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Review

Pulmonary drug delivery systems for tuberculosis treatment

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ABSTRACT

Tuberculosis (TB) remains a major global health problem as it is the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (HIV). Conventional treatments fail either because of poor patient compliance to the drug regimen or due to the emergence of multidrug-resistant tuberculosis. The aim of this review is to give an update on the information available on tuberculosis, its pathogenesis and current antitubercular chemotherapies. Direct lung delivery of anti-TB drugs using pulmonary delivery systems is then reviewed since it appears as an interesting strategy to improve first and second line drugs. A particular focus is place on research performed on inhalable dry powder formulations of antitubercular drugs to target alveolar macrophages where the bacteria develop. Numerous studies show that anti-TB drugs can be incorporated into liposomes, microparticles or nanoparticles which can be delivered as dry powders to the deep lungs for instantaneous, targeted and/or controlled release. Treatments of infected animals show a significant reduction of the number of viable bacteria as well as a decrease in tissue damage. These new formulations appear as interesting alternatives to deliver directly drugs to the lungs and favor efficient TB treatment.

Contents

Abbreviations: AMK, amikacin; anti-TB drugs, antitubercular drugs; CAP, capreomycin; CS, cycloserine; ETB, ethambutol; ETH, ethionamide; XDR-TB, extensively drug-resistant TB; FPF, fine particle fraction; HIV, human immunodeficiency virus; INH, isoniazid; KM, kanamycin; LEV, levofloxacin; AMK-LDPI, liposomal amikacin as a dry powder; MAN, mannitol; MMAD, mass median aerodynamic diameter; MIC, minimum inhibitory concentration; MDR-TB, multidrug-resistant tuberculosis; MDR, multi-drug resistance; PAS, para-aminosalicylic acid; PLA, poly(L-lactide); PLGA, poly(lactide-*co*-glycolide); PNAP, porous nanoparticle-aggregate particle; PZA, pyrazinamide; RIF, rifampicin; SM, streptomycin; TB, tuberculosis.

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1. Introduction

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* (*M. tuberculosis*). It typically affects the lungs (pulmonary TB) but can affect other sites as well (extrapulmonary TB). The disease spreads out in the air when people who are sick with pulmonary TB expel bacteria, for example by coughing. TB remains a major global health problem, affecting millions of people each year. It ranks as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (HIV). The latest estimates are that there were 8.6 million new TB cases in 2012 and 1.3 million TB deaths (Anon., 2012). Without treatment, TB mortality rates are high, with 70% of infected people dying within 10 years (Turner et al., 2011). The currently recommended treatment for patients with pulmonary TB is a six-month regimen of four first-line drugs: namely isoniazid, rifampicin, ethambutol and pyrazinamide. The treatment success rate is at least 85% (WHO, 2013). This treatment is effective in both HIV-infected and uninfected persons. Treatment failure is mostly related to lack of patient adherence to the drug regimen and to multidrug-resistant tuberculosis (MDR-TB). The treatment of MDR-TB requires second line drugs which are less effective and poorly tolerated. Prevention of resistant tuberculosis needs adequate treatment of each case of tuberculosis and improvement of patient compliance (WHO, 2012).

TB treatment with antitubercular drugs (anti-TB drugs) usually takes a period of 6–9 months, followed by consolidation treatment for a period of 1–2 years, depending on the drug cocktail given. The total duration of treatment may be up to 36 months. With such prolonged duration, the function of the liver and kidneys are overloaded and gradually declining because of the cumulative effects of drugs. Most conventional anti-TB drugs are administered by the oral route, undergo first-pass metabolism in the liver, therefore leading to side-effects. The efficacy of therapy is thus limited by constraints on drug dosage, by adverse drug reactions, especially common among patients concurrently infected with HIV (Chaisson et al., 1987), and by inadequate drug distribution in pathological sites. In addition, the recent emergence of resistant strains of TB and the rarity of new anti-TB drugs are threatening to prevent and treat TB in the future. One of the reasons for the emergence of resistant TB strains is the exposure of mycobacteria to sub-therapeutic levels of one or more antibiotics. The conventional therapy by the oral and parenteral routes does not allow providing therapeutic level of anti-TB drugs to lung lesions containing large numbers of bacteria because these lesions are poorly vascularized and fortified with thick fibrous tissue. Direct lung delivery of anti-tubercular drugs therefore, reveals an interesting strategy to prevent or reduce the spread of tuberculosis and the development of drug-resistant strains.

