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Newer Drugs and Targets in Tuberculosis.

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ABSTRACT

In the year 2013, nine million people suffered from tuberculosis. Around 1.5 million people (men, woman and children) died due to tuberculosis. About 1.1 million people with HIV developed tuberculosis. The major drawbacks of tuberculosis treatment in a patient are multidrug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB). Recently newer drugs and targets have been the key focus of research in finding the permanent cure for tuberculosis. The FDA has recently approved a new tuberculosis drug bedaquiline. The drugs under trials are delamanid, pretomanid, sutezolid and SQ109. Drugs in preclinical development showing promising results are benzothiazinone, spectinamide, capuramycin, TBI-166 (Riminophenazines antibiotic). The various lead compounds which showed promising activity against *mycobacterial tuberculosis* are SPR113, cyclopeptides, ruthenium complexes, leucyl- t- RNA inhibitors, inhA inhibitors. The various hits during drug discovery shown to have effect against tuberculosis infection are ATP synthesis inhibitors, RNA polymerase inhibitors, energy metabolism inhibitors, menaquinone inhibitors and malate synthesis inhibitors. Biologics have shown to improve the treatment outcome in tuberculosis but are still in trial or in drug development. They are immunoxel, HE2000, Oral *mycobactriumvaccae*(V7), TGF-Inhibition + COX-2 inhibition,IL-4 antibody. Some of the old drugs which have found to be effective against tuberculosis are: high dose rifampin, statins, meropenem+clavulanate, nitazoxanide.

Keywords: rifampin, bedaquiline, sutezolid, Meropenam, MDR-TB

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INTRODUCTION

India has the highest tuberculosis (TB) burden with World Health Organization (WHO) statistics for 2011 showing an incidence of 2.2 million cases of TB for India out of the global incidence of 8.7 million cases. The issue of MDR-TB and XDR-TB has been the biggest problem in the treatment and cure of tuberculosis. The WHO's Global tuberculosis report in 2012 showed that 73,000 MDR TB patients living in India where only 1,660 cases were notified and 1,136 cases were put on treatment. Around 60% of the 3.1 lakh MDR TB cases were from India, China and Russia. Also, 69 countries, including India, have reported at least one case of XDR-TB by the end of 2010 [1]. In January 2012 it was reported that twelve cases of TB had been diagnosed in Mumbai which were confirmed as totally drug resistant TDR-TB [2]. In September 2013 it was reported that out of 21 children with TB few had MDR TB, and one of them had TDR- TB[3].TDR –TB is a condition where the organism is resistant to both first and second line drugs for treatment. A recent report as per the World Health Organisation (WHO), Global TB Report 2015 for the year 2014 showed 2.2 million cases were estimated in India which is higher than any other country. India ranks 17th in incidence rate among the 22 high-burden countries in the world. The proportion of MDR cases is estimated to be 1.9-2.6 per cent among new TB cases and between 11-19 per cent among re-treatment cases [4].

As a result the search for new drugs has become a major factor in the treatment and cure of tuberculosis

Newly approved drug

Bedaquiline

It is the first anti-TB drug to interfere with bacterial energy metabolism. It has a novel mechanism of action to the treatment of pulmonary MDR-TB. It specifically inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in *mycobacterium tuberculosis*[5]. It belongs to diarylquinoline class [6].It was approved in 2012. A standard 2 month treatment in newly diagnosed MDR-TB showed rapid sputum culture conversion and showed less resistance when used with drugs used to treat MDR-TB. Bedaquiline 400mg daily for 2 weeks then 200mg for 3 times a week for 22 weeks added to MDR-TB regimen [7]. There is also CYP3A4 interaction seen with this drug. Adverse effects are QT prolongation, elevated transaminases, nausea, arthralgia, headache, hemoptysis and chest pain [8].

Drugs under trials

Delamanid

Delamanid belongs to nitroimidazole class. It inhibits mycolic acid synthesis but the exact mechanism is still unkown [9].A Randomized, placebo-controlled, multinational clinical trial Delamanid (100mg / 200mg twice daily) when added to MDR-TB or XDR-TB regimen showed an increase in sputum culture conversion at the end of 2 months compared to the group which did not receive the drug [10]. Another study, delamanid for 6 months in combination with an optimized background regimen for MDR/XDR tuberculosis, reduced mortality among patients with both multidrug-resistant and extensively drug-resistant TB. Mortality at the end of this 6 month study was just 1% [11]. Another trial a large randomised controlled one examining 6 months of treatment with delamanid in combination with a background treatment regimen with MDR-TB (including HIV patients) is currently been conducted.

