International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

A Review on Prevention, Diagnosis, Treatment and Rehabilitation of Tuberculosis

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ABSTRACT:

Tuberculosis (TB), known as the White Plague is of great significance to humanity for the magnitude of morbidity and mortality it has generated over centuries from the very start of human civilization. In this Review, we will describe the history of prevention (vaccination and management of TB infection), diagnosis, treatment, and pulmonary rehabilitation of post-treatment sequelae. The article leads the reader through the main discoveries which paved the way to the modern approach to TB prevention and care. The history of the Bacille Calmette-Guerin (BCG) vaccine and of the diagnosis and treatment of TB infection are presented, together with that of the diagnosis and treatment of TB disease. Pivotal was in 1882 the discovery by Robert Koch of the aetiological agent of TB, and his pioneering work in culturing the bacillus and developing tuberculin. Also of enormous importance was, in 1895, the discovery of the X-rays by Wilhelm Conrad Rontgen, € discovery which paved the way for the development of modern imaging technologies.To complement this, the more recent history of rehabilitation of post-treatment sequelae is summarized, given the importance, this issue has on patients' well-being and Quality of Life.

Keywords: Tuberculosis, Prevention, Disease, Treatment, Diagnosis.

INTRODUCTION:

There are several approaches to describe the history of tuberculosis (TB), a disease which has been identified for a long time as 'THE' disease, the 'consumption', or 'The White Plague'. TB is of great significance to humanity for the magnitude of morbidity and mortality it has generated over centuries from the very start of human civilization. More recently, clinicians and scientists have devoted their lives to fight TB and set the scene developing our understanding through modern scientific approach in different areas such as microbiology, vaccination and development of new drugs and regimens [1,2]. The raising evidence that an important proportion of patients completing anti-TB treatment sufferers of TB sequelae has brought the issue of rehabilitation to the attention of scientific community. In this Review, we will describe the history of prevention (vaccination and management of TB infection), diagnosis, treatment and pulmonary rehabilitation of post-treatment sequelae**.**

History of tuberculosis prevention:

TB prevention includes two main areas, vaccination and management of TB infection. While vaccination aims at preventing TB by activating immunity, management of TB infection is focused at identifying individuals harbouring TB infection and killing the bacilli to prevent future cases from occurring. In reality, TB is one of a few diseases for which the most effective form of prevention is represented by the timely diagnosis and treatment of infectious cases, a strategy traditionally known as

TB Control [3]. The TB Elimination strategy, focused on TB infection management and prevention of the occurrence of future cases, is considered an additional strategy to be undertaken particularly in higher resource low-TB incidence settings [4−11] In 2014 the World Health Organization (WHO) launched the End TB Strategy, adding in its Pillar 1 the 'Integrated patient-centred care and prevention' - which for the first time devoted diagnosis, treatment and prevention interventions amongst core prevention activities [11].

Vaccination for tuberculosis:

Bacille Calmette-Guerin (BCG) vaccination with the attenuated Mycobacterium bovis strain was developed by the French researchers Albert Calmette (1863-1933) and Camille Guerin (1872-1961) and was first used for TB prevention in 1921 [12]. Repeated subcultures of the virulent strain of M. bovis, produced a live attenuated strain that could be safely inoculated into humans. BCG was first administered to an infant in 1921 and early trials suggested it provided protection to high-risk children [13]. If administered early enough in life (ideally at birth), it prevents haematogenous spread and severe forms of TB like meningitis. The efficacy of BCG however reduces with age, and there is no evidence that re-vaccination(s) improves protection. Some discrepancies in the results of BCG clinical controlled trials were probably due to the creation of different strains of BCG in different laboratories across the globe, with genotypic and phenotypic differences. Initial acceptance was slow and then virtually stopped following the Lubeck disaster in 1930 € [14]. After World War II, vaccination was vigorously promoted by the United Nations International Children's Emergency Fund (UNICEF). For decades, BCG was the most frequently used vaccination worldwide. It is especially valuable in preventing miliary TB and TB meningitis in infants and young children, but is much less effective in elderly adults and against other forms of TB [15]. Having non-specific immunogenic properties, BCG is currently undergoing evaluation for protective efficacy against some disease [16−18]

