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CURRENT STATUS AND FUTURE PROSPECTS FOR TUBERCULOSIS

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ABSTRACT

Tuberculosis is declared to be an infectious disease of global emergency by WHO. Approximately one-third of the world's population is infected with the tuberculosis. The lengthy and laborious current treatment of 6-9 months is associated with problems like patient noncompliance, multiple drug resistance and persistence of mycobacterium and significant toxicity of drugs. The increasing emergence of drug resistance of mycobacterium highlights an urgent need to develop novel therapeutic targets and agents that are not only effective against drug resistant bacteria but can also herald the persistent form of bacteria and thereby shorten the length of TB treatment. However, an approach towards understanding the physiological characteristics of the mycobacterium and designing of such novel therapeutic agents that are effective against drug resistance & persistent bacteria can bring about a revolution in the TB chemotherapy in near future.

INTRODUCTION: Tuberculosis (TB) is a systemic chronic granulomatous disease caused by *Mycobacterium tuberculosis* [1]. With the advent of HIV, TB has become a serious health hazard worldwide & hence is declared as global emergency by W H O in 1993. [2] There are an estimated eight million new TB cases diagnosed each year and about two million deaths worldwide. Approximately one-third of the world's population is infected with the tuberculosis. [3]. India is classified amongst those countries with a high burden of TB including the MDR and XDR cases and the least prospects of a favourable time trend of the disease as of now (Group IV countries). The average prevalence of all forms of tuberculosis in India is estimated to be 5.05 per thousand, prevalence of smear-positive cases 2.27 per thousand and average annual incidence of smear-positive cases at 84 per 1,00,000 annually. According to WHO Global Tuberculosis Control Report 2009, the maximum number of cases occurred in India (2.0 million), China (1.3 million), Indonesia (0.53 million), Nigeria (0.46 million) and South Africa (0.46 million) [4].

The slow growth of mycobacterium accounts for the complications in clinical management of TB. Despite the availability of effective chemotherapeutic agents along with BCG (Bacillus Calmette- Guérin) vaccination and control programs of WHO, the incidence of this deadly disease remains unabated. Also, the poverty stress, malnutrition, increases multiple drug resistance and incomplete treatment due to lengthy and laborious treatment of 6-9 months further leads to increase rate of reactivation. [5, 6, 7]

Current Therapeutic Implications For Tuberculosis: The current TB chemotherapy consists of first line drugs (Table 1, 2), isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), ethambutol (EMB) and streptomycin(S), given for 6 months [8]. In case, the drug resistance develops, the second-line drugs are used, such as thiacetazone, paraaminosalicylic acid, ethionamide, cycloserine, fluoroquinolones, kanamycin, amikacin and capreomycin, which have generally either low anti- tubercular efficacy or high toxicity [8, 15]. Newer agents such as ciprofloxacin, ofloxacin and moxifloxacin are active against *M .tuberculosis* as well as *M. avium* complex.

They penetrate cells and kill mycobacterium lodged in macrophages as well [9.] Because of their good tolerability, they are being increasingly included in combination regimens against MDR tuberculosis and MAC infection in HIV patients. But these drugs are associated with an increased risk of tendinitis and tendon rupture. This risk is further increased in those over age 60, in kidney, heart, and lung transplant recipients, and with use of concomitant steroid therapy [10]. Other newer agents such as azithromycin and clarithromycin(Table 1) bind to the 50S subunit of bacterial ribosomes, leading to inhibition of transpeptidation, translocation, chain elongation and, ultimately, bacterial protein synthesis [11-13.]

Clarithromycin has the same macrolide, 14- membered lactone ring as erythromycin; the only difference is that, at position six, a methoxy group replaces the hydroxyl group [11.]

