(REVIEW ARTICLE)

Revolutionizing TB treatment: Breakthrough antibiotics for a healthier future A comprehensive review

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Abstract

The current treatment regiment for DS-TB(Drug Resistant Tuberculosis) was defined by 1980's since then the emergency of HIV and escalation of Drug sensitive (DS-TB)forms of TB have presented new challenges.To face these challenges, achieve goals like shortening DS -TB treatment improving DR-TB treatment and making combined TB -HIV therapy easier. A range of new drugs and treatment strategies are currently being elevated. Phase 2B and 3 clinical trials are ongoing to access combinations involving in high dose rifamycins, 8methoxyquinolines,diarylquinolines and nitroimidazoles. The new drugs advantages will contribute towards the achievement of a new treatment regimen in future. Tuberculosis according to WHO: TB is a bacterial infection that mainly affects the lungs and it is caused by the bacteria mycobacterium tuberculosis.

Keywords: Tuberculosis; Pretomanid; Delamaind; Bedaquiline.

1. Introduction

In 2014 TB surpassed HIV as the leading infectious cause of death . There are around 10.6 million incident cases of TB in 2022 with 1.3 million death's.TB consists of one of 10 prevalent cases of mortality globally. TB is spread from person to person by airborne droplets nuclei of infected person that can remain suspended in air for several hours. Symptoms include a persistent cough - lasting at least 3 weeks, phlegm which may have blood in it when they cough, a loss of appetite and weight, general feeling of fatigue, fever, night sweats, chest pain. The first line drug treatment developed in 1905 to 1970 remains lengthy which is greater than 6 months and is unforgiving to minor lapses in adherence . Despite the prognosis per patient with MDR TB remains with only 50% treatment success. Treatment outcomes for patients with exclusively drug resistant TB are extremely poor. There have been recent updates to guidance for MRD TB treatment. A short duration regimen called Bangladesh regimen showed promising results for 9 to 12 months course. A phase 3 clinical trial TREAM confirmed these results. This short course still requires use of 7 drugs given as complete regimen with no allowance for substitution or deletions. Thus this regimen may show drugs resistant patterns .The introduction of second wave of anti Tuberculosis drugs which includes BDQ ,Pretomanid, Delamaind ,Diarylquinoline,2 nitroimidazoles offers regimen for MDR TB and XDR.

1.1. Current treatment of TB

The introduction of antibiotics particularly isoniazid, rifampin and streptomycin revolutionized the treatment of TB by the mid 20th century. The current treatment of TB typically involves a combination of antibiotics, isoniazid(INH), rifampicin(RIF), pyrazinamide(PZA), Ethambutol(EMB). The treatment regimen consist of an intensive phase of usually 2 months with all four drugs followed by a continuation phase of 4 months with INH and RIF. The regimen is effective in curing vast majority of drug susceptible TB. Treating drug resistant TB is much more complex involving 2nd line antibiotics.

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1.2. Need of new anti-tubercular drugs

There are 3 reasons usually given for needing new tuberculosis drugs.

- To improve current treatment by shortening the total duration of treatment.
- To improve the treatment of MDR TB.
- To provide for more effective treatment of latent tuberculosis infection.

2. New anti tubercular drugs

Fortunately the 2nd wave of anti TB drugs development included the diarylquinolines, BDQ, 2-nitraimidazoles, Delamaind and Pretomanid offers the potential for simpler, shorter, all oral regimens of MDR and XDR - TB treatment.

2.1. **PRETOMANID:** It is also nitroimidazoles compound that particularly used in treating drugs resistance stain such as MDR TB and XDR TB .

- ***Mechanism of Action:*** Pretomanid works by inhibiting of mycolic acid synthesis which is a crucial component of bacterial cell wall in mycobacterium tuberculosis. In addition when it is activated by M TB specific F420 dependent, nitro-electric toxic nitrogen species are released killing the bacteria
- **Pharmacokinetics:** half life of Pretomanid is 16-20 hrs.
  - *Absorption*:It is administered orally and it is absorbed from GI tract and is influenced by Factors like food intake. Taking Pretomanid with food can increase bioavailability .
  - *Distribution:* Pretomanid is 94% protein bound. It has moderate volume of distribution and it can cross blood brain barrier which is important for treating CNS TB. Metabolism: it is metabolized extremely in the liver by enzyme cytochrome 18A2 , Cytochrome C19 .CYP3a is responsible for 20% of its metabolism.
  - *Excretion*: Pretomanid and it's metabolites or primary excreted through faeces with a small portion excreted in urine
  - Dosage: For the BPaL the recommended dose for Pretomanid is 200mg once a day.

