Experts review

Joining hands and making alliances to develop new strategies in combating dangerous and deadly tuberculosis

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Abstract

Mycobacterium is now believed to be millions of years old. Cases of TB continue to rise due to the ability of M. tuberculosis to adapt and develop opportunistic infection strategies. Drug resistance is rampant in TB since the length of treatment leads to people falling off the regimen and the development of strains that are resistant to multiple anti-TB therapies, or multidrug-resistant TB.

Keywords: multi drug-resistant TB (MDR TB), Novel drug TB, Linezolid, bedaquiline, delamanid, moxifloxacin

Introduction

In The genus, *Mycobacterium* is now believed to be millions of years old [1]. A history of Tuberculosis (TB) needs to start with its discovery at least 35,000 years ago and probably closer to 2.6 million or even 3 million years ago [2]. What is now known as infection with *Mycobacterium tuberculosis* (M. tb) has plagued humanity since antiquity. Evidence of infection with tuberculosis (TB) has been identified in the bones of Egyptian mummies dating back to 3300 B.C., and was depicted in the artwork and texts from Mesopotamia dating to the seventh century B.C. [2). Cases of TB continue to rise due to the ability of M. *tuberculosis* to adapt and develop opportunistic infection strategies [3,4]. Drug resistance is rampant in TB since the length of treatment leads to people falling off the regimen. Recent pathogenic strategies include co-infection with the human immunodeficiency virus (HIV), which results in HIV-associated TB, and the development of strains that are resistant to multiple anti-TB therapies, or multidrug-resistant TB (MDR TB) [5]. This is affecting millions of population worldwide and resulting in huge mortalities- morbidities which are making big impact on socioeconomic conditions of affected populations.

This needs total revamp in various aspects related to TB starting from diagnosis to treatment which is gigantic task as we can see little change in last decade as evident from availability of same drugs and treatment regimens despite observing MDR and total drug resistant TB since long time. Also adverse effects, particularly hepatotoxicity of most of currently used anti-TB drugs is of great concern. Hence recent Official ATS/CDC/ERS/IDSA clinical practice guideline prescribes many updates for TB treatment [6]. However after understanding the devastating impact of TB there is strong need to have series of new TB drugs which should able to have more effective, less toxic, shorter, simpler, affordable /less expensive drug regimes with few drug-drug interactions, so they can be safely provided for people with HIV also.

Several organizations are working to improve situation under leadership of WHO (https://www.who.int/teams/global-tuberculosis-programme/the-end-tb-strategy). TB Alliance (https://www.tballiance.org) is a not-for-profit organization dedicated to the discovery, development and delivery of better, faster-acting and affordable tuberculosis drugs that are available to those who need them. It works with a diverse network of global partners, including the world's leading pharmaceutical developers, academic institutions, and research institutes. There is also presence of working groups who have made several linkages with researchers and other stake holders for sharing knowledge, collaborating for better solutions against TB (https://www.newtbdrugs.org/about). The stop TB partnership has a working group on new TB drugs, which helps to coordinate, guide, and accelerate the speed of worldwide development of new TB therapies. Many resources are made available to educate and disseminate more and more information on various aspects of TB (https://tbfacts.org). These and such organizations are playing a pivotal role in

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Group name	Anti-tuberculosis drugs
Group 1	First-line oral drugs: isoniazid, rifampicin, ethambutol, pyrazinamide
Group 2	Quinolones: high-dose levofloxacin, moxifloxacin
Group 3	Linezolid, bedaquiline, delamanid
Group 4	Injectable second-line drugs: kanamycin, amikacin, capreomycin
Group 5	Ethionamide/prothionamide, clofazimine, carbapenems (?)
Group 6	Cycloserine, p-aminosalicylic acid, amoxicillin/clavulanate

Table 1: A proposal for a future grouping of anti-tuberculosis (Anti-TB) drugs by Caminero and Scardigli

fighting against deadly TB varieties with battery of new drugs/ regimes. TB Alliance is now promoting a treatment protocol BPaL, a six-month treatment for what is called extensively drug-resistant TB (XDR). The BPaL regimen includes bedaquiline (B), pretomanid (Pa), and linezolid (L). This regimen is expected to deliver about 90% success rate in clinical trials for drug-resistant TB. The Nix-TB trial is the first TB clinical trial to test combination of pretomanid, bedaquiline and linezolid which has the possibility of being a shorter, all oral, and affordable treatment for XDR-TB which does not require injections and comparatively less tablets are to be taken for six to nine months [7].

