TUBERCULOSIS AND NEW ANTI-TUBERCULOSIS DRUGS IN PIPELINE

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Abstract- Tuberculosis (TB) is a serious infectious disease caused by Mycobacterium tuberculosis. One thirds of the world's population is infected with this disease and hence the world is at the risk of developing active tuberculosis. The emergence of more and more drug resistant cases threatens the control of the disease. Additionally, the lengthy and complex process of diagnosis and treatment is connected with several harmful side effects and poor outcomes which highlight the need to urgently develop new and effective drugs for the treatment of tuberculosis. New drugs should target persistent, active and resistant bacteria. Recent research in this area generated various potential compounds which can act as a 'lead' and then can progress to 'hit'. Present paper discusses tuberculosis in detail, its worldwide burden, transmission, diagnosis, traditional treatment, new anti-tubercular drugs approved recently and other classes like benzothiazinone and benzothiazole which are in the pipeline to enter pre- clinical stage.

Index Terms- Anti-tubercular drugs, Benzothiazoles, Extensive drug resistant TB, Multi drug resistant TB, Tuberculosis

I. INTRODUCTION

Tuberculosis remains one of the deadliest diseases responsible for millions of deaths all over the world. It is a serious infectious disease which mainly targets the lungs but can also affect other parts of the body. The symptoms include weight loss and chest pain. Globally it was estimated that 10 million people had active Tuberculosis, of which, 6.3 million cases were new. India has the highest burden of Tuberculosis. The World Health Organization (WHO) 2018 reportestimated 2.79 million incidence cases in India(WHO, 2018). Being an air borne disease, the world is at the risk of developing active disease. The emergence of drug resistant tuberculosis further threatens disease control and continues to be a public health crisis. In 2017, the estimated number of incidence cases ofMulti Drug Resistant (MDR) Tuberculosis was 558,000. Three countries which encountered for almost half of the world's cases are India (24%), China (13%) and Russian Federation (10%). In 2017, with concerted global tuberculosis countries efforts, the mortality rate dropped down to 16% as compared to 23% in 2000.Global burden of tuberculosis for the year 2017 is shown in Figure 1. Urgent actions are required to eradicate this disease by improving the quality of diagnosis, drugs, treatment and care for people.

II. CAUSE OF TB AND ITS TRANSMISSION

Mycobacterium tuberculosis (MTB), as shown in Figure 2, is the causative agent of tuberculosis in humans which is an obligate aerobe an organism which needs oxygen to survive.

The unique characteristics of these bacteria include the resistance to various weak disinfectants, slow growth rate, survival in dry state from weeks to years. The peculiar composition of the cell wall of these bacteria is responsible for these characteristics. Sixty percent of cell wall of MTB is lipids and the presence of high molecular weight lipids provides complexity and impermeability to the cell wall. The thick cell wall constituted of lipids and other polymers poses resistance to antibiotics and host defense mechanisms(Crick D C,2001).

Being an air borne disease, these bacteria are transmitted through coughing, sneezing, singing or talking. These bacteria, when enter the healthy person with a strong immune system, lose activity and enter the state of dormancy. At this stage, the bacteria stay inside the human body but don't show any symptoms of the disease (*Latent tuberculosis*). Later on, at some stage of life when immunity is compromised, the bacteria become active and show symptoms of the disease (*Active tuberculosis*). An unhealthy person can also get active tuberculosis disease directly by inhaling these infectious agents (Flynn J L, 2001).

III. TREATMENT OF TB:

The disease can be controlled only if fast and accurate method of diagnosis is available. Sputum smear microscopy and culturing techniques are the standard techniques for the diagnosis of active Tuberculosis (Lawn S D,2011). These techniques have some limitations, therefore, new advance techniques like Fluorescence microscopy, Rapid culture and nucleic amplification tests are used in combination with standard methods. These new techniques are quite sensitive and accurate. For latent TB infections, the standard test like Tubercular skin test or Mantaux Test is very subjective and can give false positive results, is being replaced by Interferon Gamma Release Assay. This test is quite objective and helpful in the diagnosis of latent TB (Hauck F R, 2009).