Pretomanid (PA-824)

It's a bicyclic nitroimidazole like molecule. It is active against both replicating and hypoxic, non-replicating *Mycobacterium tuberculosis.* It is believed that hypoxic non replicating bacteria derive their energy from ATP. Respiration and an exogenous electron acceptor are required for maintaining viability. The mechanism of action is: 1) inhibition of mycolic acid biosynthesis 2) acts as a respiratory poison by releasing nitric oxide release and drop in intracellular ATP levels in respiratory complex [12]. A 14 day early bactericidal activity showed that (pretomanid + moxifloxacin+ pyrazinamide) combination showed higher bactericidal activity than bedaquiline alone or (bedaquiline+ pyrazinamide) or (bedaquiline + pretomanid) and comparable to standard treatment of drug sensitive tuberculosis [13].A phase IIb trial demonstrated the bactericidal activity of a new 8 week regimen i.e (moxifloxacin + pretomanid(100/200mg)+ pyrazinamide compared to

drug sensitive (DS)/drug resistant (DR) TB regimen. Post 2 months higher bactericidal activity was seen in new regimen compared to standard treatment. Goals of {pretomanid+ moxifloxacin+ pyrazinamide} are: 1) Potential to cure both TB and some forms of MDR-TB in 4 months. 2) Effectively administered alongside common antiretroviral (ARV) treatments, thereby improving treatment options for patients co-infected with TB and HIV. 3) It also shows promise for MDR-TB patients who are sensitive to the drugs in the regimen, reducing treatment from 2 years to 4 months[14]. A study of 14 day early bactericidal activity of (bedaquiline + pretomanid + pyrazinamide + clofazimine) combination was compared to standard DS-TB. Bactericidal activity in the combination of 4 drugs in the early 14 days was higher compared to standard regimen [15].

Sutezolid

It belongs to oxazolidinone class and is similar to linezolid. It prevents the initiation of protein synthesis by binding to 23s RNA in the 50S ribosomal subunit of bacteria. It is safe and well tolerated. Mycobacterial activity of sutezolid is seen at a dose of 600mg once daily or 1200mg once daily [16].

SQ109

It is 1,2-ethylenediamine analogue of ethambutol. Drug is active against both drug susceptible and drug resistant tuberculosis. The mechanism of action is as follows:[17]1) Immediate inhibition of trehalosedimycolate (TDM) production which leads to failure of attachment of mycolates to the cell wall arabinogalactan 2) The drug also targets the MmpL3 gene which results in accumulation(TMM), the precursor of TDM and cell wall mycolates.

Linezolid

Linezolid is a first-generation oxazolidinone showing clinical effectiveness against drug-resistant cases. A recent prospective randomised trial included XDR-TB patients failing previous chemotherapy had taken linezolid dosage of 300–600 mg per day [18]. About 87% of patients showed bacteriological conversion within 6 months. As four patients in the above study showed resistance during treatment more studies are necessary to assess the optimal dose and adequate duration of treatment. Due to various adverse effects of linezolid (peripheral neuropathy, optic neuropathy, gastrointestinal disorders and myelosuppression) a study from the Netherlands suggested that clarithromycin can boost the blood levels of linezolid, allowing administration of lower doses with fewer adverse events [19]. A recent meta-analysis showed favorable efficacy, safety, tolerability and proved that linezolid toxicity can be reduced by appropriate drug treatment monitoring [20,21].

Co-trimoxazole:

Co-trimoxazole has shown significant impact in treatment of tuberculosis. A double blind placebo controlled randomised clinical trial was done to assess the impact of prophylactic oral co-trimoxazole in reducing mortality in HIV positive Zambian adults being treated for pulmonary tuberculosis. It showed that prophylaxis with co-trimoxazole reduced mortality in HIV infected adults with pulmonary tuberculosis and co-trimoxazole was generally safe and well tolerated in these patients [22]. A recent in-vitro study revealed that the combination of sulfamethoxazole- trimethoprim and isoniazid or rifampin is bactericidal and prevents the emergence of drug resistance in Mycobacterium tuberculosis [23,24].

Drugs under preclinical phase:

Benzothiazinone

They inhibit the synthesis of decaprenyl-phosphoribose-2' epimerase. This enzyme is used for synthesis of D-Arabinofuranose, a component of arabinogalactan and arabinomannan. They show potent activity against 240 clinical isolates of *Mycobacterium tuberculosis* including MDR-TB & XDR-TB. There is no antagonistic activity seen with rifampicin, isoniazid, ethambutol, pretomanid, moxifloxacin and meropenem. It has synergistic activity with bedaquiline [25].

Spectinamide 1599

Invitro it lacks cross resistance with current treatment of drug sensitive tuberculosis. It has activity against multidrug-resistant (MDR) and extensively drug-resistant tuberculosis. It causes structural modification to evade the rv1258c efflux pump, upregulated in MDR strains and is implicated in macrophage-induced drug tolerance. In future it would tackle the intrinsic efflux pump mediated resistance[26].

