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Review Article

Novel Approaches for the Treatment of Drug-Resistant Tuberculosis

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ABSTRACT

Tuberculosis (TB) is a leading infectious disease that caused the deaths of a total of 1.5 million people in 2020 and is one of the top causes of death globally. India is a country with the highest TB burden, and it may affect all age groups. It is caused by the *Mycobacterium tuberculosis* bacteria, an intracellular pathogen, and its multidrug and extensively drug-resistant strains, which continue to emerge and spread, resulting in the deadliest infectious disease. After a gap of more than 40 years, the FDA approvals over the past decade of three second-line anti-TB drugs, bedaquiline, delamanid, and pretomanid, have been major forward steps in the management of drug-resistant-TB (DR-TB). Many medicinal plants such as *Zanthoxylum leprieurii, Lantana camara*, and *Cryptolepis sanguinolenta* have extensive therapeutic potential and represent a prospective option to fight against DR-TB. Some novel compounds are in the early clinical trial phases such as DprE1 inhibitors TBA-7371 and BTZ-043, and many others that are showing promising futures. This review describes DR-TB and its current chemotherapy guidelines including novel and repurposed drugs that are included in the anti-TB regimens, medicinal plants that have therapeutic potential for the development of drug-hit candidates, drugs that are currently in clinical development, host-directed therapy, and new drug delivery systems to better understand the novel therapeutic approaches that are currently being studied for the efficacious and safe management of DR-TB, a worldwide health problem.

Keywords: Drug-resistant tuberculosis, Nitroimidazoles, Medicinal plants, Nanotubes, immunomodulators.

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INTRODUCTION

Tuberculosis (TB) is a leading infectious disease that caused the deaths of a total of 1.5 million people in 2020 and is one of the top causes of death globally.[1,2] India is the country with the highest TB burden. The total number of incident TB patients (new and relapse) during 2021 were around 1.9 million, a 19% increase from 2020.[3] It is caused by the *Mycobacterium tuberculosis* (Mtb) bacteria, belonging to the family Mycobacteriaceae, discovered by Robert Koch in 1882. It is a non-motile aerobic bacillus[4] that causes pulmonary infection when an infected person, during coughing or sneezing, releases the droplets with droplet nuclei of 1-5 microns containing viable Mtb, and these droplets are inhaled and reach the respiratory alveolar units.[5] With the phagocytic efforts of the host's innate immune cells which includes primarily alveolar macrophages, dendritic cells, monocytes, and neutrophils, Mtb is still able to persist in the host and results in the formation of granulomas.[6] It is difficult to treat because its cell wall contains mycolic acids. This unusual fatty acid makes the bacteria less susceptible to antimicrobial agents and also helps the bacteria to vitiate the immune system and then hide from it.[7] Although exact host-bacillus interactions and mechanisms are still not very well understood, still this Mtb and host interaction during these initial stages of successful infection determine the outcome of TB disease. It may progress to active TB (pulmonary or extrapulmonary) or latent TB or just simply driving clearance. There is a global threat due to the continuous emergence of multidrug and extensively drug-resistant (MDR/XDR) strains, spreading and resulting in the deadliest infectious disease.[8]

The success rate of TB treatment with first-line anti-TB drugs (isoniazid, rifampicin, ethambutol, and pyrazinamide) was 86% in 2019 while the success rate of the treatment of MDR/Rifampicin Resistant-TB (RR-TB) was 59% in 2018.In 2020, 2.1 million people were diagnosed with RR-TB, almost 71% of the total 3 million bacteriologically confirmed pulmonary TB cases.[9] The prolonged and complex anti-TB chemotherapy for MDR/

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XDR-TB cases includes expensive antimicrobial agents[10] that are toxic, poorly tolerated, and has sub-optimal outcomes.[11,12] Fortunately, after a gap of more than 40 years, the USFDA approvals over the past decade of these three second-line anti-TB drugs, bedaquiline (Bdq), delamanid (Dlm), and pretomanid (Ptm), have been major forward steps in the drug-resistantTB (DR-TB) management.[13] These second-line anti-TB drugs offer the potential for shorter and simpler all-oral regimens for MDR/XDR-TB treatment.[14] Bdq has been included in the treatment regimen of DR-TB in 109 countries by the end of 2020. Many countries are using all oral longer and shorter regimens for the treatment of MDR/RR-TB.[9]