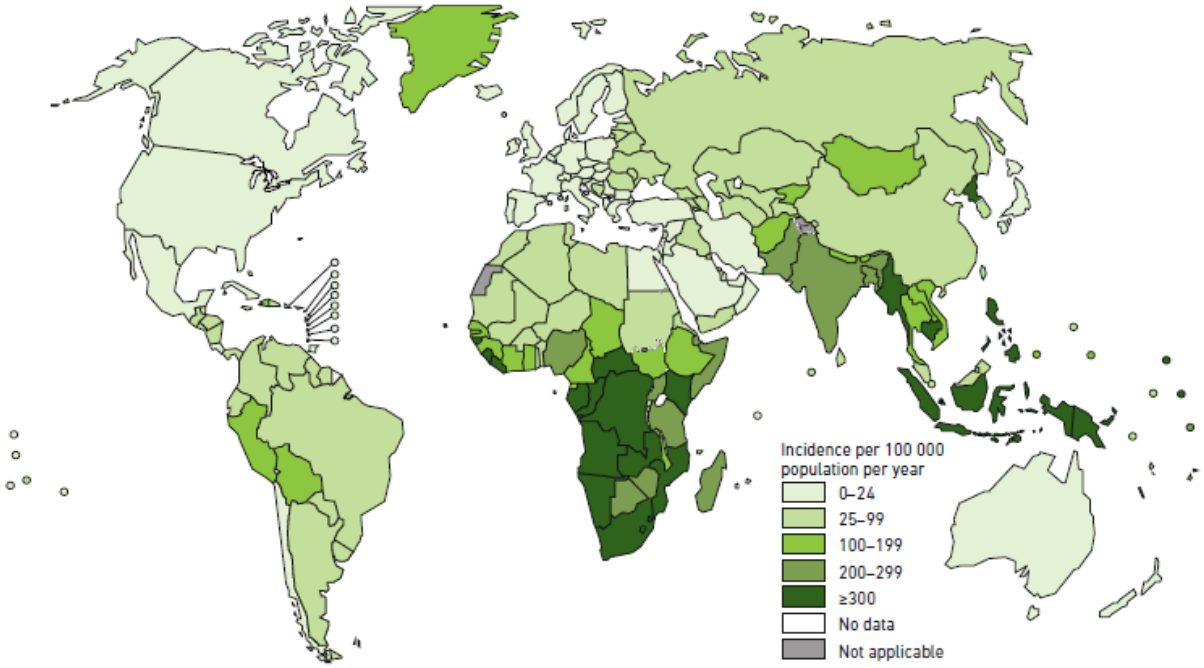


Fig. 1: Worldwide TB incident rates for 2017 (Global TB Report, 2018)

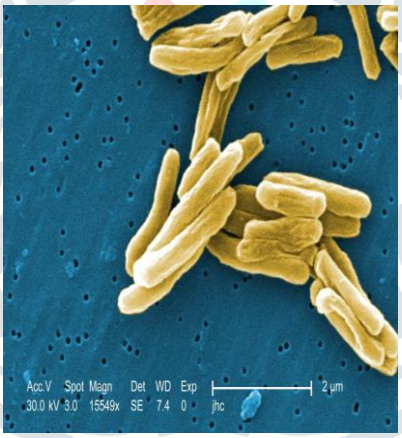


Fig 2.Scanning Electron Microscopy image of MTB (TodarK,2018)

The public health challenge of TB has been managed by a number of drugs and treatment strategies. The most effective drugs, called First Line Drugs, are used for the active TB disease and are shown in Figure 3. These drugs include Isoniazid (INH), Rifampicin (RIF), Streptomycin, Pyrazinamide and Ethambutol. These drugs are lowest in toxicity and highly efficient. These drugs reduced the burden of TB and this disease was assumed conquered at one point of time but due to the emergence of drug resistance cases, it has become global health emergency (KanabusA, 2016).

To combat with this problem, **Second Line Drugs**,as shown in Figure 4, are recommended which include:

a) Fluoroquinolones: Moxifloxacin, Gatifloxacin
b) Injectables: Kanamycin, Amikacin
c) Oral Bacteriostatic agents: *Para* amino salicylic acid
d) Drugs with unclear role: Linezolid

