EDITORIALS

Tuberculosis-A Tough Bug

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Introduction[1]

Over hundred years after Robert Koch's discovery of tubercle bacillus, Mycobacterium is still affecting mankind and may continue to do so in the near future.Tuberculosis is an age-old scourge to humankind which has afflicted throughout known history and human prehistory. Presently, the appearance of extensively drug-resistant tuberculosis (XDR-TB) in addition to multidrug- resistant TB (MDR-TB) has further complicated TB control at the global level. Equally alarming is the emergence of another form of virtually incurable drug-resistant isolates, known as extremely drug resistant TB (XXDR-TB). XXDR-TB isolates showed in-vitro resistance to all first- and second-line drugs tested. Such strains brought us back to the pre-antibiotic era and underlined the need to develop urgently new drugs and apply correctly the existing policies and strategies of TB control programs.[1]

Drug resistant (DR), Multidrug-resistant (MDR), extensively resistant (XDR) TB-Definitions[2]

Development of resistance to Antitubercular drugs is a key health issue that threatens the progress made in the management of tuberculosis globally. The primary reason for development of drug resistance is inappropriate use of anti-tubercular drug regimen in drug susceptible TB patients. Depending upon the degree of drug resistance the patients are classified into various categories like mono-drug resistance, Poly-drug resistance, Multidrug-resistant TB (MDR), extensively resistant TB (XDR TB) etc.

The term drug resistance or DR-TB was used for mono-drug resistance (resistance to one first-line anti-tubercular drug only) and poly-drug resistance (resistance to more than one first-line anti-TB drug other than both isoniazid and rifampicin). Multidrug-resistant TB (MDR-TB) is TB that does not respond to at least isoniazid and rifampicin, the 2 most powerful anti-TB drugs.Pre–XDR was referred to as multidrug resistance along with resistance to a fluoroquinolone or second-line injectable agent but not both. XDR TB is MDR TB with concomitant resistance to any fluoroquinolone and to at least 1 of 3 injectable second-line anti-TB drugs: amikacin, kanamycin, or capreomycin.

Within a year of the first reports of extensively resistant TB (XDR-TB) in 2006, isolated cases were reported in Italy that had resistance to all first-line anti-TB drugs (FLD) and second-line anti-TB drugs (SLD) that were tested. In 2009, a cohort of 15 patients in Iran was reported which were resistant to all anti-TB drugs tested. The terms 'extremely drug resistant' ('XXDR-TB') and 'totally drug-resistant TB' ('TDR-TB') were given by the respective authors reporting this group of patients. 4 patients from India with 'totally drug resistant tuberculosis ('TDR-TB') were described, along with subsequent reports of a further 8 cases. So the term TDR was coined for strains that are resistant to all the first line drugs as well as all the second line TB drugs that can be tested for. Different countries and indeed regions vary in which second line drugs they can test for. However, this term is not officially recognized by WHO yet.

Although the initial development of drug resistance in patients receiving anti-TB therapy is often due to multiple factors—primarily suboptimal drug concentrations and varying degrees of nonadherence to therapy—transmission of drug-resistant *M. tuberculosis* has been observed, particularly in countries with high numbers of patients coinfected with HIV. Due to their compromised immune systems, these patients are at higher risk for developing active TB infection and therefore may contribute significantly to the spread of MDR/XDR TB.

Prevalence of TB[3]

Despite a concerted global effort to reduce the tuberculosis burden, TB is the ninth leading cause of death worldwide and the leading cause of death from a single infectious agent, ranking above HIV/AIDS. In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people (down from 1.7 million in 2000) and an additional 374 000 deaths among HIV-positive people. An estimated 10.4 million people were affected with TB in 2016 and 56% of these patients were found in these five countries: India, Indonesia, China, the Philippines and Pakistan. Drug-resistant TB is another continuing threat. In the year of 2016, there were 600000 new cases with resistance to rifampicin (RRTB), the most effective first-line drug, of which 490 000 had multidrug-resistant TB (MDR-TB). Out of these around 47% of cases were in India, China and the Russian Federation.

India accounts for one fourth of the global TB burden. According to WHO TB report 2017, for the year 2016 estimated incidence of TB in India is 2.79 million cases (including HIV+TB) & mortality rate of 423,000 (excludes HIV+TB).Global TB Report 2016 has estimated that India has highest burden of both TB and MDR TB. An estimated 1.3 lakhs incident multi-drug resistant TB patient emerge annually in India which includes 79000 MDR-TB Patients estimates among notified pulmonary cases. India has second highest number of estimated HIV associated TB. An estimated 1.1 lakh HIV associated TB occurred in 2015 and 37,000 estimated number of patients died among them.

Prevalence of TB in urban and rural population[4]

Epidemiological variations in urban and rural population holds significance in highly populated and resource poor country like India. Considerable differences in incidence and prevalence of drug resistant Tb cases have been reported in urban and rural settings in various clinical trials across the country.