Another forward approach for the management of TB is drug repurposing or drug repositioning. It includes reinvestigation of already approved and established drugs for newer therapeutic usages.[15] Repurposing is urgently needed in the treatment of DR-TB and one such most-researched compound is clofazimine (Cfz). It is a riminophenazine that was found to have both *in vitro* and *in vivo* activity against Mtb.[16]

With the emergence of different resistant Mtb strains, the need for novel drug development has become tremendously important.[17] Medicinal plants, an important source of biologically active secondary metabolites, have extensive therapeutic potential and represent a prospective option to fight against DR-TB.[18] *Zanthoxylum leprieurii, Lantana camara*, and *Cryptolepis sanguinolenta* are among the medicinal plants that have anti-Mtb activity.[17]

Host-directed therapy (HDT) is a new and promising concept in TB treatment that can modify host responses to better control the TB progression. Small molecules such as nanoparticles (NPs), with or without additional antibodies, can be utilized as a delivery system.[19]

This review aims to report the DR-TB and its current chemotherapy guidelines including novel and repurposed drugs that are included in the anti-TB regimens. The medicinal plants that have therapeutic potential for the development of lead drug candidates and drugs that are currently in clinical development will also be discussed here. New drug delivery systems and HDT will also be discussed to better understand the novel therapeutic approaches that are currently being studied for the efficacious and safe management of DR-TB, a global health problem.

Drug resistant-TB and chemotherapy

DR-TB definition has been revised by WHO for the better management of these forms of TB. MDR-TB is defined as TB caused by Mtb strains that are resistant to at least isoniazid and rifampicin. WHO's Global TB Programme has revised the definition of XDR-TB as TB that is caused by Mtb strains that fulfill the definition of MDR/RR-TB and also Mtb strain has resistance to any fluoroquinolone (FQ) and at least one additional second-line Group A drug. It has also defined pre-XDR-TB for the very first time which only highlights the seriousness of DR-TB. The pre-XDR-TB is defined as TB caused by the Mtb strains that fulfill the definition of MDR/RR-TB and are also resistant to any FQ.[20]

Detection of drug resistance is important for the effective management of DR-TB. It includes Nucleic Acid Amplification Tests (NAAT) which includes cartridge-based NAAT (CBNAAT) and Truenat, which detects R resistance, a preferred method for the initial detection of RR-TB. This is followed by Line probe assay (LPA), which can detect resistance to R, H, and particularly FQ and second-line injectables (SLI) drugs.[21]

After assessing the efficacy and safety of the drugs and recommendations, WHO in its Consolidated Guidelines for TB Module 4: Treatment of Drug Resistant TB (2020), classified the second-line anti-TB drugs for the treatment of DR-TB into three groups:

Group A = bedaquiline, linezolid (Lzd), andlevofloxacin or moxifloxacin (FQs);

Group B = clofazimine, and cycloserine or terizidone; and

Group C = delamanid, ethambutol, pyrazinamide, amikacin (or streptomycin), imipenem–cilastatin or meropenem, p-aminosalicylic acid, andethionamide or prothionamide.[22]

Although there are predefined regimens for the chemotherapy of TB, still globally it's a huge challenge for the health system to manage TB patients.[23] WHO has provided various regimens for the treatment of DR-TB which are also being followed by the National Tuberculosis Elimination Programme (NTEP) of India. It includes a shorter oral Bdq-containing MDR/RR-TB regimen and a longer oral MDR/XDR-TB regimen. However, fully oral regimens are still getting scaled up in India, so the current shorter MDR-TB regimen with SLI is still going on.[21,22]

Bedaquiline, delamanid and pretomanid

Bdq and Dlm received speedy approvals based on their phase 2 data in 2012 and 2014, respectively,for the management of MDR-TB.[24] Bdq (TMC207 or R207910), a diarylquinoline, was developed by Janssen Pharmaceuticals in 2005 and it was endorsed by WHOin 2013for the treatment of MDR-TB.[25] It was the first novel anti-tubercular agent that was approved by the FDA in 40 years. It acts by inhibiting Mtb mitochondrial ATP synthase by binding to subunit C and starves the bacteria of ATP.[26]

