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Current Alarming Status, Strategies and Drug Development Pipeline for Tuberculosis

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ABSTRACT

From the past few decades and today tuberculosis ranks at the top amongst the world's deadliest disease's causing morbidity. Due to lack of mandatory primary health care and cost effective treatment, slow emergence of resistant strains of *mycobacterium tuberculosis* combat against the disease is still a matter of fact globally.Latent infection TB patients are at a risk of reactivation and this is one of the major barriers in controlling tuberculosis. Except pyrazinamide and to some extent INH none of the drugs currently available act on latent M. tuberculosis. Therefore, there is an urgent need to develop novel drugs that can act against both actively growing and dormant bacteria.The ameliorations in the strategies that paved the way in the search of new drugs involves improvement in the existing drugs, systematic screening, exploitation of the biological information and planned research and rational approaches. New promising drug candidates involve the recent discovery of diarylquinoline, new fluoroquinolones, rifamycin, oxazolidinones and nitroimidazopyran. Desirable targets should be involved in vital aspects of bacterial growth, metabolism and viability, whose inactivation will lead to bacterial death. India accounts for nearly one third of global TB problem. Tuberculosis Kills 14 times more people than all tropical diseases and 4.5 million TB cases with 1.8 million new cases being reported each year. Approximately 50 % of the India's population is reported to be tuberculin test positive. Annually about 0.4 million death and one million new cases of TB are reported and one person dies every minute by TB. This article intends to focus the current trends and new pipeline drug development including the new drug targets and the novel promising compounds under clinical trials.

Keywords: Mycobacterium tuberculosis, chemotherapy, anti-tuberculosis, drug candidates, tuberculin test

INTRODUCTION

Tuberculosis, the preeminent health concern of this century, effectuated by Mycobacterium Tuberculosis the etiological agent of TB, has currently affected two billion people with more than 1.6 million deaths and 9.2 million new cases being reported each year 1. With one-third of the world's population harbouring the tuberculosis bacillus, 2 million deaths due to TB occurring each year, 3 million people becoming infected with both HIV and Mycobacterium tuberculosis, and the augmenting incidence of both multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB), the need for more effective chemotherapy for the treatment of TB has never been greater 2,3 ,4 .The biggest conundrum of intensive sprawl of HIV infection and the ascendant problem of multi-drug resistant TB (MDR-TB) plays a consequential role for the need of new drugs to more effectively treat the disease in all patients 5,6,7. Current survey demonstrates that in 2008, there were estimated to be 9.4 million new M. tuberculosis infections and 1.8 million deaths as a result of TB, the most by any single infectious agent [8, 9].

PATHOGENESIS

Mycobacterium tuberculosis is a large ,complex, slow growing, gram-positive, rod-shaped, obligate ,aerobic bacteria belonging to the order actinomycitales family mycobactericae whose cell is highly rich in lipids, evolved from soil bacterium more than 10,000 years ago is an enormous contagious and respiratory transmitted disease that sprawls from person to person when a contagious person oozes TB bacilli into the air by coughing or sneezing which are then inhaled into the lungs by another individual, mainly 1–2 mm in size. [10, 11].

Once inside the lungs, the dynamic interplay between the host and pathogen can have any of the four outcomes:

(a) The initial host response may be completely effective and kill the bacilli [11];

(b) The organisms can grow and multiply immediately after infection, resulting in primary TB,

(c) The bacilli may become dormant and never cause disease at all.

(d) The latent bacilli can eventually become active and progress to disease condition. The bacilli do not remain in the airways in the lung; they enter the lung parenchyma and replicate in the tissue macrophages and monocyte-derived macrophages.

MYCOBACTERIUM TUBERCULOSIS (MTB) BACETERIUM

It is a small aerobic non-motile bacillus with high lipid content and a thick cell wall. It has a very slow generation time as compared to other bacteria like Escherichia coli and Plasmodium falciparum. As a result of the fact that MTB has a cell wall but lacks a phospholipids 'outer, it is classified as a Gram-positive bacterium [13]. However, accomplishment of Gram stain, MTB either stains very weakly Gram-positive, cell clump together due to hydrophobicity or becomes impermeable to stain. They give acid fast stain hence called as acid fast bacilli.