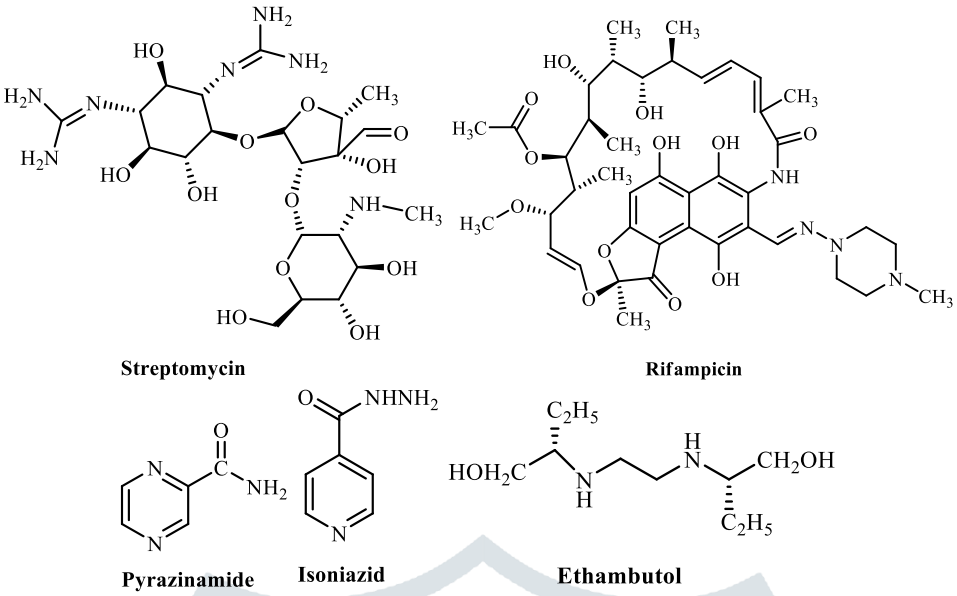


Fig 3. First line drugs for TB

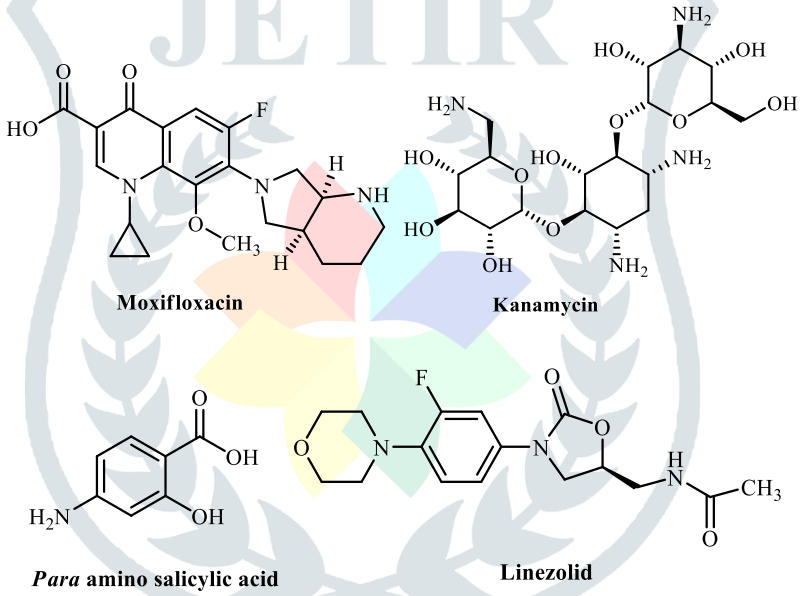


Fig 4. Second line drugs for TB

These drugs are less effective, more toxic and more expensive than First Line Drugs(JindaniA, 2004). The drug resistant cases are categorized in two classes:

a) Multi drug resistant (MDR) Tuberculosis
b) Extensively Drug Resistant (XDR) Tuberculosis

MDR-TB is the case of TB that shows resistance to Isoniazid and Rifampicin – the most effective anti-tubercular drugs (Ormerod L P, 2005). However, in XDR-TB cases, mycobacterium becomes resistant to Isoniazid, Rifampicin and any of the second line anti TB drugs. The various factors responsible for the development of resistance is due to

a) Weak TB programmes
   - Low completion / cure rates
   - Lack of treatment follow up and patient support
   - Unreliable drug supply
   - Diagnostic delay
b) Absence or inadequate infection control measures
c) Uncontrolled use of second line drugs

IV. CURRENT REGIMEN OF TB

The treatment regimen of Tuberculosis approved by the WHO guidelines is reliant on two phases – namely Intensive Phase and Continuation phase. In Intensive Phase, actively growing bacteria are targeted with most effective anti – TB drugs like Isoniazid,

Rifampicin, Pyrazinamide and Ethambutol for two months where as in continuation phase, persistent or slow growing bacteria are killed over the period of four months with rifampicin and isoniazid to prevent further relapse (ZumlaA, 2013).