Bdq has improved the efficacy of the standard treatment regimen for MDR/XDR-TB and also has a good safety profile.[23] It is metabolized by CYP450 3A4, primarily, in the liver. Hence, there are possibilities of drug interactions that could result in either toxicity or therapeutic failure. The most concerning adverse event is QTc prolongation, similar to both nitroimidazoles, Dlm and Ptm, FQs, and Cfz.[27]

Dlm (OPC-67683), a nitroimidazole, was developed by Otsuka Pharmaceutical in 2003. It was recommended by the WHO for the treatment of MDR-TB in 2014.[25] It obtained conditional approval from FDA in the same year.

Recently, Ptm (PA-824), another oral nitroimidazole antimycobacterial agent, was developed by the Global Alliance for TB Drug Development (TB Alliance) for TB treatment under license from Novartis.[14] This mycolic acid synthesis inhibitor was approved by USFDA in August 2019 as a part of a combination regimen with Bdq and Lzd for the treatment of XDR-TB or treatment-intolerant or non-responsive MDR-TB.[2,15,27]

Both nitroimidazoles, Dlm and Ptm, inhibit cell wall synthesis by inhibiting the synthesis of methoxy- and keto-mycolic acid, but they do not inhibit the synthesis of a-mycolic acid, while INH inhibits all mycolic acid subclasses. Both of them are prodrugs[27-29] that are activated by Mtb F420-dependent reductase coenzyme metabolism to produce an active free radical. Mutations have been observed in the genes that are involved in the prodrug activation and F420-dependent reductase pathway (fbiA, fbiB, fbiC).[27] Dlm has more potent *in vitro* activity than pretomanid against MDR/XDR-TB.[30] It also has a low minimum inhibitory concentration (MIC) against TB strains.[23] The most common adverse event of Dlm and Ptm is gastrointestinal. QTc prolongation is a serious adverse event ofboth nitroimidazoles, however, the same is true for other drugs used in TB such as Bdq and FQs.[27] Dlm has shown low interaction with antiretroviral therapy.[25]

Ptm is a bicyclic nitroimidazo-furan[28] that has activity against both replicating and non-replicating Mtb.[31] It was originally investigated for use in cancer chemotherapy as a radiosensitizer. It acts both in aerobic as well as anaerobic conditions and has activity against both drug-sensitive and DR-TB.[28] By inhibiting the synthesis of mycolic acid,[32] it leads to disruption of the cell wall of actively replicating Mtb bacilli, a death-inducing effect of Ptm. It also acts by its NO-releasing potential which kills anaerobic Mtb bacilli via respiratory poisoning.[23]

Repurposed Drug

Drug repurposing reduces the first stages of drug development and reduces the time and investment needed to find new treatments.[33] Cfz, Lzd, FQs (levofloxacin and moxifloxacin), carbapenems (imipenem–cilastatin and meropenem), and amikacin are all repurposed drugs that are being used for the treatment of DR-TB.[22]

Cfz, a riminophenazine, is originally used to treat patients with multibacillary leprosy, in the combination with rifampicin and dapsone, known as multidrug therapy.[34] Although its mechanism of action is not fully understood and it also has little bactericidal activity, still, recent studies have suggested that it possesses sterilizing and treatment-shortening potentials.[35] Studies suggest that like Bdq, Cfz targets the electron transport chain of Mtb[26] and cross-resistance has already been reported between both drugs.[27] Its anti-Mtb activity is mainly due to the disruption of the redox cycle and high lipophilicity.[16] It seems like it has multiple effects on Mtb which includes enzymatic reduction of Cfz by NDH-2, creation of bactericidal reactive oxygen species, and causing dysfunction and destabilization of the cell membrane of Mtb.[26] The most common adverse effects which are already seen in leprosy patients are skin pigmentation and gastrointestinal intolerance.[27]