Rehabilitation:

While recommended for use, it is important to remember these assays have reduced sensitivity in certain populations such as children and patients coinfected with HIV, as well as in extrapulmonary TB [19]. Moreover, this technology is expensive and requires laboratory facilities with continuous access to power. To overcome this obstacle in resource-limited settings, there are a number of smaller, battery-operated technologies in development. To date, the GeneXpert Omni (Omni; Cepheid) appears to be the most promising potential candidate for widespread use. In a real-world analysis, it has been shown to be a cost-effective method when used in peripheral healthcare settings [20]. It allows diagnosis to be at/near the point of care, and thus avoids further delays and costs associated with transporting samples to specialised centres. As well as the Omni, Cepheid is also developing the Xpert MTB/XDR assay. It aims to also detect resistant to INH, FLQ, ethionamide (ETH) and SLID. Similar to other Xpert assays, it is a NAAT that detects 16 clinically relevant mutations associated with resistance in under 90 min [21]. When compared with phenotypic drug sensitivity testing (pDST), it has a 94% sensitivity and 100% specificity at detecting drug resistance [21]. There are large scale multicentre clinical trials ongoing to establish its real-world efficacy as a follow-on test to current Xpert MTB/RIF and MTB/RIF Ultra assays, prior to consideration for WHO recommendation. This assay is of paramount importance as the early recognition of drug resistance is a prerequisite to shorter drug regimens, which will be discussed in further detail elsewhere in this review. While most biomolecular tests are NAAT detecting the presence

of Mtb DNA, the LF-LAM test detects a lipopolysaccharide present in mycobacterial cell walls. While not in use in most countries in the developed world, the LF-LAM assay has been recommended for use in HIV-coinfectedpatients. It is a urinary antigen test that is often employed in resource-limited settings, and is of particular benefit in cases where a sputum sample cannot be obtained. It has a 42% sensitivity in HIV patients with TB symptoms [22]. However, it cannot distinguish between mycobacterial species, and can cross react with other fungal diseases. As such, it is used as an initial test in peripheral primary care centres in areas of high TB endemicity only, to determine whether symptomatic patients with HIV should be referred for further confirmatory testing [23]

Treatment

Alongside research into obtaining accurate and timely diagnostics, there is tremendous work ongoing in developing safe, efficacious, tolerable treatment regimens. The goals of treatment are not only to eradicate disease, but to prevent long-term morbidity arising from either the disease itself or as an adverse effect of the drugs in use. Successful treatment of drug-sensitive TB (DS-TB) has been reported in 85% of patients [24]. Efficacy in drug-resistant forms is lower at 57% and is likely multifactorial [24]. To reflect this, there has been a trend towards oral drug regimens, where possible, given research highlighting patient preference and cost-effectiveness of these drugs [25]. We need to deliver a regimen that will not only aid our global goal of TB eradication, but in a manner that reflects our patients' wishes, and in doing so, promotes their compliance.

New treatment:

Drugs At present, there are 16 new drugs in phase I or II clinical trials, and 22 other drugs in discovery or preclinical phases of development, as outlined in figure 1. Of those drugs undergoing clinical trial, there are 11 drugs of new chemical classes. Of the remaining drugs, TBAJ-587 and TBAJ-876 are diarylquinolines, similar to BDQ, while delpazolid, sutezolid and TBI-223 are oxazolidinones, similar to LZD and cycloserine. At the time of publication, no new drugs have reached phase III trials or been approved for market regulation since the approval of pretomanid (Pa) in 2019. A promising candidate from a new drug class is telacebec. It induces bacterial cell death by inhibiting the mycobacterial cytochrome bc1 complex responsible for ATP synthesis. A proof-of-concept trial has shown increased rates of sputum clearance, with comparable levels of adverse events to currently approved drugs. If results from ongoing clinical trials continue to reflect this, it is likely to be approved as a third new modern drug class with anti-tuberculous activity [26]. This would be an important achievement as many of the other drugs in development are classified similarly to existing drugs, and as such their use in additive or substitutive places for their relative counterparts will be precluded due to concerns regarding toxicity or resistance. It is also interesting to note that these drugs in development are largely oral preparations, owing to patient preference and thus potential for greater adherence and cure.

