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Why Wait? The Case for Treating Tuberculosis with Inhaled Drugs

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Abstract

The discovery of drugs to treat tuberculosis (TB) was a major medical milestone in the twentieth century. However, from the outset, drug resistance was observed. Currently, of the 10 million people that exhibit TB symptoms each year, 450,000 have multidrug or extensively drug resistant (MDR or XDR) TB. While greater understanding of the host and pathogen (*Mycobacterium tuberculosis, Mtb*) coupled with scientific ingenuity will lead to new drugs and vaccines, in the meantime 4,000 people die daily from TB. Thus, efforts to improve existing TB drugs should also be prioritized. Improved efficacy and decreased dose and associated toxicity of existing drugs would translate to greater compliance, life expectancy and quality of life of *Mtb* infected individuals. One potential strategy to improve existing drugs is to deliver them by inhalation as aerosols to the lung, the primary site of *Mtb* infection. Inhaled drugs are used for other pulmonary diseases, but they have yet to be utilized for TB. Inhaled therapies for TB represent an untapped opportunity that the pharmaceutical, clinical and regulatory communities should consider.

Keywords

Inhaled drug delivery; Mycobacterium tuberculosis; Tuberculosis

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Author Contributions

All authors wrote the manuscript and reviewed the final version.

Conflict of interest

SE is CEO and owner of Collaborations Pharmaceuticals, Inc., and has filed a provisional patent “Treatment for Tuberculosis”. AJH has filed a provisional patent “Dry powder formulations of antituberculosis drug methods of treatment and using the same” and PCT/US2018/36351 “CPZEN compositions and uses”.

Introduction

Mycobacterium tuberculosis (*Mtb*) infects millions globally and it accounts for 4,000 deaths daily from tuberculosis (TB) (1). Drug discovery for TB cannot keep pace with the ability of *Mtb* to develop drug resistance. Thus, multidrug resistant (MDR) and extensively drug resistant (XDR) *Mtb* strains are one of the challenges facing the goal of ending the TB health crisis. There are approximately 450,000 new cases of MDR-TB and XDR-TB each year. The morbidity and mortality of MDR-TB and XDR-TB patients leads to great suffering (2). Until recently, the only treatment for MDR-TB was lengthy (>18 months), often toxic and only successful in 55% of patients, and treatment of XDR-TB has an even worse prognosis (1). A new triple combination treatment with pretomanid, bedaquiline and linezolid has reduced the duration of treatment to 6 months, the same as drug susceptible disease (3). However, linezolid toxicity is a concern and shortening of treatment continues to be an important objective. TB drug development is an extremely time-consuming process. While drug discovery is ongoing, strategies for increasing drug compliance, life expectancy and quality of life of MDR and XDR TB patients should be explored. A parallel can be drawn between the current MDR/XDR-TB crisis and the period immediately following the discovery of HIV as the cause of AIDS but preceding the identification of reverse transcriptase inhibitors (4). The number of patients affected was a strong inducement to the scientific and medical community to develop palliative therapies that extend the lifespan of AIDS-patients while drug discovery was underway. One such therapy was inhaled pentamidine to treat *Pneumocystis carinii* pneumonia, a secondary infection fatal in immunocompromised patients (5).

Today, TB treatment remains primarily reliant on old drugs from the golden age of antibiotic drug discovery in the 1940s-1960s. Development of new drugs, such as the recently approved bedaquiline, delamanid, and pretomanid, is a slow process (3, 6). As a quicker route to new treatments, drug repurposing for TB is being attempted with old (7) and new drugs (8) that target other diseases. However, an even faster path to the development of treatments may be to revisit and optimize ‘old’ TB drugs that are already known to work on TB (9). Such optimization could take the form of rescuing activity on drug resistant TB and/or improving activity. Alternately, different routes of drug delivery could be beneficial. Direct delivery of aerosolized TB drugs to the lung is an appealing strategy as it has the potential to supplement standard therapy to improve efficacy in treating pulmonary disease, shorten treatment time, and reduce systemic doses and associated toxicity. These potential benefits would address the “critical need for shorter, safer, and more effective drug regimens that are easily tolerated and can be delivered to patients in all care settings”, as stated in the NIH National Institute of Allergy and Infectious Disease strategic plan for tuberculosis research (10).

Inhaled TB therapies

Old drugs, new treatments

When the first cases of streptomycin resistance were observed in TB patients in the 1940s, off-label inhaled streptomycin treatments were shown effective in children (11). However, with the introduction of orally delivered anti-TB drugs that are still used today (rifampicin,

isoniazid, ethambutol, pyrazinamide), inhaled streptomycin was abandoned. The rise in HIV-TB co-infection in the 1990s revived research and clinical interest in inhaled aerosol therapy (5). However, progression to clinical studies and development of commercial products never occurred. Given increasing drug resistance, inhaled TB drugs deserve serious reconsideration (12)(13, 14). The advantage of inhaled therapies for TB is that they deliver high local concentrations of drug to the lung, which is the primary site of *Mtb* infection. As a result, inhaled TB therapies could be used to supplement conventional oral drug therapy as a strategy to improve treatment efficacy and more rapidly clear the airway to prevent transmission. These effects would allow for shorter treatment duration, which would improve patient adherence to therapy and may limit the emergence of further drug resistance. In addition, by avoiding diminishing drug levels that occur when drugs are administered orally or by injection and then migrate to the lungs (15), inhaled drugs for pulmonary diseases can be delivered at lower levels and still be effective, with the potential to reduce side effects. A recent publication describing the effects of intrapulmonary delivery of colistin on local and systemic pharmacokinetics illustrates how inhaled delivery can achieve high levels in the lung along with low systemic levels, which will help avoid toxicity (16). Recent studies demonstrate that not all orally delivered TB drugs are able to access or reach therapeutic levels in granulomas in TB patients (15, 17, 18). Inhalation may not only be a better way to deliver drugs to lungs but also, for some drugs, the high local dose may be the only way to drive delivery into granulomatous lesions that harbor *Mtb*. Inhalation is also an option for delivering drugs with poor solubility and or poor oral bioavailability that cannot be administered by other routes (19). Finally, inhalation would avoid painful intramuscular injections of parenteral drugs (20, 21).

