TUBERCULOSIS TODAY & TOMORROW

Dr. G. Srividhya, *Associate Professor*

Department of Pulmonary Medicine, Shri Sathya Sai Medical College and Research Institute, Sri Balaji Vidyapeeth, Nellikuppam, Kancheepuram Dist., Tamil Nadu – 603 108, India.

Epidemiology:

Tuberculosis (TB) is second only to HIV/AIDS as the greatest killer disease worldwide due to a single infectious agent. In 2014, 9.6 million people were diagnosed with TB, of which 1.2 million people were diagnosed with HIV[1]. 5.4 million men were diagnosed with the disease. An estimated 1 million children were struck with TB.

The largest number of new TB cases occurred in the South-East Asia and Western Pacific Regions, accounting for 58% of new cases globally in 2014. The 6 countries that contribute to largest number of incident cases in 2014 were India, Indonesia, Nigeria, Pakistan, People's Republic of China and South Africa.

Death due to TB in 2014.	
TOTAL DEATHS DUE TO TB	1.5 MILLION
DEATH DUE TO TB IN HIV	0.5 MILLION
DEATH DUE TO TB IN WOMEN	4,800,000
DEATH DUE TO TB IN WOMEN WITH HIV	1,40,000
DEATH DUE TO TB IN MEN	8,90,000
DEATH DUE TO TB IN CHILDREN	1,40,000

Drug-Resistant TB:

Globally in 2014, an estimated 480 000 people developed MultiDrug-Resistant TB (MDR TB) and there were an estimated 190 000 deaths from MDR TB. 123 000 people were diagnosed with MDR TB in 2014, about a quarter of the total 480 000 new cases of MDR-TB that occurred in 2014. Globally, data show an average cure rate of only 50% for treated MDR-TB patients.

Extensively drug-resistant tuberculosis, or XDR-TB, is a strain of tuberculosis, that is resistant to four commonly used anti-TB drugs (INH,RIF,one injectable second line drug & quinolones). XDR-TB has been reported by 105 countries by 2015. An estimated 9.7% of people with MDR-TB have XDR-TB. There are an estimated 40,000 people infected with XDR-TB today. XDR-TB is emerging as an extremely deadly global threat. There is no regulatory-approved regimen for curing XDR-TB. Treatment of XDR-TB is difficult because of longer duration of treatment with drugs that have serious toxicity & cost of treatment is also very high.

Recent Advances in diagnosis of Drug Resistant TB:

The use of the rapid test Xpert MTB/RIF has been in use since 2010. By 2015, 69% of countries recommended using Xpert MTB/RIF as the initial diagnostic test for people at risk of drug-resistant TB, and 60% recommended it as the initial diagnostic test for people living with HIV. The Xpert MTB/RIF assay, detects Mycobacterium tuberculosis with a limit of detection (LOD) of 130 CFU/ml sputum, and detects mutations in the MTB rpoB gene which cause rifampicin resistance (RIF-R).

Disadvantages of Xpert MTB/RIF:

1. Limited sensitivity (60 – 80%) in smear-negative TB.
2. False RIF resistance have been reported which is attributed to abnormal real-time PCR curves or miss-identification of RIF-susceptible (RIF-S) synonymous rpoB mutants as RIF-R.

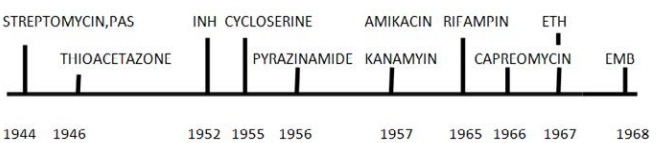
An upfront in diagnostic test for MDRTB called the GeneXpert Omni is in development. GeneXpert Omni by the virtue of its portability caters to molecular diagnostic testing into disseminated locations.

Advantages of GeneXpert Omni

- Small and Portable
- Proven Cartridge Technology
- Durable
- Low Power Consumption
- Automatic Connectivity
- Solid State
- Integrated Battery

A next-generation cartridge called **GeneXpert Ultra** is also in development. This could potentially replace conventional culture as the primary TB diagnostic tool. The Xpert MTB/RIF Ultra is a cartridge-based nested PCR amplification capable to amplify patient DNA sample more accurately. The current Xpert MTB/RIF test has a limit of detection (LOD) of 130 CFU/ml. A larger DNA reaction chamber in the cartridge will enable Xpert MTB/RIF Ultra to bring the LOD down ten-fold, to approximately 10 CFU/ml (across all strains) — a level similar to or potentially better than liquid culture. The new Ultra assay is much more sensitive than Xpert & the specificity of Ultra RIF-R is likely to be higher. The Ultra assay is expected to increase TB detection in smear-negative patients and provide more reliable RIF-R detection.