Elimination half life of Pretomanid is relatively long allowing for once daily dosing.
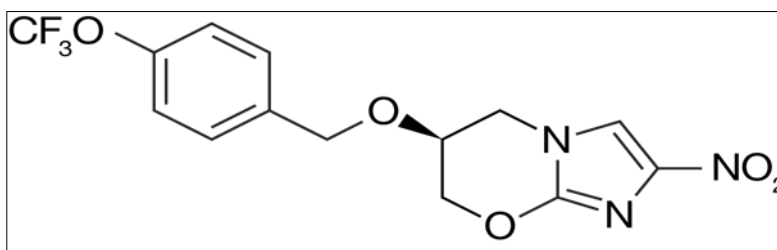
Figure 1 Structure of PRETOMANID

2.2. DELAMAID

Like Pretomanid , Delamaind { OPC - 67683 , DLM } is also a nitroimidazoles compound. Delamaind target enzyme KasA which is involved in synthesis of fatty acids in M -TB .As fatty acids are necessary for energy metabolism and cell membrane formation, inhibition of KasA by Delamaind disrupts fatty acid synthesis leading to metabolic dysfunction of bacteria. Delamaind enable the synthesis of ketomycolate, in cell wall lipid that constitute 1/3rd of M -TB dry weight. Delamaind as an extremely low minimal inhibitory concentration against M-TB and show activity against replicating and dormant bacilli. Pharmacokinetics: half life of Delamaind is 30-38hr

- *Absorption:* Delamaind administered orally and it is rapidly absorbed from GI tract. The bioavailability of Delamaind increases at higher fat content and meal intake.
- *Distribution:* Delamaind is widely distributed throughout the body and can penetrate into the blood brain barrier. The extent of protein binding to the tract is relatively high, greater than 99%.
- *Metabolism:* Delamaind undergoes extensive metabolism in liver via oxygen metabolism created by CYP450 enzymes { Cyp3A4 , Cyp2c19 and glucuronidation} mediated by UDP - glucuronosyl transferase (uGT,A9) .
- *Excretion :* Delamaind it's metabolites are primarily excreted in faeces and smaller amount is excreted in urine.
- *Adverse effects*: the adverse effects associated with Delamaind can vary in severity and occur among ,GI disturbance – nausea, vomiting , elevated liver enzymes, Prolong QT interval, peripheral neuropathy.

- Reactions: Rashes, Pruritus
- *Ocular effects:* optic neuritis and visual impairment Resistance: both Delamaind and Pretomanid required activation by coenzymes F420.Resistance mutation have been found in fbiA, fbiB,fbiC which are involved in F420 biosynthesis. The F420 cofactors are absent in mammalian cells leading towards a narrow spectrum of activity.
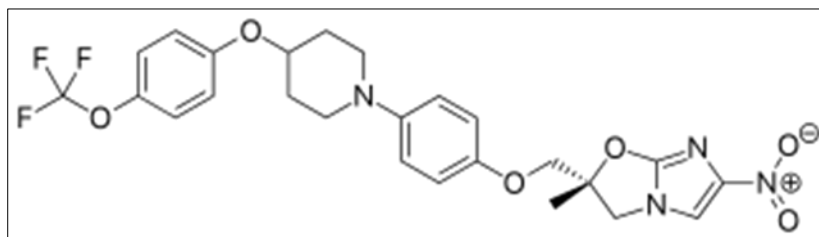

Figure 2 Structure of DELAMANID

2.3. BEDAQUILINE

BDQ is an antibiotic medicine used to treat multi drug resistant tuberculosis MDR -TB . Bedaquiline is a bactericidal, anti mycobacterial drug belonging to the class of diarylquinolines. The quinolonic center heterocyclic nucleus with alcohol and amines side chain is responsible for Bedaquiline mediated mycobacterium activity.

- *MOA:* By inhibiting ATP synthase enzyme of TB mycobacteria . ATP synthase is used in the process by which mycobacterium tuberculosis generates energy and supply. It is active against both mycobacterium tuberculosis and MDR -TB. BDQ - binding to the enzymes ring to block the route thus inhibiting ATP synthesis in enzymes catalytic Alpha3 ,f3 headpiece.
- *ADRs*: QT prolongation , headache, dizziness, nausea, vomiting and arthralgia
- **pharmacokinetics**
- *Absorption:* Food increases bioavailability.
- *Distribution:* distributed widely throughout the body it has high plasma protein binding capacity >99.9% and can cross blood brain barrier.
- *Metabolism*: Metabolism primarily by CYP3A4 to form N -monodesmethyl metabolite M2 which is 426 times less active.
- *Elimination:* BDQ and it metabolites are primary extracted through faeces.
- *Dosage:* 400mg once a day.
- The elimination of half life of BDQ is long range from 24-30 days allowing one daily dosing.
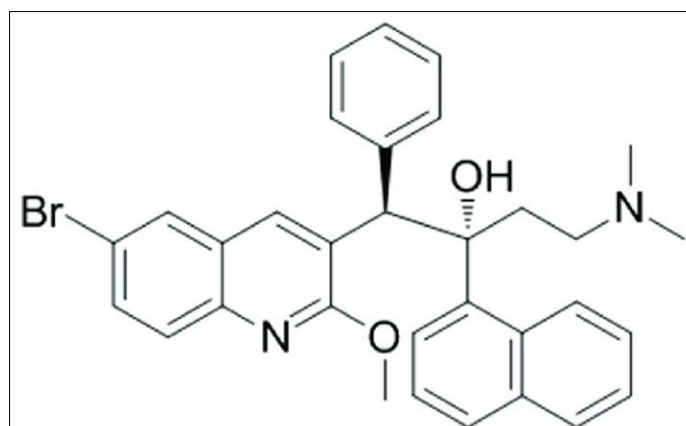
Figure 3 Structure of BEDAQUILINE

