

Tuberculosis: Treatment-related Problems and Future Facets

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Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* and is the primary cause of mortality in the world. *M. tuberculosis* strains are important intracellular pathogens causing infection in oxygen-rich macrophages in the lungs. The emergence of AIDS, declined socioeconomic standards and a lessened emphasis on TB control programs have contributed to the disease resurgence. Resistance of *M. tuberculosis* strains to anti-TB agents is an increasing problem worldwide. However, powerful new anti-TB drugs with new mechanisms of action have not been developed in the last 40 years, in spite of acute toxicity of repeated dosing of the available anti-TB drugs.

Keywords: Tuberculosis; Drug Resistance; Toxicity

1. Context

Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), is the major cause of mortalities caused by infection worldwide and roughly two million people die annually because of infection with Mtb (one person dies every 10 seconds). The world health organization (WHO) has estimated that one-third of the world's population is infected with Mtb. TB is the leading cause of death amongst people who are infected with human immunodeficiency virus known as HIV-positive (13% of AIDS deaths worldwide). According to WHO, TB is among the most important chronic communicable disease which takes people's lives worldwide each year (1). The emergence of AIDS, declined socioeconomic standards and lessened emphasis on TB control programs have contributed to the disease resurgence. The synergy between TB and the AIDS epidemic as well as the surge of multidrug-resistant (MDR-TB) isolates of Mtb have reaffirmed TB as a primary public health threat, while TB in humans is primarily caused by infection with Mtb, several other Mb species including *Mycobacterium bovis*, *Mycobacterium africanum*, *Mycobacterium microti* and *Mycobacterium canettii* may also cause this disease. Two additional species have been suggested as members of the Mtb complex including *Mycobacterium caprae* and *Mycobacterium pinnipedii*. The Mtb, like most other mycobacteria, is a gram-positive, non-motile rod-shaped bacterium (1 - 4 µm in length and 0.3 - 0.6 µm in diameter). The Mtb is a slow growing microorganism with a generation time of 12 - 20 hours and possess a unique cell wall of high lipid content, which includes mycolic acids and other glycolipids. Mycolic acids

in the Mtb cell wall are the specific features of bacteria of this genus. However, these fatty acids can also be found in the cell walls of certain bacteria. It is the low permeability of the Mtb cell wall, which is believed to play a significant role in the antibiotic resistance of Mtb. TB usually affects the lungs or pulmonary organs of patients, but can also affect other parts of the body like kidneys, bones, joints and lymph nodes (extra pulmonary-TB). TB is an airborne disease and spreads like the common cold, by the circulation of aerosols containing Mb in the air from coughing, sneezing, talking or spitting of TB patients. Inhalation of only a small number of Mtb bacilli by a person will result TB infection. A person infected with latent TB will not develop the obvious symptoms of TB, including fever, fatigue, weight loss, persistent cough and sputum production which will contain blood at the advanced stages of the disease. While a person with latent TB is not infectious, they may develop the active form of the disease if their immune system is compromised. It is estimated that one person in every 10 of the two billion infected people worldwide will develop infectious TB, which shows that the current treatments have not been successful. These include a lengthy (6 - 9 months) multi-drug treatment (MDT) program, the misuse or mismanagement of which can lead to the development of multiple drug resistance-tuberculosis (MDR-TB) or extensive drug resistant TB (XDR-TB) and co-infection of TB with the human immunodeficiency virus (HIV) (2-6).

2. Evidence Acquisition

Unique problems Associated with Mycobacteria are as follows:

Implication for health policy/practice/research/medical education:

The study is conducted for the purpose of medical education.

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- Complex outer membrane of mycobacteria,
- Extremely slow-growth
- Ability to remain quiescent for decades
- Toxicity of effective drugs
- Poor patient compliance
- Wide spread resistance
- Mycobacterium is an intracellular bacterium
- Its ability to colonize in macrophages in the lung; the Mtb cell (the tubercle bacilli) is engulfed by a macrophage and encloses the bacteria into the phagosome compartment. Typically, the phagosome fuses with the lysosome which contains digestive enzymes, low pH and reactive oxygen to destroy the foreign particles. As the bacterium proliferates, it kills the macrophage, releasing more bacteria, which are taken up by more macrophages.

3. Results

3.1. Tuberculosis-HIV Coinfection

The current estimations reveal that one-third of the 42 million people living with HIV/AIDS worldwide are coinfecting with TB. As per World Health Organization's reports, approximately 90% of the patients with both TB and HIV died within a few months after clinical symptoms. Therefore, World Health Organization (WHO) warned the world about the "greater TB-HIV crisis" and called for wide availability of free anti-TB drugs for those with HIV. According to WHO and some other studies, HIV is spreading rapidly in India with the largest number of TB cases in the World (2-6).