SYMPTOMS ASSOCIATED WITH TUBERCULOSIS INFECTION[14, 15]

- Fever
- Night-time sweating
- Unintentional loss of weight
- Persistent cough
- Constant tiredness
- Loss of appetite

DIAGNOSIS

Diagnosis of active TB disease remains difficult as clinical symptoms of tuberculosis are common to other diseases. Tests that are used for diagnosis are:

- Tuberculin Skin Test (TST) or Monteux test
- Chest Radiograph (X-ray)
- Sputum Smear Microscopy (SSM) culture
- Polymerase Chain Reaction (PCR)
- Blood Test (e.g. T-SPOT.TB)
- Expert MTB/RIF Test

MANAGEMENT OF TUBERCULOSIS[16]

Vaccination

Active immunization is one of the essential components to control tuberculosis, although the vaccination is ineffective nowadays. Until now one billion people have been vaccinated with BCG. In general, four classes of vaccine candidates are being focused and these are; rationally attenuated strains of *Mycobacterium tuberculosis,* Bacilli Calmette Guerin (BCG) vaccine, protein subunit vaccines and nucleic acid vaccines.

Chemotherapy

Chemotherapy of TB started in the 1940s. In 1943, anti-TB research resulted in discovery of the active anti-TB agent Streptomycin.17 Since then, a number of agents have been discovered, like para-aminosalicylic acid (PAS), isoniazid

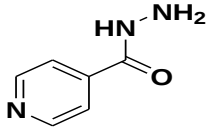
(INH), pyrazinamide (PZA), cycloserine, ethionamide (ETA), rifampicin (RMP), and ethambutol (EMB). Drugs used for treatment of tuberculosis can be divided into 3 classes:

1) First line anti-tubercular agents
2) Second line anti-tubercular agents
3) Third line anti-tubercular agents

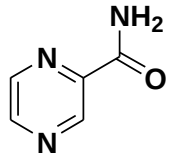
FIRST LINE ANTI-TB AGENTS[10]

Important first-line antitubercular drugs are:

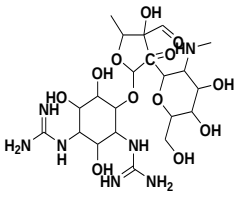
- Streptomycin,
- Isoniazid,
- Rifampicin,
- Ethambutol,
- Pyrazinamide,



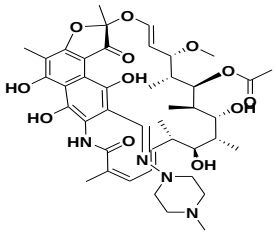
Isoniazid



Pyrazinamide



Streptomycin



Rifampicin

Fig 1: First line antitubercular drugs

SECOND LINE ANTI-TB AGENTS[10]

As per WHO second line anti-tb agents fall into six classes of second line drugs that are used in the treatment of tuberculosis.

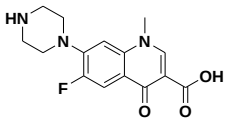
A drug may be classified as a second-line because of either of two possible reasons:

- it may have lower efficacy compared to the first-line drugs or it may have toxic side-effects
- It may be inaccessible in most developing countries.

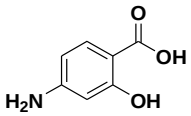
These comprise of different classes namely

- Amino Glycosides: (Amikacin, Kanamycin),

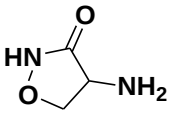
- Polypeptides: (Capreomycin, Viomycin),
- Fluoroquinolones (Fqs): (Ciprofloxacin, Moxifloxacin),
- Thioamides: (Ethionamides, Prothioamide),
- Cycloserine And *P*-Amino Salicylic Acid



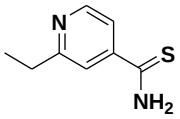
Ciprofloxacin



Para amino salicylic acid



Cyclosrine



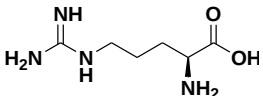
Ethionamide

Fig 2: Second line antitubercular drugs

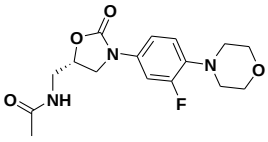
THIRD LINE ANTI-TB DRUGS[10]