3. Advantages of modern anti-tubercular drugs compared to old once

•*Increased effectiveness:* New drugs tend to have higher potency against mycobacterium tuberculosis. This means they can kill bacteria more effectively even in cases where the bacteria may develop resistance to older drugs. For example, unlike many traditional TB drugs that target cell wall synthesis like isoniazid and ethambutol or protein synthesis (like rifampicin), the newer antibiotics Pretomanid works by disrupting mycolic acid biosynthesis- a critical component of the mycobacterial cell wall. This unique mechanism allows it to effectively target TB bacteria that may be resistant to other drugs.

3.1. Broader spectrum of activity

- Bedaquiline- active against both drug sensitive and multi drug resistant (MDR) strains of mycobacterium tuberculosis.
- Delamaind- effective against MDR - TB and XDR - TB.
- Pretomanid - effective against MDR- TB and XDR- TB.
- Linezolid- active against drug resistant TB, including
- MDR- TB and XDR- TB.

3.1.1. Reduced side effects

Newer drugs often have improved safety profiles with severe adverse effects. The new anti tubercular drugs such as Bedaquiline and Delamaind have shown several advantages in terms of reduced side effects compared to older drugs like isoniazid and rifampicin, by targeting specific bacterial pathways reducing their impact on human cells thus lowering side effects. For example: Bedaquiline has shown lower hepatotoxicity compared to isoniazid, streptomycin can cause significant cardiac side effects, ethambutol may cause optic neuritis or other neurological issues. Where newer drugs have improved cardiac, neurological safety profiles.

3.1.2. Shorter treatment duration

The new drugs demonstrated 95% cure without relapse after short course chemotherapy comprising to a two month intensive phase of drugs rifampicin, pyrazinamide, isoniazid, streptomycin and ethambutol and four months continuation phase of 2 drugs (rifampicin and isoniazid).

3.1.3. Improved outcomes:

New anti tubercular drugs have shown superior efficiency especially against drug resistant strains of TB (MDR - TB and XDR - TB). They help in achieving higher cure rates compared to older treatments. These also have expanded the range of combination therapy options.

3.2. Utilization of Novel Anti tubercular medications in pediatric patients

The Otsuka clinical trials demonstrated acceptable pharmacokinetics and safety of DML in HIV infected children ≥3 years. The WHO recommends BDQ in children with MDR - TB aged 6 to 17 years. Delamaind can be used as a part of longer individualised regimen for people with MDR/RR - TB including children and adolescents who are not eligible for the 9 months all oral regimen or 6 months BPaLM/BPaL regimen.

3.2.1. In pregnancy

Among pregnant women amikacin, ethionamide, streptomycin are contraindicated while there is still little knowledge on safety of newer agents (BDQ and Delamaind). There is no consensus on the optimal DR- TB treatment regimen among pregnant women and data on efficacy, safety, tolerability, maternal and foetal outcomes are needed.Most studies have been conducted in animals are based on limited human data. The decision to use these drugs in pregnancy involves balancing the potential benefits of treating TB against the risk to both the mother and the foetus. Whenever possible, first line anti tubercular drugs (INH, RIF, PZA, EMB) are preferred during pregnancy due to their extensive safety data and establishment efficacy.

• In geriatric patient:

 The newer antibiotics (BDQ and Delamaind) have been shown to be effective in treating MDR - TB and XDR - TB in elderly patients. Elderly patients have more comorbidities and higher likelihood of polypharmacy. Age related pharmacokinetics changes can affect drug levels in the body, medical conditions like diabetes, CVDs may complicate TB

treatment. BDQ and Delamaind should be used cautiously in patients with pre-existing cardiac conditions due to risk of QT interval prolongation.

4. Conclusion

The advancements in anti-tubercular drug development mark a significant milestone in the fight against tuberculosis (TB), especially in combating multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains. Newer medications like Bedaquiline, Delamaind, and Pretomanid offer promising alternatives with improved efficacy, reduced side effects, and shorter treatment durations compared to traditional regimens. These drugs not only enhance treatment outcomes but also expand therapeutic options, particularly in vulnerable populations such as pediatric and geriatric patients. However, further research is needed to establish the safety profiles of these drugs during pregnancy and their long-term effects. The continuous development and integration of novel anti-tubercular drugs are crucial in achieving global TB control and eradication. This review underscores the importance of innovative approaches and ongoing clinical trials to optimize TB treatment protocols and improve patient prognosis.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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