Several studies on epidemiology of TB in urban/rural population from West of India included metropolitan cities such as Mumbai, Pune and major cities from Gujarat, underlining the rapid

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emergence of DR- and MDR-TB in over-populated urban locales. Increased risk of infection transmission due to crowding, Shortfalls in community TB control programs and most importantly, the high variability in the anti-TB treatment regimens prescribed by healthcare professionals, particularly in the private sector are some potential factors attributable to this upsurge.

However, studies have reported that in rural areas MDR-TB patients had higher chances of disease worsening to lead to XDR-TB; on the contrary, in patients who belonged to urban areas XDR-TB formed a smaller subset of MDR-TB patients. This may be an incidental finding and may signal at ignorance of rural patients towards available treatment options or possibly poor coverage of programmatic services in such areas. The high incidence of MDR-TB in urban setting in India highlights the need for drug susceptibility testing to be done for every patient whose culture is positive for M. tuberculosis. The anti Tb treatment given to the patients in the urban area needs to be strictly monitored, since many doctors frequently prescribe inadequate therapy.

Socioeconomic factors and drug resistant TB[5]

Association between TB and poverty is known for centuries and it also applies for MDR-TB as it is more commonly seen in patients belonging to lower socio-economic class. Poor nutrition is directly associated with adverse outcome in form of death and default in long term treatment of MDR-TB. Low socioeconomic status is associated with factors like overcrowding, poor hygiene, Illiteracy and ignorance about the disease, affordability of treatment and poor treatment adherence.

There is scarcity of data on socio-economic risk factors for tuberculosis in India. A Study showed that tuberculosis imposes high direct and indirect costs on the patients, leads to loss of wages for an average of 3 months and leads to school drop-outs in about 20% children, negatively impacting patient's life. The importance of socio-economic development in enhancing anti-TB efforts has been repeatedly emphasized. Also, successful implementation of tuberculosis control program is likely to have a direct tangible economic and social benefit.

Poor control of drug resistant TB[6]

There are many challenges in the management of drug resistant TB in Indian set up. The country hasmany problems of proper management by program personnel, continuous supply of quality assured drugs, implementation of DOTS in its true spirit, political commitment in form of monetary support, maintenance of quality assurance diagnostics, and proper reporting and recording of cases. While the availability of inexpensive drugs facilitates drug-resistant TB, it's only one factor.

Inaccurate diagnostic testing of drug resistance is another important issue contributing to poor control of drug resistance to TB. The United Nations–based, Stop TB Partnership reports that India's public health sector relies almost entirely on smear microscopy to diagnose TB. The drug-resistance testing is offered only to a small subset of all TB patients.Inadequate and inaccurate testing, and other issues, often means substandard treatment. About 60%– 80% of Indian population with TB choose private over public care. But many private practitioners defy government rules and don't report the disease, much less follow up with patients to ensure they are following standard treatment. Another factor contributing to the increase in DR-TB, is nonadherence to the AntiTB therapy, although concrete figures are elusive. Few patients quit when they begin to feel better after a few weeks, while others do so as the drugs are too expensive for them. Side effects, particularly with DR-TB treatment, can also lead to noncompliance.

Study by Dr Swapnil Jain & his group from Ujjain looks at the clinico radiological & socio economical profile of 474 patients of MDR TB in rural set up. They studied MDR TB patients over 3 years from 2013 to 2016 at DR TB center at Medical College & observed their socio economic, clinical & radiological pattern. It is seen that delay in diagnosis, improper treatment, lack of awareness, poor compliance, poor nutrition are few of the important features that needs urgent attention. Treatment of Associated co morbidity is of equal importance in overall management of patients. Their study observes significant prevalence of MDR TB in productive age group. This trend will have huge long term consequences on our country economy.

Way forward[7]

Overall, the emergence of XDR-TB reminds that global TB control necessitates a sustained dedication by scientific, political and financial authorities. One of the important priorities is to effectively diagnose XDR-TB in clinical practice by strengthening the laboratories worldwide. All the reference laboratories in the country should be well equipped with high quality conventional Drug sensitivity testing (DST) for all the Second line drugs (SLDs) to diagnose XDR-TB effectively. Based on the current scenario, the effective management of XDR-TB depends on well thought out prescription of SLDs to reduce morbidity and mortality and transmission. The TB control programs should emphasize on policies focusing on the effective use of first-line drugs in every new patient so as to prevent the emergence of MDR-TB, XDR-TB and XXDR-TB or TDR-TB.

