the variance in apparent isoniazid clearance in a ratio of 88 percent to that of isoniazid preparation and body weight, respectively. Isoniazid clearance with the number of high activity alleles of NAT2 is correlated linearly [16]. An individualized isoniazid dose schedule was recommended in light of this study. One potential reason for sporadic treatment failure or relapse in quick acetylators could be low plasma isoniazid levels. [17] On the other hand, increased concentrations in slow acetylators might make people more poisonous. As a result, NAT2 genotyping

before the administration of isoniazid might aid clinicians in predicting the variability of pharmacokinetics and alter the isoniazid dose. One reason why once-weekly isoniazid regimens failed was likely inadequate coverage and exposure among rapid acetylators, according to significant disparities in the exposure and coverage between the rapid and slow acetylators. For the patients receiving a once in week regimen, Weiner et al. (2010) demonstrate the poor results of the treatment that were related to isoniazid acetylator status. [17] Rapid acetylators are further hindered by the inadequate bioavailability of antituberculosis medications in HIV-infected tuberculosis patients, where it has been demonstrated. According to this study, reducing the isoniazid dose in the slow acetylators was necessary to lower the frequency of adverse effects [18,19,20]. The age, disease process and the acetylator status may all need to be considered when determining the appropriate isoniazid doses, according to pharmacokinetic research, Jeena et al. (2011) in children having tuberculosis. [21] Isoniazid is quite safe at standard doses; however, it can have two well-known side effects: hepatotoxicity (2% to 28%) and peripheral neuropathy (with high doses, usually among slow acetylators) [22]

## Rifampicin

A crucial first-line treatment for tuberculosis is rifampicin. Under both vitro and vivo circumstances, rifampicin exhibits concentration-dependent action against M. tuberculosis. [23,24] To investigate the causes of the significant interindividual variability in rifampicin levels and polymorphisms in the SLCO1B1 gene, Weiner et al. (2003) conducted a pharmacokinetic investigation. This study showed the impact of SLCO1B1 463 CA genotype on the rifampicin exposure, which was lower than CC genotype by 36 percent. According to a study, high dose of rifampicin are a huge benefit to the carriers of SLCOB1B1 polymorphism but still more research is needed in this field [17,20].

## Aminoglycosides

In the treatment of tuberculosis, aminoglycosides like kanamycin, streptomycin and amikacin are utilized. To comprehend the relationship between the mitochondrial mutations and aminoglycoside induced ototoxicity, Zhao et al. (2004) performed a molecular characterization investigation for a Chinese family. It was found that aminoglycosides could either cause or exacerbate the phenotype of deafness associated with C. T. 1494 12S rRNA gene polymorphism [25].

## Conclusion

Genetic variables influence the metabolism and disposition of the antituberculosis medication isoniazid. It is observed that there is no association of the isoniazid driven substantial gene variant with hepatoxicity. Therefore, the combination, including the polymorphisms may affect the pharmacokinetics of isoniazid. Large clinical trials will be required to evaluate the benefits of geno typing and to adjust the dosage of drugs for treatment of tuberculosis. Studies are also necessary to comprehend how first- and second-line anti-tuberculous medications' pharmacokinetics are affected by gene polymorphism.

Improved TB treatment options include incorporating novel agents with novel mechanisms and a narrow spectrum of activity, confirming antimicrobial's clinical efficacy created for further indications but have been used to treat TB, changing drug dosages, or developing new formulations for drugs already used in therapy. Designing an effective, well-tolerated and short-time course regimens that may be utilized in a varied TB patient population, including diabetics, children, substance abusers and pregnant women, and those receiving antiretroviral therapy for the HIV illness, is a problem in pharmacotherapy. Creating treatment regimens that are successful against strains of M. tuberculosis that are resistant to fluoroquinolones, isoniazid, aminoglycosides and rifampin is also crucial for the future of TB control.

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