In MDR TB, where the intensive phase lasts for a minimum of eight months, four potentially active drugs are used to treat MDR TB and at least six active drugs target XDR TB. In the continuation phase (12-18 months), three drugs for MDR and four drugs for XDR are used. The WHO recommended duration of treatment should be guided by the monitoring of specific test results. The results for MDR and XDR are still sub-optimum. To restrict the development of active TB, latent TB is also considered in high risk groups. The WHO recommends 6-9 months INH or 3-4 months INH and RIF or 4-months RIF alone (ZumlaA, 2015).

Unique public health philosophy like DOTS (Directly Observed Treatment Short course) has evolved to reduce the global burden of TB. In this programme, the patient is observed while taking medication which ensures the right combination of drugs and correct duration for which it has to be taken (SepkowitzK, 2001).

V. ANTI-TB DRUGS IN PIPELINE

The current First Line anti-TB drugs were discovered primarily in1950s to 1970s that extended to 1980s. The subsequent years faced the lag in research for the development of efficient and new anti-TB drugs. As the challenge is to synthesize new drug, which kills not only the active multiplying bacilli but targets slow growing as well as dormant bacilli. Novel drugs must ensure effective synergistic drug combination rather than single drug to avoid drug resistance. It should be safely and efficiently administered to the patients and shorten the duration of the treatment. While awaiting new drugs and regimes, the already available drugs were repurposed to treat MDR TB. The major chemical classes involved are:

a) Fluoroquinolones
b) Diarylquinoline
c) Nitroimidazole
d) Oxazolidinone
e) Benzothiazinone
f) Benzothiazole

Figure 5 shows one of the compounds from each major chemical class of anti-TB drugs in pipeline.

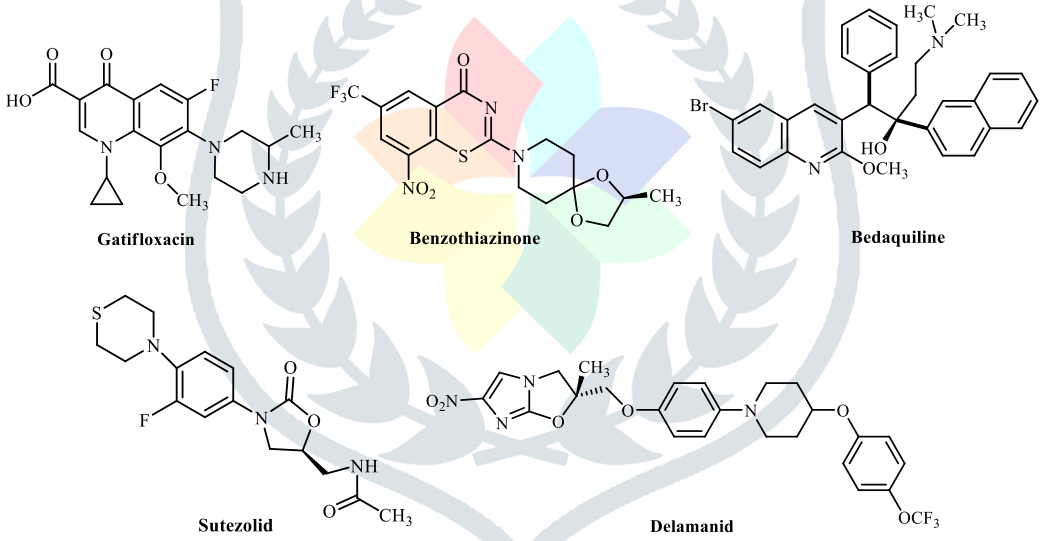


Fig 5. Anti-TB drugs in Pipeline

5.1 Fluoroquinolones: These are broad spectrum anti-microbial agents. Several members of this class have been used as second line drug in the treatment of MDR TB. Among these fluoroquinolones, Moxifloxacin and Gatifloxacin are used for the treatment of TB (Gay J D, 1984).