Table 1: CURRENT THERAPEUTIC IMPLICATIONS FOR TUBERCULOSIS

DRUGS	DOSE	MECHANISM OF ACTION	ADVERSE EFFECTS	MARKETED PRODUCTS
Isoniazid	100, 300 mg Tabs	Inhibit synthesis of mycolic acid	Hepatitis, mental disturbances	ISONEX
Rifampin	150, 300 ,450, 600mg	Inhibit DND dependent RNA synthesis	Respirator syndrome, cutaneous syndrome	RCIN
Pyrazinamide	o. 5, 0.75, 1.0 g tablet	Inhibit synthesis of mycolic acid	Hepatotoxicity, hyperuricemia	PYINA
Ethionamide	0.5 -0.75 g	Act on both extra and intracellular organisms	Anorexia ,nausea, optic neuritis	ETHIDE, ETHIOCID
Ethambutol	0.2, 0.6, 0.8, 1.0 g tab	Inhibit arabinogalactan synthesis	Loss of visual acuity, optic neuritis	MYCOBUTOL, MYAMBUTOL
cycloserine	250 mg BD	Inhibit bacterial cell wall synthesis	CNS toxicity, tremorconvulsions	CYCLORINE, COXERIN
Para-amino salicylic acid	10-12 g	Inhibit folate synthase	Goitre, liver dysfunction, blood dyscrasias	
Clarithromycin	250, 500mg tablet	Inhibit bacterial wall synthesis	Hepatic dysfunctioning, rhabdomyolysis	CLARIBID' CLARIMAC
Azithromycin	250, 500mg capsules	Inhibit bacterial wall synthesis	Dizziness, headache, sinusitis	AZITHRAL, AZIWORK

Table 2: RECOMMENDED DOSES FOR TUBERCULOSIS [3]

Anti –TB Drugs	Daily treatment (mg/kg)	Maximum daily dose	Intermittent treatment three times per week(mg/kg)
Isoniazid(H)	5 (4- 10)	300 mg	10
Rifampicin(R)	10 (8- 20)	600 mg	10
Pyrazinamide(Z)	25 (20- 30)	2 g	35
Ethambutol(E)	20 (in children); 15 (in adults)	1,2 g	30
Streptomycin	15	1 g; (500- 750mg, if > 60 yrs or < 50 kg)	15

Azithromycin, in comparison, has a 15-membered ring and methyl- substituted nitrogen replacing the 9A carbonyl group. For this reason, azithromycin is more precisely referred to as an azalide rather than a macrolides. These structural changes have made the newer macrolides more acid-stable than erythromycin, providing improved oral absorption, tolerance, and pharmacokinetic properties.

The newer macrolides also have a broader spectrum of antibacterial activity than erythromycin [14] .However, both these drugs are also associated with side effects such as severe allergic reactions (rash; hives; itching; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); bloody stools; confusion; decreased urination; depression; emotional or mood changes; hallucinations; nightmares; severe diarrhoea; severe abdominal cramps; trouble sleeping. [9]

Drug Resistance in Tuberculosis: Drug resistance in mycobacterium is defined as a decrease in sensitivity of the bacteria with an agent to a sufficient degree to be reasonably certain that the strain concerned is different from a sample of wild strains of human type that have never come in contact with the drugs [15] . The current global concern in the treatment of tuberculosis (TB) is the emergence of resistance to the two most potent drugs *viz*., isoniazid and rifampicin.[16]

Types of Drug Resistance: There are two types of drug resistance in TB *viz.*, primary or acquired. When drug resistance is observed in a patient who has never received anti- TB treatment previously, it is termed primary drug resistance [13, 18].The level of initial drug resistance is an epidemiological indicator to assess the success of the TB control programme. Though drug resistance in TB has frequently been reported from India, most of the available information is localized, sketchy or incomplete [18, 19].

Acquired resistance is that which occurs in subjects as a result of specific previous treatment. The level of primary resistance in a given population is considered to reflect the efficacy of TB control measures in the past, while the level of acquired resistance is a measure of on-going TB control measures. However, the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Diseases (IUATLD), after several international discussions, have replaced the term primary resistance by the term “drug resistance among new cases” and acquired resistance by the term “drug resistance among previously treated cases” [17] .

Causes of Drug Resistance: The increasing emergence of multiple drug resistance [20, 21] in *M. tuberculosis* have been associated with a variety of management, medical health provider and patient-related factors (Table 3). This poses an urgent need of novel effective therapy that can not only be active against drug resistant TB but also shortens the duration of therapy.

TABLE 3: CAUSES OF DRUG RESISTANCE IN TUBERCULOSIS

List of Causes of Bacterial Drug Resistance
Deficient or deteriorating TB control programmes resulting in inadequate administration of effective treatment;
Poor case holding, administration of sub-standard drugs, inadequate or irregular drug supply and lack of supervision;
Ignorance of health care workers in epidemiology, treatment and control;
Improper prescription of regimens;
Interruption of chemotherapy due to side effects;
Non-adherence of patients to the prescribed drug therapy;
Availability of anti-TB drugs across the counter, without prescription;
Massive bacillary load;
Illiteracy and low socio-economic status of the patients;
Epidemic of HIV infection;
Laboratory delays in identification and susceptibility testing of *M. tuberculosis* isolates;
Use of nonstandardized laboratory techniques, poor quality drug powders and lack of quality control measures;
Use of anti-TB drugs for indications other than tuberculosis.