3.2. Chemotherapy and Associated Problems

In most parts of the world, we are limited to combine five drugs to treat TB effectively, namely rifampicin (RIF), isoniazid (INH), ethambutol (ETH), streptomycin (STR) and pyrazinamide (PZA). Antituberculosis chemotherapy problems arise when patients develop bacterial resistance to any of these first-line drugs and since the second-line drugs, such as ethionamide, aminosalicylic acid (PASA), cycloserine (CYC), amikacin, kanamycin and capreomycin, are very toxic they cannot be employed simultaneously. TB chemotherapy was first introduced in 1946, when STR was used to treat the disease. By 1955, a regimen had been developed for the treatment of TB involving the combination of STR, PASA and INH. The current chemotherapy of infectious TB involves an initial two month treatment regimen with either: STR, INH, RIF and PZA or INH, RIF, PZA and ETH (first-line drugs). This is followed by treatment with INH and RIF over a four to seven month period. Current chemotherapy of latent TB involves treatment with INH for 6 - 9 months in order to prevent the development of the active form of the disease (7).

The difficulty of managing TB includes the prolonged treatment, the emergence of drug resistance and coinfection with HIV/AIDS. Resistance of Mtb strains to anti-TB

agents is a globally increasing problem. The key features of an anti-TB regimen are: (a) development of long-acting drugs with extended-interval dosing in order to facilitate directly observed treatment, short course (DOTS) and enhance patient compliance, (b) prevention of MDR-TB strains by using drugs, which exhibit potent early microbicidal activity and (c) eradication of slowly metabolizing and, if possible, dormant Mtb population that cause relapse, using new classes of anti-TB drugs. Despite the current use of RIF and PZA, the 6-month TB therapy is the shortest time for TB treatment. To decrease the risk of reactivation TB bacteriological, long-term therapies for more than 6 months are generally needed. This frequently leads to patient non-adherence, thereby causing the emergence/increase of MDR-TB strains. Notably, the cost of treating MDR-TB patients is much higher than patients carrying drug susceptible Mtb strains. In addition, it is estimated that two billion people are latently infected with TB. Since dormant types of Mtb may survive *in vivo* for several decades, new drugs effective against dormant Mtb would be highly useful in preventing bacteriological reactivation of Mtb in such populations. Thus, the development of new anti-TB drugs that are effective against a persistent Mtb infection is urgently required. Among the standard anti-TB agents, in spite of toxicity of repeated dosing, INH is still considered as the first-line drug for TB chemotherapy. At this stage, no remarkable breakthrough has been achieved in the discovery of an efficient drug to treat TB; the quest for development of better, cheaper and faster drugs continues. In the present context new drugs to treat TB are urgently required, specifically for short treatment regimen and to treat MDR, XDR and latent diseases. Development of chemotherapeutics that specifically target dormant bacilli, provide more effective treatment of MDR-TB, XDR-TB and latent TB infections are also in great need (8-11).

The currently available key medications (first line) used in the regimen have serious side effects such as severe damage to the eighth cranial nerve, induce irreversible impairment of auditory function, hypersensitivity reactions (STR), are potentially hepatotoxic and may lead to drug associated hepatitis (INH, PZA and RIF (RIF, rifabutin, rifapentine) and thrombocytopenic purpura (RIF). Second line anti-TB drugs are more toxic than first line drugs, amikacin and kanamycin cause kidney damage as well as hearing loss, viomycin and capreomycin cause nephrotoxicity and eighth cranial nerve toxicity, fluoroquinolones (ciprofloxacin, moxifloxacin, ofloxacin (levofloxacin, the chiral form of ofloxacin is more effective) and gatifloxacin, trovafloxacin, enoxacin and sparfloxacin, etc.). Fluoroquinolones are increasingly contraindicated for patients due to the growing prevalence of antibiotic resistance. Ethionamid and prothionamide (structural analogues of INH) cause adverse effects such as gastrointestinal disorders (such as anorexia, salivation, nausea, abdominal pain and diarrhea), diverse mental

disturbances (such as depression, anxiety psychosis, dizziness, drowsiness and headache) and hypersensitivity. The CYC side effects are mainly CNS manifestations such as headache, irritability, depression, convulsions. PASA causes gastro intestinal tract problems including anorexia, nausea, epigastric pain, abdominal distress, and diarrhea, peptic ulcers and hypersensitivity reactions (12, 13).

3.3. Drug-Resistant Tuberculosis

Mtb drug resistance is an important obstacle for the treatment and control of TB. This resistance is traditionally the result of unusual multi-layer cell envelope and active multidrug efflux pumps. Recent insights into the mechanisms that neutralize the toxicity of antibiotics in the cytoplasm have revealed other systems that function in synergy with the permeability barrier and efflux systems to provide natural resistance. Drugs that inhibit these intrinsic systems would enable many antibiotics, which are already available but have not been used for TB, to gain new activities against Mtb (11-14).

