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Inhaled drug treatment for tuberculosis: Past progress and future prospects

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ABSTRACT

Since the 1990s the rising incidence of multiple drug resistant TB, particularly in the context of human immunodeficiency virus co-infected patients, has threatened global TB control. At that time funding agencies began to support formal investigation of aerosol therapy which until then had been the subject of case reports of individual investigators. Over the last decade, proponents of aerosol therapy have increased in number within the TB research community as the incidence of multiple and extremely drug resistant TB has increased dramatically around the world. Aerosol therapy offers the potential to deliver drug at target concentrations directly into the lungs, use the alveolar-capillary interface to achieve systemic levels, while reducing the risk of systemic toxicity seen with parentally administered doses. In addition, there are insufficient new drugs in the pipeline to anticipate the appearance of a new regimen in time to assure future control of drug resistance. Consequently, alternative strategies are critical to achieving global TB control, and inhaled therapies should be considered as one such strategy.

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1. Introduction

Inhaled therapy for tuberculosis first appeared in the modern literature in the late 1940s and early 1950s when concern over streptomycin resistance resulted in alternative approaches being considered [1]. The major advantage of this route and method of drug administration was then, as now, the ability to deliver high local doses while avoiding systemic exposure that would increase the potential for toxic side effects. Avoiding repeated painful intramuscular injections required for parenteral drugs is equally important, especially for wasted adults and small children with little muscle mass. As multiple-drug resistant tuberculosis increases globally, we continue to be faced with the challenge of finding effective treatment and prevention strategies. Ideally, a steady stream of new drugs or drug regimens would be sufficient to address all manifestations of disease, and enormous effort is being expended to that end, but with limited results to date [2]. Inhaled therapy using new and existing drugs may offer a supplementary approach that would help control drug resistance while other more comprehensive strategies are developed [3]. There is historical precedent for this approach in the use of pentamidine to treat *Pneumocystis carinii* pneumonia infections in acquired immunodeficiency disease syndrome (AIDS) patients during the 1980s and 1990s. At the time, mortality attributable to this pulmonary infection approached 100% while therapies for AIDS had yet to be developed [4].

A wide range of drugs used in tuberculosis therapy have been evaluated for inclusion in a variety of inhaled dosage forms [5]. However, few have been tested in animal models of disease and none have undergone a complete pharmaceutical development approach for entry to the clinic [6].

The majority of the published research in the last two decades has been preclinical evaluation, but in recent years several clinical studies have been conducted. However, for the approach to reach its full potential, many more clinical studies are required. Specialized reviews on this topic have been published in several pharmaceutical and disease orientated journals [3,6–8]. Also, in the period since 2009, there were two international meetings (New Delhi, 2009, Tokyo, 2013) on 'Inhaled Tuberculosis Therapy' and a third will occur this year (Parma, Italy, 2015).

With this background, it is timely to review the work published to date and discuss the most effective designs and conduct of future clinical trials in order to demonstrate the utility of aerosol therapy.

1.1. Pathogenesis of disease

Fig. 1 illustrates the major steps in tuberculosis infection. Infectious droplet nuclei containing the microorganism originate in larger airborne droplets ejected from the respiratory tract of infected individuals, most effectively by coughing or sneezing. Following a period of dehydration in the ambient environment, one or more droplet nuclei are inhaled by the host and deposit in the lungs as a function of their particle size and aerodynamic properties [9]. The phenotype of

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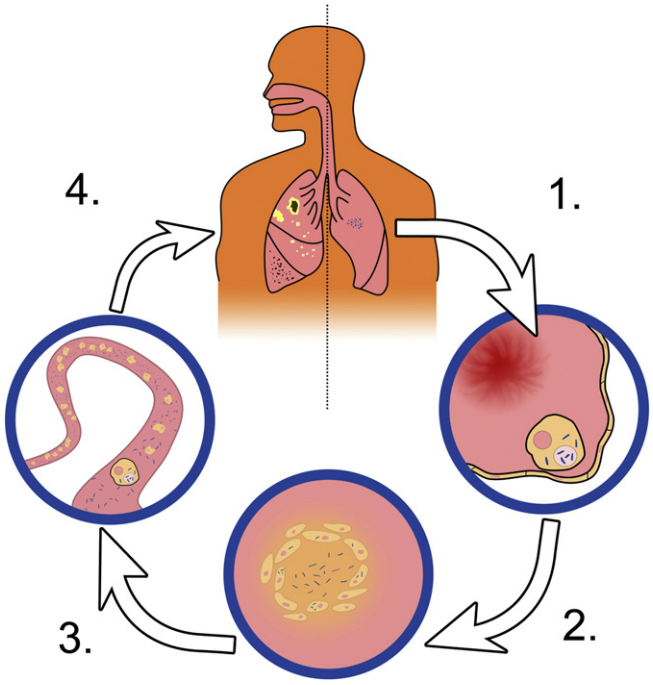

Fig. 1. Schematic representation of the pathogenesis of disease. 1. Airborne transmission and uptake by macrophages; 2. Cell recruitment and granuloma formation; 3. Bacillemia and disposition from the lungs; 4. Secondary lung infection and tubercle formation. Left lung depicts schematically early infection and right lung late infection.