Pulmonary delivery systems have been widely investigated for the treatment of pulmonary-related diseases to reduce side effects of systemic administration and enhance therapeutic efficacy by delivery the drug directly to its site of action. In particular, inhalable dry powders were developed for the aerosol delivery of anti-TB drugs to lungs. These powders made of anti-TB drug-loaded particles can be delivered directly to the lung. They are designed for intracellular targeting of the alveolar macrophages where the bacteria develop. Local delivery may lead to high drug concentration localized in the lung might thereby reducing the duration of treatment and preventing multi-drug resistance (MDR). In the present review, after an update on tuberculosis and its pathogenesis, current anti-TB chemotherapies and their challenges are described. Finally the inhalable dry powder formulations proposed during the last 2 decades and their pros and cons are reviewed.

2. Update on tuberculosis

2.1. The epidemiology of TB infection

In 2012, the World Health Organization estimated 8.6 million incident cases of TB and 1.3 million people died of TB. Among these

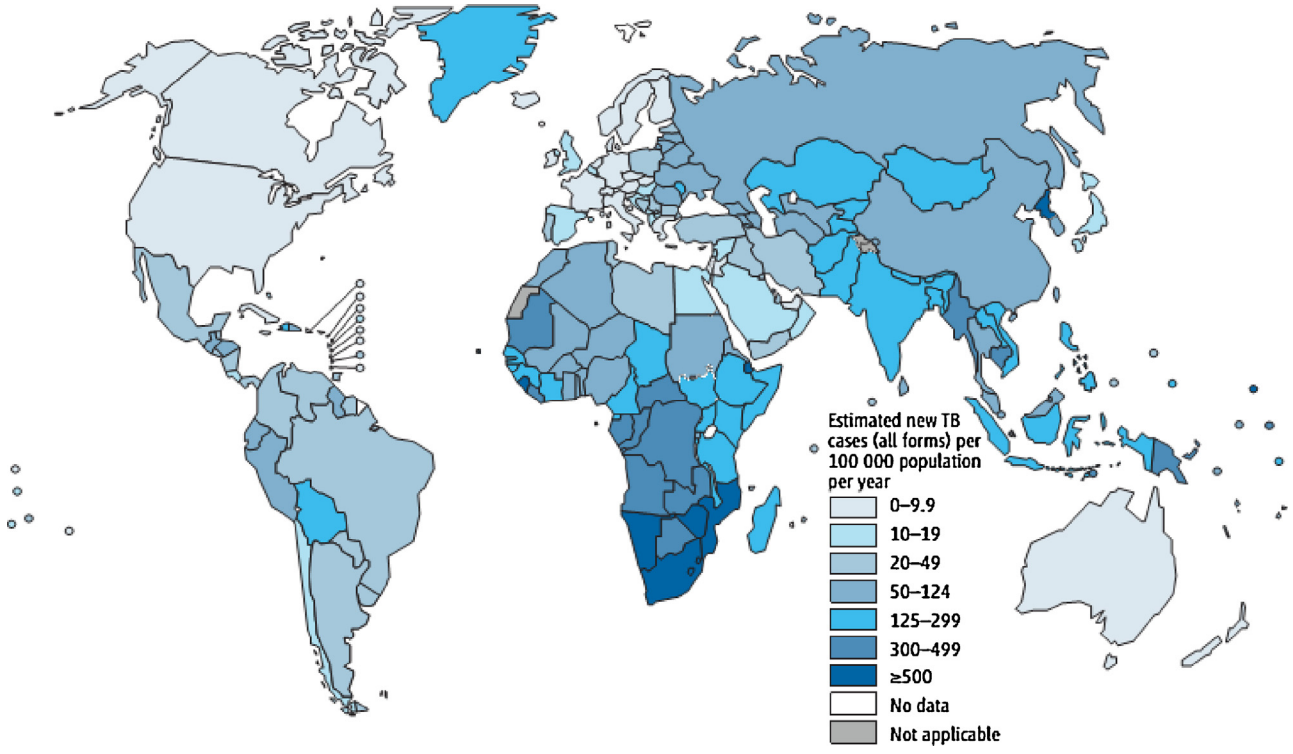

Fig. 1. Estimated TB incidence rate in 2012 of World Health Organization. Reprinted from Global tuberculosis report 2013 of WHO.