Future Prospects: Better and more effective therapeutic approach is needed to combat with the problems associated with complete eradication of TB. Understanding the bacterial structure, various aspects of its survival, biosynthesis of essential components and metabolism and then designing of such novel therapeutic agents which targets on these vital aspects of bacteria will help in bacterial death or unable it to persist. The availability of genome sequence of mycobacterium, mycobacterial genetic tools such as transposon mutagenesis, gene transfer and gene knockout, contributes greatly in target identification. In addition, targets involved in the biosynthesis of essential components of bacterial cell wall as well as the pathogenesis of the disease should also be considered for drug development. Besides identifying new targets, a systems biology approach is needed for using multiple drug combinations that hit multiple targets in different pathways to achieve the desired action [22].

Novel Drug Targets for Combating Tuberculosis:

1. **Mycobacterium Proteasome Inhibitors:** Recently, it has been reported that a protein- cleaving complex known as a proteasome is essential for the TB bacterium survival. This proteasome helps to remove damaged proteins and this clean up mechanism allows the mycobacterium to persist in the macrophages and possibly go on to cause active TB infection. Therefore, an approach to inhibit these proteasome can greatly improve the prospects for developing proteasome-based anti-tuberculosis treatments. One of the major complications in designing such compounds is that human cells also contain proteasome for degrading damaged proteins and hence this cleanup process is essential for human survival. So any drug intended for use as anti-TB should be highly specific in action. Understanding the unique structure and biochemistry of bacterial proteasome and designingsuch compounds that specifically inhibit the activity of Mycobacterium tuberculosis proteasome, could also serve as a novel target for effective treatment for TB [23].

2. **NAD^+ Synthetase Inhibitors:** NAD^+ is a coenzyme found in all living cells and is involved in a number of biosynthetic pathways such as regulating various cellular processes and in oxidation-reduction reactions. In humans, the NAD^+ biosynthetic pathways are independent of NAD^+ synthetase activity. But this enzyme is crucial for the survival of Mycobacterium tuberculosis and therefore an important drug target. Currently available anti-TB drugs target only the active form of mycobacterium and have very little effect on latent or non-replicating bacteria. Recent study reveals the fact that inhibiting NAD^+ synthetase enzyme also kills the non-replicating mycobacterium [24]. A structure-based drug designing of inhibitors that specifically inhibit *M. tuberculosis* NAD^+ synthetase enzyme may emerge as a potential therapeutic approach to combat and eliminate this infectious disease.

3. **Copper-Repressor Proteins Deactivators:** Researchers have now discovered a unique copper-repressing protein in the mycobacterium that may pave the way for new anti-TB treatment. When the host's immune cells (macrophages) engulf the invading bacterium, they dump excessive amount of copper onto the invader bacterium which leads to its cell death. Unfortunately, the invaders have developed their own defence mechanism in the form of a unique copper repressor protein that blocks the excessive copper and thereby protects the bacterium from host's copper attack [25]. An approach in a direction to design such compounds that diable the bacterium to fight against the host body's defense mechanisms by inhibiting the bacterium copper repressor protein could serve as a potential weapon against tuberculosis infection.

4. **LipB Protein Inhibitors:** LipB is an essential protein for the mycobacterium as it activates cellular machinery that drives bacterium's metabolism. Moreover, the M.tuberculosis has no backup mechanism that could take over LipB protein's role. Therefore, an inhibitor blocking the active sites of LipB would interfere with the metabolic processes of the bacterium needed for its survival and replication [26]. This would probably serve as an effective strategy for treating this infectious disease.

5. **LXR Protein Activators:** Liver X receptors (LXRs) are identified as key regulators of macrophage function, involved in lipid homeostasis and inflammation processes. An interesting study carried out by Korf et al, 2009 states that the mice treated with molecules that target LXRs were found to have a 10-fold decrease of the pulmonary bacterial burden and a comparable increase of Th1/Th17 function in the lungs [27]. This study revealed that the molecules that activate LXRs provided substantial protection from both a new mycobacterium infection and established infections. Therefore, LXR proteins can be suggested as a potential weapon in a war against TB.