WHO recommends a stepwise process based on five groups of anti-tuberculosis (Anti-TB) drugs and anti-TB regimen for MDR/XDR-TB. Caminero and Scardigli suggested a new Classification of antituberculosis drugs based on the most recent evidence which makes six groups as given in table 1 [8].

The choice of the drugs is based on their efficacy and toxicity, where group 1 includes first-line drugs and group 2–5 include second line drugs. Group 5 includes the drugs with potentially limited efficacy or limited clinical evidence.

Pipeline of New TB drugs and vaccines under development

The term Pipeline in drug development refers to all the drugs which are at different stages of development and how the drugs are progressing down the “pipeline” through the various stages from preclinical to clinical trial phases. Once they cross phase 3 of clinical trial, they can be utilized for treatment of various form of TB in which these drugs are found highly effective during studies. In addition to development of new drugs, the emphasis is also given to expedite developments with TB diagnostics & make "pipeline" of vaccines [9].

The drugs which have crossed phase 3 of clinical trial and available for treatment:-

1. Bedaquiline:-

Bedaquiline is a member of the diarylquinoline class of drugs and has a unique mechanism of action, targeting the adenosine triphosphate (ATP) synthase enzyme of the TB mycobacteria. It is active against both MTB and the drug-resistant TB bacteria that cause MDR-TB. Laboratory tests and clinical trials have shown it to have strong bactericidal and sterilizing properties.

2. Nitroimidazoles:-

Nitroimidazoles are an existing class of drugs known to have antimicrobial activity. Two “next generation” or derivatives of this class of drugs, PA-824 (Pretomanid) and OPC-67683 (Delamanid) are considered as potential TB drugs. Pretomanid is a nitroimidazooxazine antimycobacterial drug which kills actively replicating M. *tuberculosis* by inhibiting mycolic acid biosynthesis, thereby blocking cell wall production. Under anaerobic conditions, against non-replicating bacteria, pretomanid acts as a respiratory poison following nitric oxide release. It can potentially be used for the treatment of both drug sensitive and drug resistant TB. It has shown activity against both latent TB and active TB disease. In August 2019 Pretomanid received US approval for the use of Pretomanid in combination regimens with bedaquiline and linezolid for people with XDR TB or treatment intolerant or non responsive MDR TB [7]. Delamanid also believed to have similar mechanism of action and being studied as a part of anti- TB treatment.

3. Linezolid:-

A member of the oxazolidinone class of drugs, linezolid is active against most Gram-positive bacteria that cause disease, including tuberculosis, streptococci, vancomycin-resistant enterococci (VRE), and methicillin-resistant *Staphylococcus aureus* (MRSA). As a protein synthesis inhibitor, it stops the growth of bacteria by disrupting their production of proteins, acting as a bacteriostatic agent. The exact mechanism of action of linezolid appears to be unique in that it blocks the initiation of protein production, and not one of the later steps, hence bacterial resistance to linezolid has remained very low. Discovered in the 1990s and first approved for use in 2000, linezolid was the first commercially available 1,3-oxazolidinone antibiotic.

4. Fluoroquinolones:-

Several members of the fluoroquinoles class of drugs are currently already used as second line TB drugs for the treatment of multi drug resistant TB. The older drugs such as ofloxacin and levofloxacin are often used rather than the newer fluoroquinolones moxifloxacin and gatifloxacin. Moxifloxacin and gatifloxacin are currently being evaluated for the treatment of drug sensitive TB and currently undergoing evaluation in a phase 3 trial for (i) confirming impact when it is substituted for either ethambutol or isoniazid and (ii) to shorten the treatment of drug sensitive TB from the standard six months to four months. The gatifloxacin trial is being conducted by the Oflotub Consortium and moxifloxacin is being developed by Bayer and the TB Alliance. A meta analysis suggested that

fluoroquinolone substitution for isoniazid or ethambutol in short course regimens might result in more frequent unfavourable treatment outcomes compared with the standard regimen, in particular an increased incidence of relapse [10, 11].