3.4. Multi Drugs Resistant Tuberculosis

Multi-drug-resistant (MDR) TB refers to simultaneous resistance to at least two or more of the five first-line anti-TB drugs (INH, RIF, PZA, ETH and STR. MDR-TB), caused by sharing of genes between different species or genera, generally mediated by small pieces of extra-chromosomal DNA, known as transposons or plasmids. Treatment for multi-drug-resistance tuberculosis is a prolonged, less effective, costly, and poorly tolerated therapy (13-16).

3.5. Extensively-Drug-Resistant Tuberculosis

Extensively-drug-resistant (XDR) TB, is defined as resistance to at least INH and RIF, in addition to any quinolone and at least one injectable second-line agent (any fluoroquinolone, capreomycin, amikacin and kanamycin). The principles used for MDR-TB and XDR-TB treatment are the same. The main difference is that XDR-TB is associated with a much higher mortality rate than MDR-TB, because of the reduced number of effective treatment options. Hence, there is an urgent need for novel drugs that are active against Mtb in order to shorten the duration of treatment (13-16).

3.6. Future Prospects

TB control programs require new drugs that act on novel targets to help combat resistant Mtb and reduce the treatment duration. In spite of the availability of various chemotherapeutic agents, TB remains as a leading cause of mortality worldwide. This is mainly due to the lack of new drugs, particularly for effective treatment against MDR-TB, XDR-TB, and patients co-infected with HIV/AIDS. Therefore, there is an urgent need for the development of new and effective anti-TB drugs particularly against resistant

strains with fewer side-effects. More importantly, newly developed drugs are required to reduce the duration of treatment. New anti-TB compounds need to be developed, thus further understanding of the molecular mechanisms of drug action and drug resistance are required. Focusing on the anti-TB targets for drug development may be of limited value because chances of resistance by mutation in the protein target may reduce the drugs ineffectiveness. Precisely, because of this drug-resistance, it is essential to develop smart new drugs that inhibit novel targets, which are structurally and functionally different from those currently available. Medicinal chemists will be interested to work on new molecules against Mtb. Overall; the above-mentioned facts inspire research on new derivatives, particularly those against Mtb. Different new molecules will be synthesized in the future to develop new anti-TB molecules. Currently, a few novel promising drugs are in their clinical phase of development. These drugs have been shown to be active against MDR-TB strains *in vitro* therefore are potentially effective against MDR-TB. There is an urgent need for innovative thinking in the field of clinical trials for new TB drugs. The current major limitation is the difficulty in diagnosis of patients with TB. This problem is even more acute in cases with XDR-TB. The combination of XDR-TB and HIV infection leads to develop a highly aggressive form of TB that causes death in a very short amount of time. The emergence and rapid spread of XDR-TB in high HIV prevalence settings represent a major threat to the global health (14-16). The main objective is to synthetically design pharmacologically active compounds by modifying the existing structure or pharmacophore of available compounds to produce novel drugs. The structural modifications provide an advanced structure with some useful biological characteristics which can be exploited for solving the existing problems, such as resistance. These adverse effects lead to a requirement for the synthesis of new compounds with a potent therapeutic value and eliminated side effects. Thus, the most essential objective is to minimize the costs for the development and biological testing of drugs, to provide cheaper, safer and easily available drugs. Now, it has been established that drug actions depend not on cellular but also on molecular structure of the particular drug. The basic requirement is not only the design and preparation of the drug but also the development of testing methods which are essential for establishing drug action and its utility. Various nucleuses can be used for the development of various synthetic products and their new compounds improved pharmacological activity. New compounds are designed to prepare potent compounds with minimum side effects (17, 18).

4. Conclusions

Molecular structure variation of compounds often causes a marked difference in their biological activities due to the different characteristics of substituents that

are being synthesized and tested for diverse biological activities, to form better therapeutic molecules. There has been considerable interest for the development of new compounds with anti-TB activities against various pathogenic microorganisms. These different parts constitute an important class of drug. Therefore, many researchers have synthesized compounds and evaluated their anti-TB activities. These observations have been guided for the development of new compounds that possess potent anti-TB activity with minimum or without side effects and resistance. Currently, much attention has been paid to new compounds, which have an advantageous structure for molecular exploration and development of bioactive molecules with different biological actions. Based on the observation, we hope to obtain more potent drugs as to various functionalized and structural modifications were made. These structural changes resulted in some fruitful biological activities. Many synthetic heterocyclic compounds are known to have different biological activities and the development of new derivatives will show promising anti-TB activity in the future. This is a good starting point for the development of new anti-TB drugs with the least or no side effects and resistance. Recently, several synthetic strategies have been reported for the preparation of new derivatives.

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