Recent Advances in Treatment of Tuberculosis:



From the above line diagram it is quite evident that there has been no discovery in the anti tubercular treatment over the past 45 years.

Short falls of current TB regimens:

- Long duration of treatment (6-9 months duration)
- High relapse rate in some subgroups (15%)
- Interactions with HIV treatment
- Inadequate drugs to treat XDR strains.

Why do we need new drugs to treat TB?

- Shorten overall treatment duration
- Lower relapse rates
- Development of regimens with fewer adverse effects, particularly less hepatotoxicity
- Novel drugs that can be given easily and safely in combination with Anti Retroviral Therapy
- Regimens that are effective in treating MDR-TB/XDR-TB & shorten the duration of treatment.

Novel drugs in clinical trials are:

NEWER DRUG	PHASE OF CLINICAL TRIAL
DELAMANID	PHASE 2
PA 824	PHASE 2
SQ109	PHASE 2
LL 3858	PHASE 2
SUTEZOLID	PHASE 2
AZD -5847	PHASE 1

Repurposed drugs include members of the fluoroquinolone, oxazolidinone, riminophenazine and rifamycin families.

Bedaquiline is a diarylquinoline which inhibits Mycobacterial ATP Synthase & approved by the FDA in December 2012, & it was the first new medicine formulated against TB after forty years.

Considerable controversy exists regarding approval of the drug, as the FDA's ruling was based on a treatment outcome Vs patient deaths. In the clinical trials, death rates among patients taking Bedaquiline were more (a rate of death of 11.4% in the treatment group, compared to 2.5% in the control group)[5], even though they had resolution of TB based on sputum cultures. It is for this reason that the label comes with a caution of "INCREASED MORTALITY; QT PROLONGATION" & it is used only when an effective alternative treatment regimen is not available.

Delamanid (OPC67683), a dihydro-nitroimidazooxazole derivative is an experimental drug for the treatment of MDR TB .It is a pro-drug that is activated by the enzyme deazaflavin dependent nitroreductase (Rv3547). A reactive intermediate metabolite, formed between delamanid and desnitro-imidazooxazole derivative, is known to inhibit mycolic acid production. It inhibits the synthesis of mycobacterial cell wall components, namely the methoxy mycolic acid and ketomycolic acid . Delamanid also causes QT prolongation[6].

Delamanid was associated with an increase in sputum-culture conversion at 2 months among patients with MDR TB. Delamanid remains a promising drug in treating MDR-TB, XDR-TB, and TB in HIV because of its better efficacy, minimal toxicity, and absence of interaction with ART.

Pretomanid (PA 824) is a bicyclic nitroimidazole-like molecule with a very complex mechanism of action. It is active against both replicating and hypoxic, non-replicating Mycobacterium tuberculosis. The aerobic bactericidal mechanism of this drug appears to involve inhibition of cell wall mycolic acid synthesis. The respiratory poisoning through NO release seems to be important for its anaerobic activity .

The combination of Moxifloxacin, Pretomanid, and Pyrazinamide (MPaZ regimen)[4] with the aim of shortening the duration of treatment is under trial . In phase 2 trial it was a safe, well tolerated regimen with better bactericidal activity in drug-susceptible tuberculosis during 8 weeks of treatment. Results are consistent with both drug-susceptible and MDR tuberculosis. This regimen is ready for phase 3 trials in patients with drug-susceptible tuberculosis and MDR-tuberculosis.

Nix-TB tests a 3 drug regimen consisting of **Bedaquiline**, a drug with conditional regulatory approval; **Pretomanid**, which is under trial; and **linezolid**, an oxazolidinone antibiotic that has been used off-label to treat TB. This trial may be effective in people with XDR-TB who have no other treatment options. It includes patients as young as 14 and those who are co-infected with HIV with a CD4 count of 50 or higher. Nix-TB is an open-label trial that enables patients to be assessed at regular intervals with the aim of being cured in six to nine months. Participants are also monitored for two years after completing treatment to ensure they do not relapse.