5. Rifamycins:-
The Rifamycins are potent inhibitors of mycobacterial activity. Three semi synthetic rifamycins - rifampicin, rifapentine, and rifabutin - have been used for the treatment of various microbial infections. Rifampicin is a key component of first line drug treatment for TB. Rifapentine is attractive as a possible TB drug for shortening treatment, and for intermittent TB drug treatment, and clinical trials are under way to further assess this [12].

The drugs which approaching towards phase 3 of clinical trials are listed below-

A) Phase-II-

1. AZD5847:-
AZD5847 is a potential new TB drug being developed by AstraZeneca. In December 2012 it was announced that the first patient had been enrolled in a Phase 2A trial of the drug in South Africa, to assess the effectiveness of the drug for patients with TB, including patients with HIV and TB coinfection.7 The study is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), which is part of the U.S. National Institutes of Health.

2. Sutezolid:-
Sutezolid is in the same class of drugs as linezolid (oxazolidinones). Tests conducted over the past decade have indicated that sutezolid may have an improved therapeutic potential when compared to linezolid, which is currently recommended by the World Health Organization as a treatment option for drug-resistant forms of TB.

3. TBA-7371:-
The enzyme DprE1 is involved in the synthesis of arabinans which are an essential part of mycobacterial cell walls. This is a new target and these inhibitors are active against M. tb strains resistant to known TB drugs. TBA-7371 has demonstrated *invivo* efficacy and a thus far acceptable safety profile.

4. OPC-167832:-
OPC-167832 is a newly synthesized carbostyril derivative which shows anti-mycobacterial activity by inhibiting decaprenylphosphoryl-β-D-ribose 2'-oxidase (DprE1), an essential enzyme for cell wall biosynthesis of Mycobacterium tuberculosis (MTB). The minimum inhibitory concentrations of OPC-167832 against MTB on both laboratory strains and clinically isolated strains including multidrug resistant/extensively drug resistant MTB ranged from 0.00024 to 0.002 μg/mL. OPC-167832 showed potent bactericidal activity against both growing and intracellular bacilli and therapeutic effect in an experimental mouse model of chronic TB at lower doses than other anti-TB drugs. OPC-167832 did not show antagonistic effects with the other anti-TB drugs in in vitro checkerboard agar dilution method and in a mouse model of chronic TB. Furthermore, OPC-167832 in regimens combined with delamanid showed superior efficacies to a standard regimen RHZE (rifampicin + isoniazid + pyrazinamide + ethambutol) in mice. We concluded that OPC-167832 is a new anti-TB drug candidate and could be a member of new generation anti-TB regimens which have potential to shorten the period of TB treatment [13, 14].

5. BTZ-043
BTZ-043 efficiently inhibits MTB cell wall synthesis by blocking the decaprenyl- phosphoribose-2′-epimerase (DprE1), necessary for the synthesis of D-Arabinofuranose, a component of arabinogalactan and arabinomannan. Its mechanism of action is highly selective for mycobacterial species. BTZ-043 is active against all tested MTB strains including clinical isolated from MDR and XDR patients. The in vitro MIC ranges between ~0.1 - 80 ng/ml for fast growers, and from 1 - 30 ng/ml for members of the M. *tuberculosis* complex. In vivo BTZ-043 shows superior activity to INH in mouse models, most prominent after 2 months and thereafter. Synergistic effects with rifampicin and bedaquiline were detected. In preclinical toxicology (GLP) studies, BTZ-043 showed a low toxicologic potential, it was well tolerated up to 170 mg/kg (NOAEL) in rats over 28 days and it showed a NOAEL of 360mg/kg in minipigs. BTZ-043 showed low interaction with the CYP450 enzymes. The safety panel (neurotoxicity, cardiotoxicity and respiratory toxicity) was conducted under GLP standards and within the NOAELs determined in the toxicolo [15, 16].