Considering the mammoth impact of TB on Indian healthcare Prime Minister Narendra Modi has Launched the TB Free India Campaign at 'Delhi End TB Summit' and has set a target for complete elimination of Tuberculosis (TB) by 2025, five years ahead of the global target of 2030. The government is implementing a national strategic plan (NSP) to end TB by 2025 for the next three years to ensure every TB patient has access to quality diagnosis, treatment and support. The new NSP adopts a multi-pronged approach which aims to detect all TB patients with an emphasis on reaching TB patients seeking care from private providers and undiagnosed TB in high-risk populations, treat all patients irrespective of where they seek care adopting a patient-centric approach, prevent emergence of TB in susceptible population groups and build empowered institutions and human resources to streamline implementation.

Considering the alarming rise in the incidence of drug resistance to anti TB drugs, this may be our last chance to combat this deadly disease. As my teacher Prof Dir Dr. K. C. Mohanty used to say, "Life takes one full circle!". We must choose wisely or having exploited all options, we will again be left banking on potions or prayers to control TB.

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Immune Checkpoint Inhibitors Discovery Bag the Nobel

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The Nobel Prize in Physiology and Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation. Cancer still continues to be the greatest health challenge as it kills millions globally. By stimulating the inherent ability of our immune system to attack tumor cells, this year's Nobel Laureates have established an entirely new principle for cancer therapy. James P. Allison studied cytotoxic T lymphocyte antigen 4 (CTLA 4) that functions as a brake on the immune system.[1] The potential of releasing this brake can unleash our immune cells to attack tumors. This concept has been utilised to create an anti-cancer drugs which have revolutionised the treatment of metastatic cancers. Simultaneously, Tasuku Honjo discovered a protein on immune cells responsible for programmed cell death (PD-1) which also operates as a brake. The seminal discoveries by these two Laureates constitute a landmark in the fight against cancer. Cancer therapeutics have earlier also received Nobel prizes. For e.g. Hormone treatment for prostate cancer (Huggins, 1966), chemotherapy (Elion and Hitchins, 1988), and bone marrow transplantation for leukemia (Thomas 1990).

The fundamental property of our immune system is the ability to discriminate "self" from "non-self" antigens. T cells that bind to non-self antigens trigger the immune system to engage in self-defense. T cell accelerators or T cell brakes can augment or ameliorate the T cell immune responses respectively. This intricate balance between accelerators and brakes is essential for tight control of the functioning of the T cell mediated immune response. Way back in 1990 James P. Allison at University of California, Berkeley studied the T-cell protein CTLA-4 and developed an antibody that could bind to CTLA-4 and block its function. He investigated if CTLA-4 blockade could disengage the T-cell brake and unleash the immune system to attack cancer cells. He was successful in treating the cancer in the experimental mice in 1994. Finally in 2010 his experiment got translated into an important clinical study which cured patients suffering from advanced melanoma and thus; the anti CTLA 4 drug Ipilimumab was born which received approval from FDA for the treatment of Refractory Melanoma.

In 1992, a few years before Allison's discovery, Tasuku Honjo discovered PD-1, another protein expressed on the surface of T-cells. In animal experiments, PD-1 blockade was also shown to be a promising strategy in the fight against cancer, as demonstrated by Honjo. In 2012, a key clinical trial demonstrated the efficacy of anti PD-1 drugs in the treatment of patients with different types of cancer. Results were dramatic, leading to long-term remission and possible cure in several patients with metastatic cancer, a condition that had previously been considered essentially untreatable.

Immune checkpoint therapy for cancer today and in the future

After the initial studies showing the effects of CTLA-4 and PD-1 blockade, the clinical development has been dramatic. We now know that the treatment, often referred to as "immune checkpoint therapy", has fundamentally changed the outcome for patients with advanced cancer. But similar to other cancer therapies, adverse side effects are seen, which can be serious and sometimes even life-threatening. They are caused by an overactive immune response leading to autoimmune reactions, but are usually manageable. Intense continuing research is focused on elucidating mechanisms of action, with an aim of improving therapies and reducing side effects. Of the two treatment strategies, checkpoint therapy against PD-1 has proven more effective and positive results are being observed in several types of cancer, including lung cancer,[2] renal cancer,[3] hepatocellular carcinoma,[4] and melanoma.[5] New clinical studies indicate that combination therapy, targeting both CTLA-4 and PD-1, can be even more effective, as demonstrated in patients with melanoma by combination of Ipilimumab (anti CTLA 4 antibody) and Nivolumab (anti PD1) or Pembrolizumab(anti PD-1 inhibitors). Thus, Allison and Honjo have inspired efforts to combine different strategies to release the brakes on the immune system with the aim of eliminating tumor cells even more efficiently. A large number of immune checkpoint therapy trials are currently underway against different types of cancer, and new immune checkpoint proteins are being tested as targets.

For more than 100 years scientists attempted to engage the immune system in the fight against cancer. "Immune Checkpoint" therapy has now revolutionized cancer treatment and has fundamentally changed the way we view how metastatic cancer can be managed.

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