Capuramycin SQ641

It inhibits translocase-I enzyme. It is bactericidal and kills faster than any existing antitubercular drugs (isoniazid and rifampin). It acts on fast and slow growing bacteria in 24 hours. Active against all strains of multidrug-resistant clinical strains [27].

TBI-166 (Riminophenazines antibiotic)

Its mechanism of action is same like clofazimine. It avoids skin discoloration which is predominantly seen in clofazimine [28,29].

Promising targets of newer anti-tubercular drugs

Lead is a chemical compound that has pharmacological or biological activity likely to be therapeutically useful, but may still have suboptimal structure that requires modification to fit better to the target

DprE inhibitors

They are identified by high-throughput screening against mycobacterial whole cells. DprE1: essential mycobacterial enzyme that is involved in the synthesis of mycobacterial cell wall. DprE1, MoeW, Molybdenum are some of the factors responsible for cell wall synthesis. TCA1 molecule acts on DprE and also down regulates genes involved in persistence of the bacilli [30].

Cyclopeptides

Griselimycin, a natural cyclic peptide isolated from Streptomyces species. During lead optimization cyclohexylgriselimycin was obtained. The target is DNA polymerase sliding clamp (DnaN). It has potent bactericidal activity in vitro and in vivo against drug resistant tuberculosis strains. DnaN is the gene that codes for the DNA clamp (also known as β sliding clamp) of DNA polymerase III. The β clamp physically locks Pol III onto a DNA strand during replication to help increase its processivity [31].

Ruthenium II phosphine / picolinate complexes

These are inorganic compounds and are highly selective for *Mycobacterial tuberculosis.* Minimum Inhibitory Concentration (MIC) levels were comparable to first line drugs in in-vitro. Nanotechnology is used to improve bioavailability, stability and controlled release of these compounds. It was found that picolinate complex affects intra macrophage tuberculosis growth [32].

LeuRS INHIBITORS

The target is leucyl–t RNA synthetase enzyme. This enzyme is involved in cellular translation and protein synthesis. This drug shows good in-vitro and in-vivo activity against *mycobacterial tuberculosis* [33].

inhA inhibitors

Isoniazid is activated within the mycobacterial cell by the KatG (catalase peroxidase). KatG couples isonicotinic acyl with NADH to form isonicotinic acyl-NADH complex. This complex binds tightly to the enoyl-acyl carrier protein reductase (InhA), blocking the natural enoyl-AcpM substrate and action of fatty acid synthase which are responsible for mycolic acid synthesis. Most isoniazid resistance are due to mutations in

KatG leading to the inability to activate the drug .Thiadiazole series are direct inhA inhibitors which do not involve KatG gene [34].

ATP synthesis inhibitors:

They inhibit ATP synthase enzyme. Cytochrome, Ndh-2 are some substances which have such enzyme inhibiting property. ATP synthase is an essential enzyme for production of ATP [35].

RNA polymerase inhibitors

RNA polymerase is the enzyme that transcribes genetic information from DNA into RNA which in turn directs the assembly of proteins that carry out most biological activity and key structural components of cells. They can kill both active and dormant tuberculosis. High doses of rifamycin are tried out but problems of rifamycin are resisitance and toxicity [35].

Energy metabolism inhibitors

The targets are the electron transport chain and the energy metabolism pathway [35].

Menaquinone inhibitors

They inhibit enzyme Men A in the Menaquinone biosynthesis pathway. Earlier it was developed as cholesterol synthesis inhibitor [35].

Malate synthesis Inhibitors

It is seen that persistent infections of mycobacterial tuberculosis requires the glyoxylate pathway to bypass the energy generated by tricyclic acid (TCA). (Glyoxylate pathway = isocitratelyase + malate synthase). The inhibitors target and block the malate synthase enzymes which have hydrophobic binding domain [35].

BIOLOGICS

Immunoxel

It is a water – alcohol phytoconcentrate of 25 herbs. Earlier it was used as an immune supplement to treat various infectious diseases like seasonal flu, TB, HIV. There are published studies spanning over 15 years were 20 clinical trials accounting 1500 TB and HIV patients were studied. Herbal extract + conventional drugs: can clear bacteria in 2-4 months instead of usual 6-24 months.

Four types of solid sublingual formulations: sugar dragées, sugar-coated pills, gelatin pastilles and dried-honey lozenges were administered once-daily along with TB drugs (DS-TB, MDR-TB, TB/HIV). After 1 month, 84.1% of TB patients became sputum-negative with rates in individual groups of 89.5, 70, 76.9 and 100%, respectively. They increase the number of lymphocytes, CD4 and CD8 cells, IFN-γ , IL-2, levels which are required for killing of mycobacteria [36].

HE 2000

It acts as an immunomodulator. HE2000 is a synthetically modified androstane adrenal hormone. In HIV-infected patients, HE2000 decreases inflammatory cytokines and increases circulating dendritic cells, T-natural killer(NK) cells and HIV-specific activated CD8 T cells [37].