6. Telacebec (**Q203**):-
Q203 is the first-in-class, orally-available antibiotic for the treatment of tuberculosis (TB). Telacebec is a selective inhibitor with high specificity for the cytochrome bc1 complex of *Mycobacterium tuberculosis*. This complex is a critical component of the electron transport chain, and inhibition disrupts the bacterium's ability to generate energy [17].

7. Macozinone (MCZ, PBTZ-169)-
PBTZ169 is a piperazinobenzothiazinone derivative optimized by medicinal chemistry from the lead BTZ043. PBTZ169 has several advantages compared to BTZ043, amongst which are easier chemical synthesis, due to the absence of chiral centers, low cost of goods and better pharmacodynamics. PBTZ169 covalently inhibits DprE1, an enzyme essential for the biosynthesis of key cell wall components. The drug has additive effects with many TB therapeutic agents, both marketed and in development, and has synergic effects with bedaquiline and clofazimine in preclinical models [18].

8. GSK 3036656:-
Leucyl-tRNA synthetase (LeuRS) is an essential enzyme for protein synthesis. LeuRS has two catalytic sites, an aminoacylation site, which charges tRNALeu with leucine and an editing or proof-reading site that hydrolyses incorrectly charged tRNALeu. Evaluation various Mtb LeuRS inhibitors led to the discovery of GSK070, which exhibits potent inhibition of Mtb LeuRS [19].

9. SQ109:-
SQ109 is a novel 1,2-ethylene diamine small molecule drug with 3 unique mechanisms of action that are distinct from other antibiotics used for the treatment of tuberculosis [20].

10. Delpazolid (LCB01-0371)-
A novel oxazolidinone with cyclic amidrazone [21].
B) Phase-I:-

1. **TBI-223**:-
Oxazolidinones are mainly used as antimicrobials. The antibacterial effect of oxazolidinones occurs by working as protein synthesis inhibitors, targeting an early step involving the binding of N-formylmethionyl-tRNA to the ribosome. Oxazolidinones have shown activity against M. tb and several are either in development for, or already used, to treat TB. Linezolid, sutezolid, and delpazolid are all members of the oxazolidinone class [22].

2. **TBAJ-587**-
The development of the anti-TB drug bedaquiline introduced both a novel chemical class—diarylquinolines (DARQs)—as well as a novel MTB-selective mechanism of action (direct inhibition of MTB ATP synthase). This next-generation diarylquinoline project has shown potential to maintain bedaquiline's impressive anti-TB activities while introducing improved safety properties [23].

3. **TBAJ-876**:-
This diarylquinoline appears more efficacious and potent against TB than bedaquiline as well as the investigational diarylquinoline TBAJ-587, with a lower predicted clinical dose than either of those compounds. Similar to TBAJ-587, TBAJ-876 possesses improved safety properties compared to bedaquiline [23].

4. **GSK 2556286** (GSK-286):-
GSK-286 is a new chemical entity with a novel mechanism of action related to cholesterol catabolism. GSK-286 selectively kills intracellular MTB. It penetrates into necrotic lesions (MALDI) and reduces inflammation.

5. **Macozinone** (MCZ, PBTZ-169):-
PBTZ169 is a piperazinobenzothiazinone derivative optimized by medicinal chemistry from the lead BTZ043. PBTZ169 has several advantages compared to BTZ043, amongst which are easier chemical synthesis, due to the absence of chiral centers, low cost of goods and better pharmacodynamics. PBTZ169 covalently inhibits DprE1, an enzyme essential for the biosynthesis of key cell wall components. The drug has additive effects with many TB therapeutic agents, both marketed and in development, and has synergic effects with bedaquiline and clofazimine in preclinical models [23].

6. **TBA-7371**:-
AZ 7371 is a non-covalent inhibitor of decaprenylphosphoryl-β-D-ribose 2'-epimerase (DprE1) with an IC50 value of 10 nM. It also inhibits PDE6 with an IC50 value of 4 μM. 23.