CONCLUSION: The currently available anti-TB drugs were developed 40 years ago and there is a great need for a new generation of TB drugs that can meet the challenges of drug resistance tuberculosis as well as persistence of mycobacterium. The work done by scientists in the recent past years promises to provide desperately needed compounds that can be developed into drugs to treat tuberculosis more effectively, with an outcome of complete eradication of this global burden.

REFERENCES:

1. Cole E and Cook C: Characterization of infectious aerosols in health care facilities: an aid to effective engineering controls and preventive strategies. Am J Infect Control 1998; 26 (4): 453–464.
2. Global Tuberculosis Control Report 2009. Available from:URL:http://www.who.int/tb/publications/global_report/2009/pdf/full_report.pdf.
3. Varaine F et al: Tuberculosis , 5th edition 2010; 84-86.
4. WHO: Tuberculosis, a global emergency Bull 1996; 74: 840.
5. Corbett EL. et al: The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. Arch. Intern. Med. 2003; 163: 1009–1021.
6. Nachega JB and Chaisson RE: Tuberculosis drug resistance: a global threat. Clin. Infect. Dis. 2003; 36 (Suppl. 1): S24–S30.
7. Blumberg HM et al: American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am. J. Respir. Crit. Care Med. 2003; 167: 603–662.
8. Griffith D and Kerr C: Tuberculosis: disease of the past, disease of the present. J Perianesth Nurs 1996; 11 (4): 240–245.
9. Kumar V et al: Robbins Basic Pathology, 8th ed. Saunders Elsevier 2007; 516–522.
10. Kaufmann S: Protection against tuberculosis: cytokines, T cells and macrophages. Ann Rheum Dis 2002; 61(2): 54–58.
11. Stugill MC, Rapp R: Clarithromycin: Review of a new macrolides antibiotic with improved microbiologic spectrum and favoravle pharmavokinetic and adverse effect profiles. Ann Pharmacother 1992; 26: 1099.
12. Devaki V et al: Direct sensitivity test for isoniazid. Indian J Med Res 1969; 57: 1006-1010.
13. Jain NK et al: Initial and acquired isoniazid and rifampicin resistance to Mycobacterium tuberculosis and its implication for treatment. Indian J Tuberc 1992; 39: 121-124.
14. Rapp RP et al: New macrolides antibiotics: Usefulness in infections caused by mycobacteria other than Mycobacterium tuberculosis. Ann Pharmacother 1994; 28:1255.
15. Mitchison, DA: Drug resistance in mycobacteria. Br Med Bull 1984; 40: 84-90.
16. Sensi P et al: Rifomycin, a new antibiotic—preliminary report". Farmaco Ed Sci 1959; 14: 146–147
17. WHO/IUATLD: Global Project on Anti-tuberculosis Drug Resistance Surveillance. Anti-tuberculosis drug resistance in the world. Report No.2. WHO/CDS/TB/2000.278.
18. Paramasivan CN: An overview of drug resistant tuberculosis in India. Indian J Tuberc 1998; 45: 73-81.
19. Snider DE et al: Infection and disease among contacts of tuberculosis cases with drug resistant and drug susceptible bacilli. Am Rev Respir Dis 1985; 132: 125-132.
20. Jawahar MS. Multi-drug resistant tuberculosis. ICMR Bull 1999; 29: 105-1014.
21. Dorman SE and Chaisson RE: From magic bullets back to the magic mountain: the rise of extensively drug-resistant tuberculosis. Nat Med 2007; 13: 295–298.
22. Zhang Y: The magic bullets and tuberculosis drug targets. Annu. Rev. Pharmacol. Toxicol. 2005; 45, 529–564.
23. Cheng Y and Pieters J*:* Novel Proteasome Inhibitors as Potential Drugs to Combat Tuberculosis. Journal of Molecular Cell Biology 2010, *1:* 1-3.
24. LaRonde-LeBlanc et al: Regulation of active site coupling in glutamine-dependent NAD synthetase**.** Nature Structural & Molecular Biology 2009; 16: 421-429.
25. *Wilmot CM:* Fighting toxic copper in a bacterial pathogen. Nature Chemical Biology 2007*;* 3, 15 – 16.
26. Butcher EC et al: Systems biology in drug discovery .Nat.Biotechnol 2004; 22, 1253-1259.
27. Korf et al: Liver X receptors contribute to the protective immune response against Mycobacterium tuberculosis in mice. Journal of Clinical Investigation 2009; 119(6): 1626–1637.