These are not in WHO list:

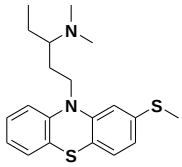
- Rifabutin
- Macrolides: e.g., clarithromycin (CLR)
- Linezolid (LZD)
- Thioacetazone (T)
- Thioridazine
- Arginine
- Vitamin D
- R207910



Arginine



Linezolid



Thioridazine

Fig 3: Third line antitubercular drugs

VEXATION IN THE WAY OF DEVELOPMENT OF NEW TREATMENT

The biggest conundrums in the advancement of new treatments are:

a. The crave for novel and ingenious drug regimens,
b. Novel trial designs,
c. Studies in paediatric populations,
d. Amplify clinical trial capacity,
e. Clear regulatory guidelines,
f. Biomarkers for prediction of the long-term outcome[18].

CHEMOTHERAPY PROBLEMS AND REQUIREMENTS [19]

Current requirements

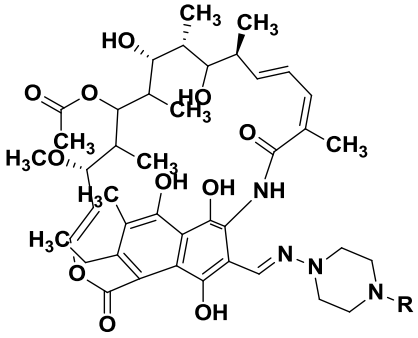
a) Shortening the duration of treatment
b) New quality drugs or its combination with new agents
c) Find out new drugs for persistent infection
d) Economical methods of production of quality drugs
e) Public private partnership programme.

Limitations of old drugs

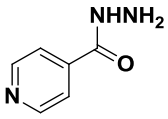
a) Drug resistance (MDR & XDR TB)
b) TB & HIV synergy
c) Latent tuberculosis and persistent infection
d) Problems with DOTS
e) Long treatment schedule
f) Paediatric tuberculosis
g) Tuberculosis in diabetic cases

TREATMENT REGIMENS

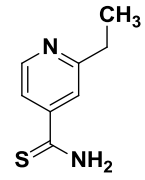
Current short-course TB therapy used to treat drug-susceptible *Mycobacterium tuberculosis* consists of 2 months treatment with four drugs so-called first-line drugs including rifampin (RIF), isoniazid (INH), pyrazinamide (PZA), and ethambutol (EMB), followed by 4 months treatment with RIF and INH. Infection by MDR-TB strains requires treatment with second-line drugs such as kanamycin, amikacin, capreomycin, *p*-aminosalicylic acid (PAS), fluoroquinolones (e.g., levofloxacin), ethionamide and cycloserine where treatments often extend for as long as 2 years. All of these drugs are aged and unappealing by today's standards. Many patients fail to complete therapy because of the complicated drug regimen.