7. **BVL-GSK098**:-
BVL-GSK098 in combination with ethionamide (Eto)/prothionamide (Pto) as an oral treatment of pulmonary tuberculosis. BVL-GSK098 acts via a new mechanism on bacterial transcriptional regulators, stimulating novel bioactivation pathways for Eto resulting in an increase of Eto efficacy, while simultaneously overcoming resistance to Eto. BVL-GSK098 renders Eto rapidly bactericidal and reduces the emergence of Eto-resistance development in vitro and in vivo [24].
8. **TBI-166**:-
TB Alliance has pursued compounds that mirror clofazimine's potential as an anti-TB drug while possessing a superior side effect profile. TBI-166 was identified through a lead optimization.

C) Preclinical stages-

1. FNDR-20081:-
[4-{4-[5-(4-Isopropyl-phenyl)-[1,2,4]oxadiazol-3-ylmethyl]-piperazin-1-yl}-7-pyridin-3-yl-quinoline] is a novel, first in class anti-tubercular pre-clinical candidate against sensitive and drug-resistant *Mycobacterium tuberculosis* (MTB). In-vitro combination studies of FNDR-20081 with first- and second-line drugs exhibited no antagonism, suggesting its compatibility for developing new combination-regimens. FNDR-20081, which is non-toxic with no CYP3A4 liability demonstrated exposure-dependent killing of replicating-MTB, as well as the non-replicating-MTB, and efficacy in a mouse model of infection [25].

2. **OTB-658**:-
OTB-658 showed bacteriostatic effectiveness with a lower MIC than linezolid against *Mycobacterium tuberculosis*. The minimal bactericidal concentrations and time-kill curves for OTB-658 indicated inhibition activity similar to that of linezolid. OTB-658 entered macrophages to inhibit M. tuberculosis growth. OTB-658 had a low mutation frequency (10-8), which would prevent drug-resistant mutations from emerging in combination regimens [26].

3. FNDR 20364:-
A natural product derived peptide antibiotic with excellent *invitro* and *invivo* activity in mouse and guinea pig TB infection models. Peptide candidate kills TB through a novel mode of action by inhibiting ribosome associated GTPase activity blocking protein translation. Several *in-vivo*, inhalation combination studies with Isoniazid and Rifampicin or second line drugs revealed superiority of peptide containing combinations.

4. **TB47**:-
TB47, a new drug candidate targeting QcrB in the electron transport chain, has shown a unique synergistic activity with clofazimine and forms a highly sterilizing combination. Here, we investigated the sterilizing effects of several all-oral regimens containing TB47 plus clofazimine and linezolid as a block and the roles of fluoroquinolones and pyrazinamide in them. All these regimens cured tuberculosis within 4 to 6 months in a well-established mouse model, and adding pyrazinamide showed a significant difference in bactericidal effects [27].

5. **GSK839**:-
GSK839 is a new chemical class that inhibits M. *tuberculosis* tryptophan synthase (TrpAB) in a selective manner.

6. **MBX-4888A**:-

MBX-4888A using structure-based design, a new semisynthetic series of spectinomycin analogs with selective ribosomal inhibition and narrow-spectrum antitubercular activity had been generated. In multiple murine infection models, these spectinamides were well tolerated, significantly reduced lung mycobacterial burden and increased survival. *Invitro* studies demonstrated a lack of cross resistance with existing tuberculosis therapeutics, activity against multidrug-resistant (MDR) and extensively drug-resistant tuberculosis and an excellent pharmacological profile.

7. **Sanfetrinem**:-

Sanfetrinem the oral beta-lactam sanfetrinem cilexetil, a first-in-class tricyclic carbapenem. Sanfetrinem was identified in a screen of ca. 2,000 beta-lactams as the most active against intracellular M. tuberculosis

Conclusion:

The last few decades has captured a significant rise of development of new drugs, repurposed drugs and various treatment regimens for TB. In various studies the drugs with poor efficacy like ethambutol and pyrazinamide were placed efficiently owing to their excellent biodistribution. Drugs like bedaquiline and delamanid contain two or more aromatic moieties, which makes them highly lipophilic. Multiple drugs were being docked, designed and synthesised which were in different phases of clinical and preclinical studies. Increasing number of MDT were handled by rational prescription and various drug regulatory authorities. We are expecting not only expecting new drugs but also novel mycobarial targets. So it is anticipated that careful designing of new molecules will lead to the development of new compounds that can solve all the problems which society is facing.

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