Mycobacterium tuberculosis (Mtb) required for infection is not known definitively. However, the first step in infection is phagocytosis of the pathogen by resident alveolar macrophages [10]. The Mtb effectively neutralizes the host defense presented by the phago-lysosomal compartment and creates a vacuole from which the host cell is co-opted to support growth and division of the bacterium until cell death and pathogen release occurs [11]. As this process develops, macrophages produce a number of inflammatory mediators, notably cytokines and chemokines, and initiate a T-cell mediated immune response by recruiting immune cells and ultimately walling off the site of infection in granulomas, leading to caseous and necrotic tubercle formation [12].

In parallel to the induction of elements of the immune system intended to protect the lungs, migration of infected cells through the lymphatics to the systemic circulation occurs. This process results in the bacillemic phase of distribution of the pathogen to remote sites and finally secondary foci in the lungs via the blood supply.

The ideal approach to drug or immune-based treatment would target specific elements of this infection cycle to protect the lung, adjacent (thoracic lymph system) and remote (other organ and tissue) sites.

1.2. History of aerosol therapy

The use of a variety of pharmacological agents as vapors and smokes for the broad treatment of pulmonary disease can be traced back to classical times and earlier [13,14]. Undoubtedly, tuberculosis, the cause of which was unknown, would have been grouped with many other chest diseases that warranted direct pulmonary intervention during this period of medical history [14,15].

In modern times as shown in Fig. 2 the initial interest in inhaled therapy for tuberculosis was co-incident with the rapid development of streptomycin resistance. In the late 1940s and early 1950s a number of reports appeared on aerosol therapy. Unfortunately, the discovery of new drugs for TB therapy—notably isoniazid, rifampicin and pyrazinamide followed by fluoroquinolones in the thirty year period following the initial aerosol assessment-reduced the need for and dampened the enthusiasm in inhaled therapy for TB.

The notable appearance of (AIDS) in the early 1980s brought attention to a condition that predisposed its victims to a higher susceptibility to TB. Moreover, the increased incidence of disease in human immunodeficiency virus (HIV) patients facilitated the evolution of multiple and extremely drug-resistant (MDR-TB and XDR-TB) micro-organisms. In the 1990s, a renewed interest in treating TB with inhaled therapy developed.

Today, as noted, the continued interest in TB therapy with inhaled aerosols stems from: 1) the absence of sufficient new drug candidates or regimens that can significantly alleviate MDR-TB and XDR-TB; 2) a clinical desire to avoid the local pain of injections and systemic toxicity

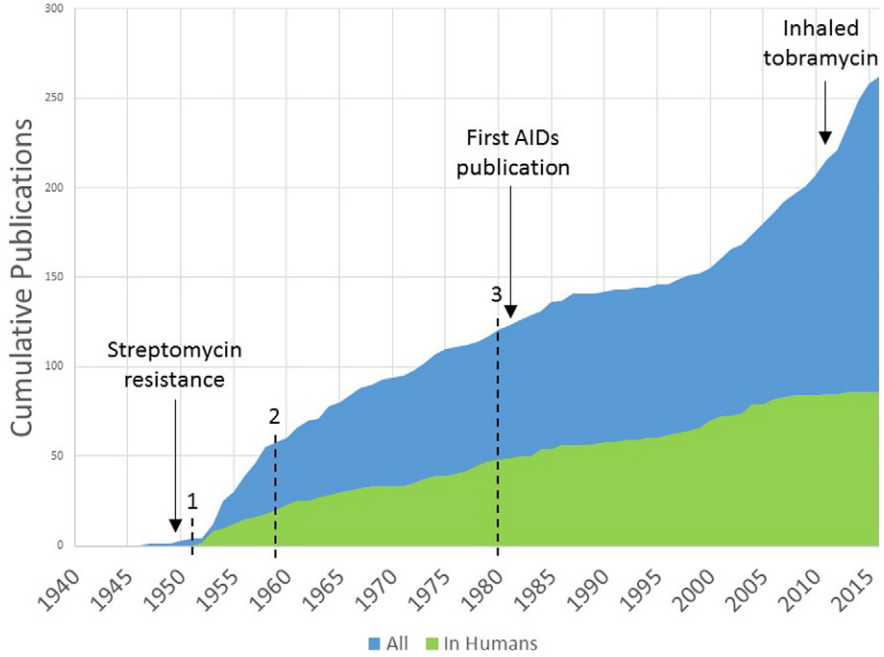

Fig. 2. Cumulative publications (from PubMed) describing aerosol therapy for tuberculosis. The upper line presents all entries and the lower those involving human studies. Dates of discovery of 1. Pyrazinamide; 2. Isoniazid and Rifampicin and; 3. Fluoroquinolones are shown.

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