5.2 Diarylquinoline: It is another important class in the pipeline which yielded and important drug, Bedaquiline in 2012 after over 40 years. This drug was conditionally approved by FDA only for the treatment of MDR TB patients(Godebo A, 2015). Its safety and efficiency was unclear at the time of approval but over the years, research suggested that is effective with some adverse effects. It has potent bactericidal and sterilizing activity due to which it can reduce the duration of the therapy. According to the WHO guidelines, this has to be given in combination with other anti-TB drugs to avoid resistance. Research is still going on to acquire in-depth knowledge of its interaction with other drugs.

5.3 Nitroimidazole: These were initially synthesized to treat cancer which later on was found to be equally potent to treat tuberculosis. Extensive research on this class of compounds led to the synthesis of Delamanid (Lewis J, 2015). This drug was approved by European Medicinal Agency in 2012 to treat MDR TB after about 4 decades. Special guidelines are given for the use of this drug after it was conditionally approved. The most important of them are, this should be given to MDR patients only and should

not be given alone to avoid resistance. It should be monitored when in use. Over the years it has been found to be safe and well tolerated but more studies are required to understand its interaction with other drugs, toxicity and latent TB infections.

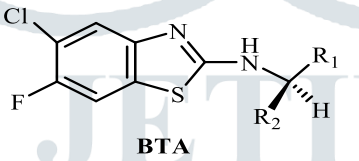
5.4 Oxazolidinone: This new class of compounds is in the pipeline to treat TB. They were initially used to treat bacterial infections, however, 5-membered ring with oxygen and nitrogen as hetero atom with modifications was identified, which can be used to treat tuberculosis. Linezolid and Sutezolid are important members of this class to treat tuberculosis (Gregory W A, 1989).

5.5 Benzothiazinone: It is the recently described as potent anti-TB drug which is much more potent that the most effective anti-TB drug Isoniazid (Poce G, 2014). It is also found to be synergistic with Rifampicin and Bedaquiline. The major problem with this drug is its solubility. Research is going on to increase its bio availability.

5.6 Benzothiazole: This is an important class of compound which has a wide range of pharmacological activities (Prabhu P P, 2015). The derivatives of these compounds reported some anti-TB activities but still they were not well explored for several decades.

VI. RESEARCH WORK AT THE UWI

Realizing importance of benzothiazole, we started working on its compounds in our laboratory. Several benzothiazole derivatives were successfully synthesized in our lab with different substituents like cyclohexyl, *n*-butyl, phenyl and substituted halophenylgroups asshown in Figure 6.



BTA

BTA-1 R_1=Me, R_2= cyclohexyl
BTA-2 R_1=Me, R_2= n-butyl
BTA-3 R_1=Me, R_2= Ph
BTA-4 R_1=Me, R_2=4-ClC_6H_4
BTA-5 R_1=Me, R_2= 4-BrC_6H_4
BTA-6 R_1=Me, R_2=4-FC_6H_4
BTA-7 R_1=Me, R_2= n-hexyl
BTA-8 R_1=Et, R_2= Ph

Fig 6. General structure of synthesized 2-aminobenzothiazole at the UWI

These compounds were biologically evaluated against MTB. The Minimum Inhibitory Concentration (MIC) of these compounds was found which are shown in Table 1. MIC range of these compounds fall between 5-100 µg/ml. The compounds with MIC of 5 µg/ml and 10 µg/ml seem to be promising therefore further modification on these compounds were performed.

For the synthesis of new compounds the base compound with MIC 5 and 10 µg /ml were chosen. Some of the heterocyclic groups were substituted at its most significant position. We expect to see better results when heterocyclic groups with medicinal importance are introduced to already promising compounds.

Table 1In vitro anti-TB results for 2-aminobenzothiazoles

Compounds	**R_1**	**R_2**	**$H_{37}R_v$ MIC (µg/ml)**
BTA-1	Me	cyclohexyl	5
BTA-2	Me	*n*-butyl	40
BTA-3	Me	Ph	10
BTA-4	Me	4-ClC_6H_4	20
BTA-5	Me	4-BrC_6H_4	100
BTA-6	Me	4-FC_6H_4	40
BTA-7	Me	*n*-hexyl	50
BTA-8	Et	Ph	5

vII. CONCLUSION

TB is still not a history. The global burden of this disease showed some rate of declination but not sufficient to end the epidemic of the disease. Efforts are being done to improve diagnosis, prevent infection and control but many more new anti-TB drugs are needed to sustain effective and productive pipeline. New drugs with strong, synergistic activities are required to shorten the therapy. The involvement of industry, academia, drug regulatory agencies and policy makers should collaborate to work against this dreadful disease.

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