Biomedicine & Pharmacotherapy 99 (2018) 735–745

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Recent therapeutic approaches for the management of tuberculosis: Challenges and opportunities

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ARTICLE INFO

Keywords:
Tuberculosis
Drug discovery
Repurposed drug
Novel drug delivery system

ABSTRACT

Tuberculosis is a highly contagious disease spread by *Mycobacterium tuberculosis*. It is responsible for highest numbers of death and soon will surpass the deaths caused by HIV. The pandemic disease causes, estimated 10.4 million new infections, among which 5.9 million were men, 3.5 million were women, 1.0 million were children and the HIV patients co-infected with tuberculosis accounted for 1.2 million of all new cases in 2015, alone. The increased number of drug resistant (MDR/XDR) strains and the failure of the conventional regimens against this strain are the challenges of the coming decades. The goals of new therapeutic approaches are to ensure cure without relapse, to inhibit deaths, contagions and the formation of drug-resistant strains. The main approaches of anti-tubercular therapy involves either development of new chemical entity with a novel mechanism of action or repurposing of old drugs which show significant activity on drug-resistant strains. Repurposing existing drugs is a promising alternative to the expensive and time-consuming process of drug discovery. A number of carrier-based drug delivery systems incorporating the principal anti-tuberculosis drug has been developed to provide targeted action with reduced dosing frequency in order to improve the patient compliance which is a major reason for therapeutic treatment failure. This article reviews the recent approaches to the treatment of tuberculosis in terms of discovery of new chemical entity, repurposing of old drugs and the use of novel drug delivery technology such as liposomes, niosomes, liquid crystals, solid lipid nanoparticles, polymeric micelles, dendrimers, nanoemulsion, nanosuspension, silica nanoparticles, polymeric nanoparticles and microparticles for complete eradication of *Mycobacterium tuberculosis*.

1. Introduction

Tuberculosis is a chronic communicable disease caused by *Mycobacterium tuberculosis* (MTb), mainly occurs in the lungs called as pulmonary tuberculosis but can also infect other organs called extra-pulmonary tuberculosis. The MTb is a highly infectious gram-positive aerobic rod-shaped acid-fast bacilli. Tubercle bacilli can be able to survive within macrophages as its cell wall has high lipid contains [1,2]. Humans are the primary host for MTb. The infection spread by air droplet nuclei from infected patient, which contains the viable tubercle bacilli that transmit the infection to an uninfected person.

The droplet containing viable tubercle bacilli is subsequently inhaled and enters the lungs to the alveoli. Tubercle bacilli are phagocytosed by alveolar macrophages and multiply within them. Contaminant macrophages form a hard shell called as granuloma and keeps the bacilli under control. The bacilli replicate within the granuloma and then burst outside to develop the active disease (Fig. 1). The threat of development of active disease depends on various factors as age of patient, period of latent infection and most importantly the immunity of the patient [3]. The tuberculosis mortality rate in untreated smear positive patients ranges from 50 to 80%, while it decreases to 30% with inconsistent control programmes and further reduces to less than 5% when treated with directly observed therapy and other TB control programs [4].

Tuberculosis is responsible for the highest numbers of deaths worldwide and even it exceeds the death caused by human immunodeficiency virus (HIV). According to the world health organization, a one third of the world's population are epidemic with MTb [5]. TB increases the poverty level of a country, thrives on poverty and the poor have a five-time higher chance of getting TB [6]. In addition, day by day emerging resistance in MTb strains made it extremely difficult to treat. These multi-drug resistant tuberculosis strains offer very low cure rates and high mortality rates [7,8]. Moreover, patients with total drug resistant tuberculosis (TDR-TB) have been reported in the clinics

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https://doi.org/10.1016/j.biopha.2018.01.115
Received 17 November 2017; Received in revised form 23 January 2018; Accepted 24 January 2018