Vaccination:

Given the current prevalence of TB infection, with the associated lifetime risk of progressing to active disease, it is paramount that we protect future generations from this burden by halting transmission entirely. With greater understanding of the cellular processes involved in Mtb susceptibility and pathogenesis, scientists have been able to identify various potential targets with a role in vaccination. Central to this is the cellular immune response, with a need to upregulate T-helper cell (Th)1, and

downregulate Th2 and regulatory T-cell responses [27]. It appears that Mtb has also recognised the need to adapt to this hypo-inflammatory phenotype with more modern strains displaying shorter latency and higher virulence than previously seen [28].

Culture-based drug sensitivity testing (DST)

As previously mentioned, the major advantage of liquid culture is rapidity of growth, which has led to more widespread use of liquid broth-based methods such as the MGIT. BACTEC MGIT 960 is a fully automated system that delivers results within 2 weeks [29]. Culture-based DST remains the gold standard for determining drug resistance at present. The two approaches currently in use are the critical concentration and minimum inhibitory concentration (MIC). Classically, critical concentration was defined as the lowest concentration of a drug that inhibits growth of 95% of Mtb strain present. Owing to ongoing research, these critical concentrations are regularly updated with a recent reduction in the critical concentration required to determine RIF resistance, allowing for greater concordance between genotypic and phenotypic sensitivity results [30]. Alternatively, the MIC method is defined as the lowest concentration of a drug that results in complete inhibition of visual growth of the Mtb strain in vitro. Following extensive work completed by national reference laboratories, and international discussion and agreement, a new reference MIC protocol has been set andvalidated by European consortia [31]

Diagnosis:

Improving the efficiency and accuracy of TB diagnosis contributes to treatment efficacy. Pulmonary TB should be suspected when patients present with classical symptoms such as non-resolving cough, haemoptysis, fevers, night sweats and weight loss. Extrapulmonary TB, including TB lymphadenitis, TB meningitis, laryngeal TB, Pott's disease and abdominal TB, presents in a variety of manners. Special consideration should always be given to patients who have potential TB exposure, as well as immunocompromised patients who may present atypically. The diagnosis must be made by confirming the presence of the causative pathogen, Mtb. A variety of methods are employed to confirm the diagnosis. In addition, it is essential that there is emphasis on early detection of potential drug resistance. Drug resistance is a growing issue that threatens TB care worldwide. Traditionally this was categorised into rifampicin-resistant TB (RR-TB), multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB). MDR-TB is resistant to both rifampicin (RIF) and isoniazid (INH). Recently definitions have been updated to include pre-XDR-TB, which is TB that fulfils the definition for MDR-TB and RR-TB that is also resistant to any fluoroquinolone (FLQ). The updated definition for XDR-TB is strains that fulfil the definition for MDR-TB/RR-TB which are also resistant to any group A drug (namely levofloxacin (LFX), moxifloxacin (MFX), bedaquiline (BDQ) and linezolid (LZD)) [32]. Replacing the old XDR-TB definition referencing second-line injectable drugs (SLID), it highlights the trend towards use of oral regimens comprising recently developed or repurposed drugs. Despite the importance of early recognition, only 61% of patients with a new diagnosis of bacteriologically confirmed TB disease in 2019 were tested for RIF resistance [33]. This is in part related to access to diagnostics in resource-limited settings. There are numerous methods currently available, and under development, to determine drug resistance. For these diagnostics to be beneficial on a global scale they need to provide timely, accurate, cost-effective results in centres where access to power, equipment and technical expertise remains limited.

CONCLUSION:

The future is bright for TB treatment. Never before has there been such a global effort to develop new technologies and treatment for TB patients. Combining these advancements, it is possible that we will base each patient's treatment on their own protein biosignatures in conjunction with the genomic expression of mutations in the Mtb strain they have been affected with. If we are to achieve our goal of global eradication of TB, it is essential that we continue to collaborate and share our expertise on an international scale to ensure each patient gets the appropriate treatment and support to overcome their TB diagnosis without significant morbidity.

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