Rh- interferon- γ

Experimental studies showed moderately encouraging results. The uses for recombinant interferon γ are aimed at 1) Prophylactic treatment of latent TB 2) Decrease the duration of chemotherapy regimen. Aerosolized IFN-γ could be beneficial for HIV patients [38].

Oral *Mycobacterium vaccae* (V7)

It is a novel immunotherapeutic agent. Oral tablet containing heat killed *Mycobacterium vaccae* was used with conventional drugs once a day. It was used at a dose of 10mcg/pill. Two randomized placebo controlled phase II trials showed that in one month – sputum smear conversion was seen in 72% patients with conventional drugs and oral pill. Around 50-60% patients with drug resistant tuberculosis and difficult to treat cases (HIV+ TB) showed sputum smear conversion when the oral pill was added to conventional regimen. The above results of sputum smear conversion in MDR-TB patients are seen in 12-24 months as opposed to 1 month [39].

TGF- β Inhibition + Cox-2 inhibition

TGF- β has various role in the suppression of immunity and as a result its inhibition is very important. The action of TGF- β are: 1) Suppresses cell mediated immunity 2) Blocks IFN- γ induced macrophage activation causing inhibition of IL-1, TNF-α, iNOS. 3) Blocks IFN- γ and MHC – II 4) Suppress IL-2 5) It blocks lymphocyte proliferation and function (CD-4). PGE_2 is more active at the latent phase and decrease the expression of IFN-γ, TNF-α, iNOS. As a result Cox-2 inhibition can prevent PGE_2 from its action. Murine pulmonary T.B models showed that combination therapy resulted in clearance of bacilli from lungs [40].

Drugs for repurpose

High dose of rifampin

Patients with drug-susceptible tuberculosis were enrolled into a control group of eight patients receiving the standard dose of 10 mg/kg rifampin, followed by consecutive experimental groups with 15 patients each receiving rifampin 20, 25, 30, and 35 mg/kg, respectively, for 14 days. In all patients isoniazid, pyrazinamide, and ethambutol were added in standard doses for the second 7 days of treatment. It showed that 35 mg/kg was safe, well tolerated and showed greater fall in bactericidal load [41].

High dose of statin

It showed enhanced bactericidal activity when combined with first line drugs. Optimal statin dosing still remains a question. A recent study of statins role in killing of *mycobacterium tuberculosis* showed that statins caused reduction in cholesterol levels within phagosomal membranes and promote host induced autophagy thereby augmenting host protection against tuberculosis [42].

Carbapenems

Meropenem +clavulanate was shown to be effective against XDR strains in the early 14 days of treatment. Faropenem, a carbapenem class of drug showed the following properties: a) stable compound b) Kills *Mycobacterium tuberculosis* in absence of amox/clav c) Target enzyme: L,D transpeptidase (more inactivation than meropenem) d) Active against non-growing metabolically active cells (responsible for relapse) [43].

Nitazoxanide

Autophagy is regulated by mammalian Target OfRapamycin Complex I (mTORC1). mTORC1: a nutrient energy and growth factor sensing master regulator of cell growth and metabolism It is stimulated by growth factors and nutrients and is involved in translation and protein synthesis in mycobacteria. Mechanism of Nitazoxanide [44] : a) Stimulates autophagy, inhibits mTORC1 signalling, inhibits M.tuberculosis intracellular proliferation b) Inhibits the enzymatic activity of human quinoneoxidoreductase NQ01 probably acting upstream for mTORC1.

Tedizolid

Tedizolid phosphate is a prodrug activated by plasma or intestinal phosphatases to tedizolid. After activation tedizolid exerts its bacteriostatic microbial activity through inhibition of protein synthesis by binding

to the 50S ribosomal subunit of the bacteria [45]. Tedizolid, a novel oxazolidinone and ACH-70(isothiazoloquinolone) were tested against M. tuberculosis infected THP-1 macrophages. These two compounds significantly decreased the number of intracellular mycobacteria significantly comparable to rifampicin and moxifloxacin against multidrug resistant bacteria [46].

Rifapentine

It is synthesized in one step from rifampicin. The drug is used for prevention of active tuberculosis in HIV-negative individuals with latent TB. It is found that a weekly directly observed regimen of rifapentine with isoniazid for three months was effective as a daily self -administered regimen of isoniazid for nine months in patients with latent TB. The rifapentine-isoniazid regimen had higher rates of treatment completion and lower rates of hepatotoxicity [47].

CONCLUSION

Tuberculosis is a very important disease at national and international level. The search for cure for this disease has been the prime objective of various researchers around the world. As a result it is important to know the various advances and drugs in pipeline for the treatment of tuberculosis in various forms.

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