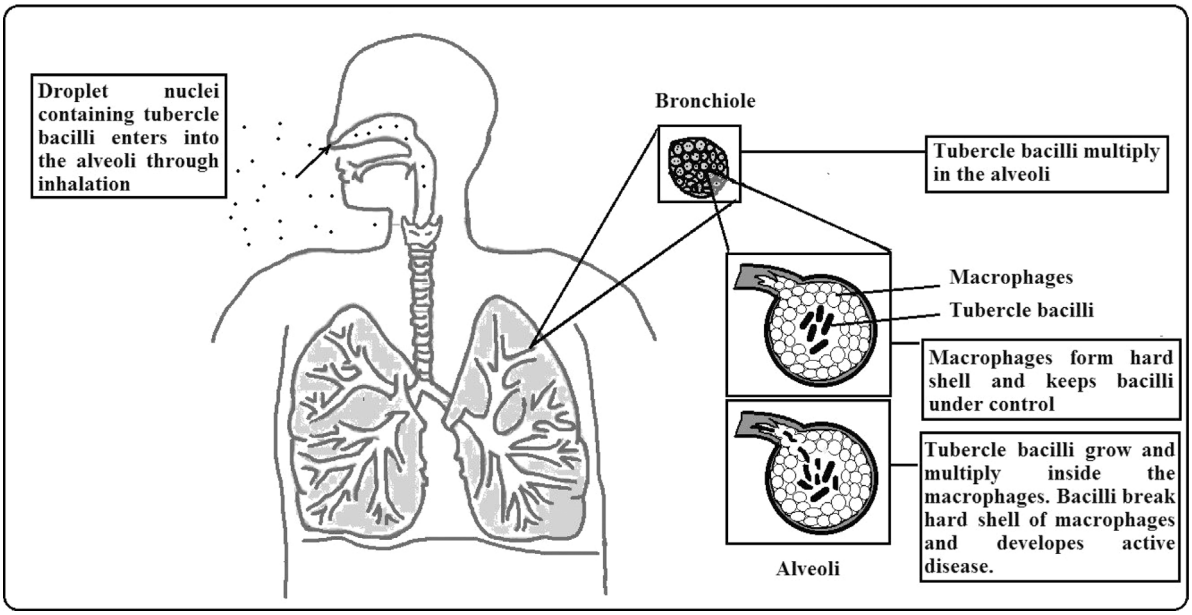

Fig. 1. Pathogenesis of Tuberculosis.

[9,10,11].

As per the recent report of the world health organization the global epidemiology of tuberculosis accounted for estimated 10.4 million new infections of tuberculosis among which 5.9 million were men, 3.5 million were women, 1.0 million were children and the HIV patients co-infected with tuberculosis accounted for 1.2 million of all new cases (Fig. 2) [5]. However, the cure rate of tuberculosis remained at only 1.5% and the rate of new cases is occurring at one per second [5].

Worldwide six countries, India, Indonesia, China, Pakistan and South Africa are contributing more than 60% of the new tuberculosis incidence Fig. 3) [12]. Therefor the global progress mainly depends on the advancement of tuberculosis prevention and care in this country. Alone India accounts for one fourth of the global incidents TB cases per year [5].

2. Drug-resistant tuberculosis

Drug resistant tuberculosis poses a major hurdle to control the disease worldwide [13]. Drug resistant tuberculosis particularly refers to multi drug resistant (MDR) and extensively drug resistant (XDR) tuberculosis (TB). MDR-TB is defined as the strains of MTb, which are resistant to two important first line anti-TB drugs rifampicin and isoniazid. While XDR-TB refers resistant to at least one fluoroquinolone and one injectable second-line anti-TB drug in addition to isoniazid and rifampicin [14]. Over 480,000 cases of MDR-TB occurs every year globally, 9% of them are affected by XDR-TB [5]. MDR-TB treatment requires minimum about 2 years therapy with second line anti-TB drugs while treatment of XDR-TB becomes more complicated as the option further limited because of resistance to fluoroquinolone and injectable second line anti-TB drugs. Moreover the treatment of XDR-TB is lengthy, costly, low cure rate and cause life threatening side effects [15,16]. The success rate of MDR-TB and XDR-TB was found to be around 50% and 27% respectively, and less than 20% among cases with resistance patterns beyond XDR [17,18]. There are many ways by which tubercle bacilli produces resistance to drugs such as by reduced permeability or uptake of the drug, by the enhanced efflux of the drug from cells, by enzymatic inactivation of the drug, by altering the drug target and by genetic mutation at specific genes (Table 1) responsible for loss of enzymes involved in drug activation.

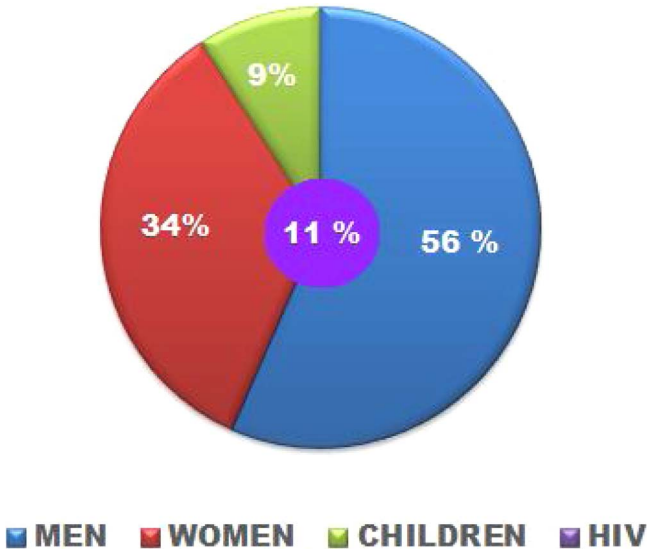

Fig. 2. Epidemiology of Tuberculosis (WHO [17]).

3. Conventional tuberculosis therapy

Conventional chemotherapy of tuberculosis consists of five major classes of drug (Table 1). The first line agents are very effective on drug susceptible TB, while second line agents are effective when first line regimen are failing, because of the development of drug resistance. Drug susceptible tuberculosis consists of a daily regimen of four oral antibiotics for a period of six to nine months. The treatment of drug susceptible tuberculosis mainly consists of two phases. Intensive Phase, which consists of treatment with four first line antibiotics for two months, during this phase most of the viable bacilli killed. The second phase is a continuation phase, the bacteria survived in the initiation phase are targeted in the continuation phase with two main first line drugs rifampicin and isoniazid either daily or three times a week for 4–6 months to sterilize lesion containing fewer and slower-growing bacilli (Table 2). This complicated long term treatment with life threatening adverse effects of drugs (Table 1) may lead to patient non-compliance and further contribute to the development of drug resistant strains. New treatment strategies with novel approaches are strongly needed to combat the global tuberculosis epidemic and the spread of