Lzd is an oxazolidinone. After the production of synthetic antibacterial agents for agricultural use in 1978, oxazolidinones were first used in humans in the 1980s. Lzd was approved in 2000 by the USFDA for the management of infections caused by Gram+ve bacteria. It inhibits protein synthesis by acting on the 50S subunit of the ribosome.[27] It has demonstrated efficacy in anti-Mtb activity but its safety profile limits its use other than DR-TB.[35] Mutations in the drug-binding domain in the ribosome cause the development of resistance.[27]

Medicinal plants for DR-TB treatment

The word "Phytochemicals" means the plant-based chemicals that are produced during their primary or secondary metabolism to help them in protection from various predators or pathogens. Although these chemical compounds have a vast history of being used in various therapeutic measures, limited studies have been conducted to explore these phytochemicals in the treatment of TB. The phytochemical studies need further exploration in the field of Mtb infection management.[36]

Garlic (*Allium sativum*), a common food ingredient, is known for its strong antibacterial activity. Allicin, thio-2-propene-1-sulfinic acid S-allyl ester, is the main constituent of garlic that inhibits sulfhydryl metabolic enzymes to exert their antimicrobial effects. Extract of allicin has shown promising results against both drug-sensitive and -resistant strains of Mtb. Ajoene, another compound from garlic, induces ROS synthesis and autophagy and has been found effective in the treatment of TB.[36] The garlic extracts exert tremendous scientific importance in their effectiveness against clinical isolates of MDR-TB and offer hope for developing alternative drugs.[37]

Curcumin, derived from turmeric, is a yellow-colored curcuminoid. It has been used as a food ingredient and herbal medicine for centuries.[38] It has been found to reduce the burden of Mtb bacilli in the monocytic human cell line (THP-1) and at higher concentrations, it induces the apoptosis of infected THP-1 cells. But poor bioavailability is an issue.[39] However, the bioavailability issue can be addressed by developing curcumin nanoparticles. These formulations not only increase efficacy but also decreases the chances of hepatotoxicity when given with INH.[40]

Many other plants have been reported in recent years that may be effective in the management of DR-TB such as *Zanthoxylum leprieurii*,[41,42] *Lantana camara, Cryptolepis sanguinolenta*,[42] Musa spp. AAB, cv. "Manzano" plant,[43] *Levisticum officinale*,[44] *Punica granatum, Andrographis paniculate, Diospyros montana, Ventilago madraspatana, Plumeria bicolor, Urtica dioica, Vetiveria zizanioides, Piper nigrum* L., *Croton tonkinensis, Ranunculi ternate* Radix, *Andrographis paniculata, Annona muricata, Centella asiatica, Pluchea indica* and *Rhoeospathacea*.[45]

New anti-TB drugs in clinical development

There are some novel compounds in the early clinical trial showing promising futures. The decaprenylphosphoryl-β-D-ribose-2′-epimerase (DprE) is a heterodimeric enzyme that comprises DprE1 and DprE2 proteins. DprE1, a key enzyme in the arabinan biosynthesis pathway and thus in the cell wall synthesis of Mtb.[46] Four novel compounds that are highly potent DprE1 inhibitors, identified in high-content screening platforms, are TBA-7371, BTZ-043, Macozinone (PBTZ-169), and OPC-167832.[13] BTZ-043 and Macozinone (PBTZ-169), both belong to the benzothiazinone class. They are very potent bactericidal drugs acting against replicating Mtb bacillus and MDR strains.OPC-167832 is a 3,4-dihydrocarostyril derivative that displays bactericidal activity against both replicating as well as intracellular bacilli.[47] TBA-7371, an azaindole, has the potential to shorten the standard therapy course.[46] All of them are in the phase 2 trial except Macozinone (PBTZ-169) which is in the phase 1 trial.[13]

Another novel cell wall synthesis inhibitor is SQ109, a 1,2-ethylene diamine like ethambutol, but in preclinical studies, it has shown many times more activity.[48] Its mechanism of action also differs from ethambutol, as well as its potency and antibacterial activity. It acts by inhibiting the MmpL3, a transmembrane transport protein that is essential for the synthesis of the cell wall. It transports trehalose monomycolate. In the phase 2 study, it has shown good bactericidal activity against Mtb and acts against both extracellular and intracellular bacillus. It increased the efficacy of first-line anti-TB drugs and also MDR-TB regimens. It has also shown good synergistic activity with Bdq.[47]