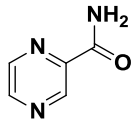
R = CH3, Rifampicin



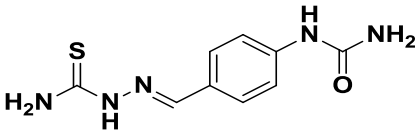
Isoniazid



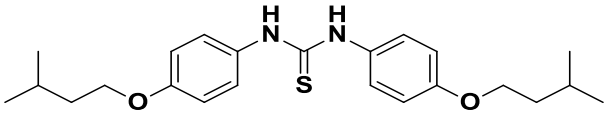
Ethionamide



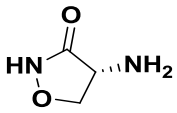
Pyrazinamide



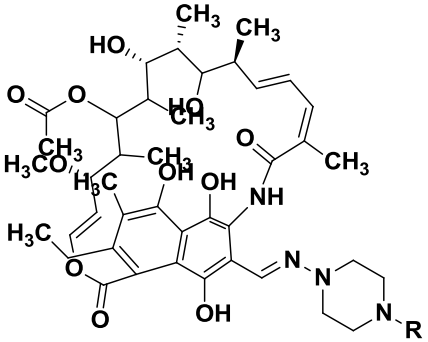
Thioacetazone



Isoxyl

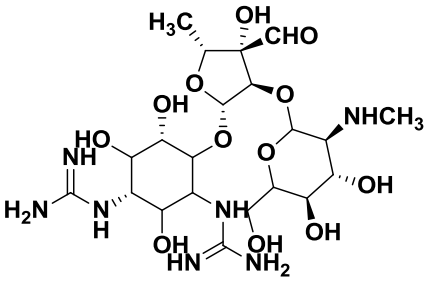


Cycloserine



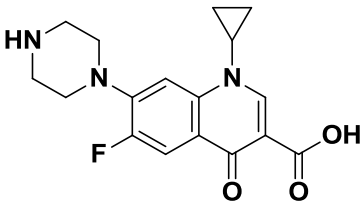
R = CH3, Rifabutin

R =  : Rifapentine

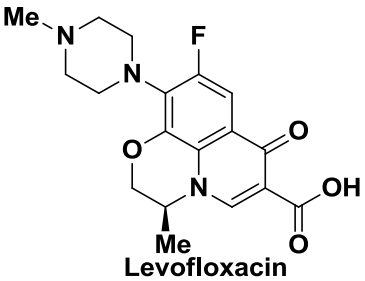


Streptomycin

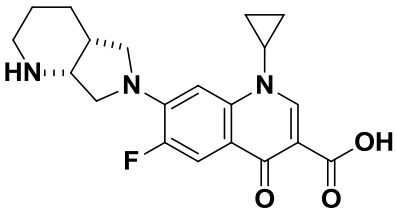
Fig 4: Currently used first line antitubercular and second line antitubercular drugs



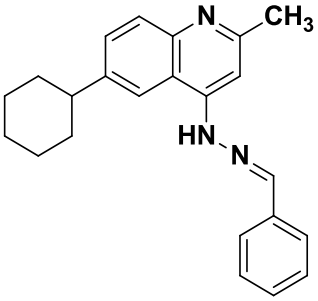
Ciprafloxacin



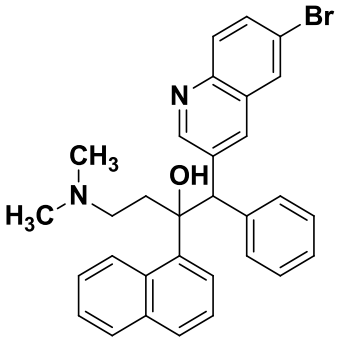
Levofloxacin



Moxifloxacin



4-Quiolyhydrazones



Diaryl Quinoline

Fig 5: Molecules under preclinical and clinical trials

TARGETS UNDER STUDY[24]

Cell wall biosynthesis
a) Peptidoglycan biosynthesis
b) Arabinogalactan biosynthesis
c) Mycolic acid biosynthesis
Amino acid biosynthesis
a) Shikimic acid pathway
b) Arginine biosynthesis
c) Branched amino acid biosynthesis
Cofactor biosynthesis
a) Folic acid biosynthesis
b) Pantothenic acid biosynthesis
c) Riboflavin biosynthesis
d) Reductive sulphur assimilation
Mycothiol biosynthesis
Terpenoid biosynthesis
DNA synthesis
ATP biosynthesis
Menaquinoneoxidoreductase (Type II NADH) inhibition
Tubulin polymerase inhibition

EXTENSIVELY DRUG RESISTANT TUBERCULOSIS (XDR-TB): A GLOBAL THREAT

The term XDR Tuberculosis, firstly coined by the US Centre for Disease Control and Prevention. It is defined as infection caused by Mycobacterium tuberculosis that is resistant to isoniazid, rifampin any fluoroquinoline and any injectable drug (amino glycosides or polypeptides) [20, 21, 22.] At the outset XDR-TB was defined as malady caused by *M. tuberculosis* not alone resistant to isoniazid and rifampin but rather to at least 3 of the 6 classes of second-line agents approved for the treatment of TB (amino glycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicyclic acid). The World Health Organization Global Task Force on XDR-TB modified the definition in October 2006 following the report of the outbreak in Kwazulu Natal. Since drug susceptibility testing is reliable only for amikacin, kanamycin, capreomycin, and fluoroquinolones among the second-line agents, the definition of extensively drug-resistant TB is now resistance to isoniazid and rifampin in addition to resistance to any fluoroquinolone and any of the second-line injectable drugs: amikacin, kanamycin, and capreomycin[22].