Newer Vaccines

The only vaccine against M. TB, Bacille Calmette-Guérin (BCG), discovered in 1921, has variable protective efficacy. WHO recommends vaccinating HIV-uninfected infants with BCG as it provides protection against severe extrapulmonary forms of paediatric TB. However its efficacy in protecting against pulmonary TB is variable .

A safe, effective and cheap vaccine against TB will contribute to a great advance in the control of Tuberculosis. 16 TB vaccine candidates are in Phase IIb studies in the field at present. 5 of which are based on whole cell mycobacteria, and the rest are sub-unit vaccines in which MTB antigens are expressed as recombinant proteins that are formulated with adjuvants or presented in recombinant viral vectors.

"Modified Vaccinia Ankara", MVA- a pox virus vectored vaccine expressing the Mycobacterium tuberculosis antigen 85A, is under phase IIb "Proof-of-concept" (PoC) trial in South Africa.

Current TB vaccine candidates are designed to be either

- A prime vaccine that prevents TB infection as well as disease in infants who have not been infected with MTB.
- A booster vaccine, which when administered during adolescence would prevent reinfection or arrest progression to active disease for those who are latently infected, as BCG immunity wanes.
- Immunotherapeutic vaccine as an adjuvant with ATT for TB patients, to shorten the duration of treatment and/or reducing relapse rates.

Auxotrophic Vaccine

To overcome the adverse affects of BCG vaccines in immunodeficient patients , auxotrophic strains of BCG are under study to assess their safety profile and efficacy against tuberculosis in people at risk for HIV.

DNA Vaccine

A novel tuberculosis (TB) vaccine; a combination of the DNA vaccines expressing mycobacterial heat shock protein 65 (HSP65) and interleukin 12 (IL-12) delivered by the hemagglutinating virus of Japan (HVJ)-liposome or-envelope (HSP65 + IL-12/HVJ) is under development. The addition of IL-12 was found to augment Th1 response in a dose-dependent manner and offered a protective immune response against a virulent challenge.

Subunit Vaccine

By using the techniques of recombinant DNA, several antigens like heat shock protein (hsp) 60, hsp70, Ag85, ESAT-6 and CFP10 etc have been identified as new candidate vaccines against TB.[7]

The ESAT-6 antigen from Mycobacterium tuberculosis is a dominant target for cell-mediated immunity in the early phase of tuberculosis (TB) in TB patients as well as in various animal models. Vaccination with ESAT-6 delivered in a combination of monophosphoryl lipid A(MPL) an immunomodulator and dimethyl dioctadecyl ammoniumbromide (DDA) provoked a strong ESAT-6-specific T-cell response and protective immunity comparable to that achieved with Mycobacterium bovis BCG has been showed in various studies.

Adjuvants

There is a marked difference in the immune responses induced by the different adjuvants and both IFA (incomplete Freund's

adjuvant), (DDA) are identified as potential adjuvants for a TB subunit vaccine. DDA coadjuvanted with either the Th1-stimulating polymer poly (I-C) or other cytokines like IFN gamma, interleukin 2 (IL-2), and IL-12 are under trial[8].

REFERENCES:

1. WHO Global Tuberculosis Report 2015.
2. Multidrug-resistant tuberculosis (MDR-TB) 2015 update.
3. Xpert MTB/RIF Ultra: A New Near-Patient TB Test With Sensitivity Equal to Culture David Alland, Rutgers New Jersey Medical School, Newark, NJ, United States.
4. Expert Opin Investig Drugs. 2013 Jul;22(7):927-32. doi: 10.1517 /13543784.2013.801958. Epub 2013 May 21. PA-824, moxifloxacin and pyrazinamide combination therapy for tuberculosis.
5. Dawson R, Diacon A. Mahajan, R. (2013). Bedaquiline: First FDA-approved tuberculosis drug in 40 years". International Journal of Applied and Basic Medical Research 3(1): 1–2.
6. Gler, M. T et al .Delamanid for Multidrug-Resistant Pulmonary Tuberculosis. New England Journal of Medicine 2012; 366 (23): 2151–2160.
7. Current Pharmaceutical Biotechnology, Volume 2, Number 2.
8. Biotechnology in the Development of New Vaccines and Diagnostic Reagents Against Tuberculosis.