Four novel compounds that act on Electron Transport Chain (ETC) are TBAJ-876, TBAJ-587, TBI-166, and Telacebec (Q203). TBAJ-876 and TBAJ-587 are two promising novel second-generation diarylquinoline compounds. They have shown activity against Bdq-resistant strains with improved safety profile. They inhibit ETC by inhibiting ATP synthase and are in phase 1 study. TBI-166, a riminophenazine, acts on Electron transport and reactive oxygen production. It is the phase 1 trial and has better activity and safety profile in comparison to Cfz.[13] Another ETC inhibitor that acts on cytochrome bc1 complex is Telacebec (Q203), an imidazopyridine amide. It is in the phase 2 study and has shown good bactericidal activity.[13,47]

Oxazolidinone includes one approved compound, Lzd. Three Lzdanalogs, Sutezolid (PNU-100480), Delpazolid (LCB01–0371), and TBI-223 are in different phases of the clinical trial. They act by inhibiting protein synthesis by binding to 23S rRNA. Sutezolid acts against both intracellular and extracellular Mtb and shows a very potent bactericidal activity. At the doses of 600mg twice daily, it was found to be safe and well tolerated in a phase 2b trial. Delpazolid and TBI-223 are novel oxazolidinones. They both have shown potent bactericidal activity against Mtb with lower potency for mitochondrial protein synthesis, so a better safety profile in comparison to Lzd. Delpazolid is entering into phase 2b trials in drug-sensitive TB patients, aiming for shortening the TB treatment. Sutezolid and delpazolid may also be used for DR-TB after successful development. TBI-223 is in phase 1 trial and is being in ascending dose studies.[13]

GSK 3,036,656 (GSK-656) is an oxoborole that has a novel mechanism of action. It inhibits protein synthesis by inhibiting the leucyl-tRNA synthetase enzyme. It does not have activity against mitochondrial protein synthesis, so it may replace oxazolidinone, however, it is still in phase 1 trial.[13]

SPR720 is a DNA Synthesis Inhibitor by acting on GyrB. It has shown activity against FQ-resistant strains. GSK2556286 (GSK-286) is a Cholesterol Catabolism Inhibition that can penetrate lesions in TB disease and reduce relapse rates. BVL-GSK098 is a Transcriptional Regulators Inhibitor by acting as an EthR transcriptional repressor. It is a novel regulator of bacterial transcription. It increases the Ethionamide efficacy and reduces its resistance development in Mtb. All these three novel compounds are in the phase 1 trial.[13]

New drug delivery system

Drugs used in the management of TB have various serious adverse effects including hepatotoxicity and these may lead to the dropping out of the treatment of the patients which allows the development of resistance to the anti-TB drugs. Another reason for the development of resistance is the subtherapeutic levels of the drugs. All this can be avoided with the selective introduction of the drug into the macrophages where Mtb replicates. The non-systemic exposure and optimal concentration would minimize the emergence of resistance. Nano-delivery system is ideally suited for this targeted delivery of the drug into the macrophages of infected organs such as the lungs, liver, and spleen. It will also shield the drug from metabolism before the delivery into the infected organs with Mtb.[28] Nanotechnology is an extensively studied emerging technology in the field of medicine and has shown promising results in the diagnosis and management of TB.[49]

It has been shown in the studies that carbon nanotubes (CNTs), in the form of either nanoparticle suspension or nanofluids, have the potential to be used in diagnosis as well as therapy. It can hinder MDR and causes cell wall destruction by targeted drug delivery.