Medications Currently Available for the Treatment of Extensively Drug-resistant TB [23]

CATEGORY	AGENT	MECHANISM OF ACTION	TOXICITY AND COMMENTS
Ethambutol		Inhibits arabinosyl transferase,an important enzyme in the synthesis of Arabinogalactan, a mycobacterium cell wall constituent.	Optic neuritis
Pyrazinamide		Inhibits fatty acid synthetase I	Hyperuricemia, arthralgia, hepatitis
Amino glycosides	Streptomycin Kanamycin Amikacin	Misreading of the genetic code and Inhibition of translocation by binding to the 30S ribosomal bacterial subunit.	Commonest toxicities: nephrotoxicity, ototoxicity Amikacin is the preferred drug.Cross-resistance is common.
Polypeptides	Capreomycin	Unknown	Nephrotoxicity, ototoxicity Cross-resistance with amino glycosides is common.
Quinolones	Ofloxacin Moxifloxacin Gatifloxacin	Inhibits DNA gyrase	Confusion, seizures, tendinopathy, QT prolongation. Level of cross resistance with other quinolones is uncertain.
Thioamides	Ethionamide Prothionamide	Inhibits synthesis of mycolic acid	Gastrointestinal toxicity, peripheral neuropathy. Requires use of concomitant vitamin B6.
	Para-amino salicylic Acid	Competitive antagonism with Para amino benzoic Acid	Gastrointestinal toxicity, haemolytic anaemia, especially with G6PD deficiency.
	Cycloserine	For incorporation into the bacterial cell wall competes with D-alanine	Peripheral neuropathy, psychosis, seizures. Use of concomitant vitamin B6 is required.

(***Abbreviation***: ***G6PD_glucose-6-phosphate dehydrogenase)***

Agents in Clinical Evaluation [24]

DRUG	CHEMICAL CLASS	CELLULAR TARGET
Gatifloxacin	Fluoroquinolone	DNA gyrase, DNA replication and transcription
Moxifloxacin	Fluoroquinolone	DNA gyrase, DNA replication and transcription
Levofloxacin	Fluoroquinoline	DNA gyrase, DNA replication and transcription
Linezolid	Oxazolidinones	protein synthesis
Metronidazole	Nitroimidazole	cytochrome P450a
TMC207	Diarylquinoline	ATP synthesis
PA-824	Nitroimadazooxazine	mycolic acid biosynthesis and protein synthesis
OPC-67683	Nitroimidazo-Oxazole	cell wall biosynthesis
LL-3858	Pyrrole	Unknown
SQ109	Ethylenediamine	fatty acid biosynthesis
SCV-07	Dipeptide	none, immunomodulator

Tuberculosis drug candidates in development [25]

POTENTIAL DRUG	ACTIVE OR PRO-DRUG	DESCRIPTION	CELLULAR PROCESS INHIBITED	STAGE OF DEVELOPMENT
PA-824	Pro-drug	Nitroimidazo-oxazine	Mycolic acid synthesis	Phase II
OPC-67683	Pro-drug	Nitroimidazo-oxazole	Mycolic acid synthesis	Phase II
R207910	Active	Diarylquinoline	ATP synthesis	Phase II
SQ109	Active	Ethylenediamine derivative	Lipid/cell wall synthesis	Phase I
Compound 5	Pro-drug	Quinoxaline-oxide derivative	Unidentified	Preclinical
Compound 7	Unknown	Quinoline-isoxazole derivative	Unidentified	Preclinical

CONCLUSION

Many M. tuberculosis biochemical transformations have been identified as potential targets at the bench level for anti-tuberculosis treatment today. The key issue is to control both drug-susceptible and drug-resistant tuberculosis, which could be successfully achieved through the sound implementation of the *DOTS* strategy and the careful introduction of second-line drugs. To come to grips with TB and with resurgent infectious diseases as a whole, more effective policies are urgently needed. In particular, it is essential to develop active agents that are potentially bactericidal against persistent and dormant organism of *MTB*, in order to shorten the duration of directly observed, short-course of TB patients and to eliminate the reservoir of *MTB*, especially in developing countries. The most urgent goal of chemotherapy for TB is to develop highly active but low-cost drugs that can be used not only in industrialized but also developing countries.

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