A synergistic combination of fluoxetine and isoniazid in CNT has been found to inhibit Mtb growth. Fluoxetine increases the TNF-α secretion and induces the autophagy of the macrophages that are infected with Mtb.[50]

A synergistic effect of trapped silver nanoparticles in biopolymers induces cytotoxicity and can also function as a nanocarrier to deliver anti-Mtb drugs. One more example of these functionalized biodegradable polymers is the use of Curdlan nanoparticles conjugated with cyclodextrin. The dectin-1 receptor on macrophages recognizes Curdlan. Thus, it releases drugs into macrophages and possesses anti-infective and immunomodulatory properties. Similarly, mannose-modified nanostructured lipid carriers loaded with isoniazid can target infected macrophages and increase the intracellular efficacy of anti-TB drugs.[51]

In another recent study, a novel nano-delivery system was reported. It is an inorganic nanolayer based on magnesium-layered hydroxides (MgLH). Inorganic nanolayers are biocompatible as they are biodegradable and can carry a drug and release it in a sustained manner at the targeted site. MgLH and intercalated para-aminosalicylic acid (PAS) second-line anti-TB drug has shown highly encouraging results in the study.[52]

These studies highlight the remarkable potential of nanostructures with long shelf life, better bioavailability of the drugs, and better safety profiles and thus better clinical outcomes.[5]

Host-directed therapy

With increased MDR/XDR strains, the search for host targets that can be manipulated to boost the immune response of the infected patients has gained considerable interest recently.[53] Host-directed therapy (HDT) improves the treatment efficacy for TB,[54] by augmenting the immune response of the host and/or immunomodulation and increasing the infection/disease clearance chances, improving the TB management outcome. The HDT can impair Mtb replication and, thus, survival by interfering with Mtb manipulation of the macrophage pathway, making bacteria more vulnerable to host defense. HDT has been proposed as adjunctive therapy for TB treatment.[55] They additively or synergistically enhance the anti-TB drug activity. The modulation of the immune response results in reduced lung pathology, improved treatment efficacy, and thus better disease outcomes.[56] Recently, macrophage-targeted HDT has unfolded as an encouraging therapeutic strategy for both drug-susceptible and DR-TB. Ion channel blockers are one of the most promising potential HDTs against TB.[57] The fusion of lysosome with autophagosome is the defense mechanism against Mtb. Acidification of the auto phagolysosome prevents the growth of Mtb. Mtb prevents this fusion and acidification while HDT compounds such as Vitamin D_3 and phenylbutyrate activate host defense, induce the production of LL-37, an antimicrobial peptide, and inhibit Mtb growth.[56]

CONCLUSION

TB is a global health issue with India having the highest TB burden. This disease affects all age groups and with the emergence of resistant strains, the management of DR-TB has become a challenge. WHO has introduced all-oral regimens for better efficacy and safety but still there are concerns which are needed to be entertained efficiently and require the development of novel drugs and tremendous work in this field. Many medicinal plants have shown potential for the development of drug-hit candidates and many other drugs are currently in different phases of clinical trials. New drug delivery systems are currently being studied for the effective delivery of drugs to increase efficacy and reduce the chances of toxicity with the delivery of the drugs to the targeted site. HDT is also being studied to augment the immune response and effectively control the growth of MTB bacilli in the macrophages. Considerable work is going on but a lot is still required to reduce the time duration and increase the efficacy and safety of the management of DR-TB.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TB: Tuberculosis; **DR:** Drug-resistant; **Mtb:** Mycobacterium tuberculosis; **MDR:** Multidrug drug-resistant; **XDR:** Extensively drug-resistant; **RR:** Rifampicin Resistant; **Bdq:** Bedaquiline; **Dlm:** Delamanid; **Ptm:** Pretomanid; **Cfz:** Clofazimine; **HDT:** Host-directed therapy; **NPs:** Nanoparticles; **FQ:** Fluoroquinolone; **NAAT:** Nucleic Acid Amplification Tests; **CBNAAT:** Cartridge-based NAAT; **LPA:** Line probe assay; **SLI:** Second-line injectable drugs; **Lzd:** Linezolid; **NTEP:** National Tuberculosis Elimination Programme; **MIC:** Minimum inhibitory concentration; **DprE:** Decaprenylphosphoryl-β-D-ribose-2′-epimerase; **ETC:** Electron Transport Chain; **CNTs:** Carbon nanotubes; **MgLH:** Magnesium-layered hydroxides; **PAS:** Para-aminosalicylic acid.

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