For other pulmonary diseases (*e.g.* asthma, chronic obstructive pulmonary disease, cystic fibrosis) inhaled therapies have proven stable, easy to deliver and effective (22–25). There is significant research underway on pre-clinical development of inhaled therapies for TB (Table 1).

Experiments conducted in mice and guinea pigs show inhaled therapy to be a promising approach for TB treatment (Table 1) (20, 48, 49). Guinea pigs, unlike most strains of mice, form granulomas with necrotic hypoxic centers that are hallmarks of progressive human granulomas (50, 51). Guinea pigs are also regularly used for studying inhaled therapies and they are the small animal model most commonly used in preclinical studies of pulmonary diseases such as asthma and Chronic Obstructive Pulmonary Disease (COPD) (52, 53). Thus, many studies of inhaled drugs for TB use guinea pigs. Using guinea pigs, treatment efficacy for inhaled rifampicin, capreomycin, PA-824, pyrazinoic acid esters (PAEs) and pyrazinoic acid/ester dry powder (PDP) was demonstrated (39, 40, 43, 44, 47, 54, 55) (Table 1). Capreomycin provides an example of an injected second-line TB drug that when delivered by inhalation as a spray-dried powder at a low dose of 4mg/kg was as effective in reducing *Mtb* burden in guinea pig lungs as a higher intramuscular injection dose of 20mg/kg (54). Further, inhaled capreomycin was well tolerated in a Phase I clinical trial (31). Inhaled PDP is an example of a drug analog with potential to rescue activity on drug resistant *Mtb*. PDP is a combination of pyrazinamide (PZA) analogs [pyrazinoic acid (POA), the active moiety of PZA, and pyrazinoic acid ester (PAE)] (56), both of which are effective on the most common category of PZA-resistant *Mtb* (57–59). Studies in mice and guinea

pigs demonstrate orally delivered POA is not effective at a tolerable dose (60) (unpublished Braunstein and Hickey). However, inhaled PDP (3.9mg/kg), when tested in combination with oral rifampicin (50mg/kg), reduced the *Mtb* burden compared to untreated guinea pigs (40). The effect of PDP on pathology was even more noteworthy. Compared to other treatments, rifampicin plus inhaled PDP was more effective in clearing necrotic granulomas, which are associated with the subpopulation of *Mtb* that persist during host immune responses or drug treatment (61). The better effect in clearing necrotic granulomas suggests a unique ability of inhaled PDP in resolving disease, because other TB treatments, including standard first-line oral drug combinations, preferentially clear non-necrotic granulomas (62–64). These results reveal the possibility of using PDP or other inhaled drugs as an add-on to standard therapy to improve clearance of *Mtb* in more recalcitrant necrotic granulomas and demonstrate the value of inhaled delivery to treat persistent organisms that are inaccessible to oral or parenteral therapy.

Inhaled aminoglycosides provide immediate opportunities for development of a new TB therapy. Aminoglycosides such as amikacin, kanamycin, and streptomycin are second-line drugs delivered by injections to treat MDR-TB and XDR-TB, but they have systemic toxicities associated with long-term use. Targeted delivery of aminoglycosides to the lung has great appeal as a means of limiting the systemic dose of drug. Moreover, when used as a supplement to current therapy for pulmonary nontuberculous mycobacteria (NTM) infections, inhaled aminoglycosides improve outcomes (32–35). In fact, inhaled liposomal amikacin (Arikayce, Insmed Inc) was recently approved by the US Food and Drug Administration for treating patients with pulmonary NTM infections. The success with inhaled aminoglycosides for treating NTM infections provides a strong case for pursuing this approach for treating MDR-TB and XDR-TB. Further, in addition to inhaled streptomycin use in the 1940s, there are recent reports of inhaled aminoglycosides being beneficial when used to treat refractory pulmonary TB as an adjunctive salvage therapy (36, 37).

Inhaler devices

Over the past 30 years, great progress has been made developing inhaled drug delivery systems (48): pressurized metered dose inhalers, dry powder inhalers (DPI) and nebulizers. It is noteworthy that it is often the case that initial clinical trials and market entry of inhaled products are conducted with a nebulized product, which may then be superseded by dry powder products. DPI products are portable and avoid the need for, needles, cold storage, or electricity. Thus, they are preferable for application in TB high-burden countries. While DPIs commonly require potent drugs in low doses in lactose blends (65, 66), recent developments in preparing spray dried particles with optimal delivery characteristics now enable high dose delivery of mostly drug particles, without lactose, for the treatment of lung infection (22, 67). A consideration for the use of reusable inhalers to treat infectious disease is patient re-exposure to the infectious agent from the inhaler and bacterial resistance building (68). The solution to that concern could be disposable single-use spacers (69, 70). Effective inhaled drug delivery requires patient training to assure compliance with appropriate technique.

Translation to the clinic

Only clinical studies will establish the utility of inhaled TB therapies. However, in spite of encouraging pre-clinical results, there are few reports of human studies of inhaled TB drugs (Table 1) and no controlled clinical trials of efficacy. These efforts could be implemented at relatively minimal cost as add-ons to current therapy and arms of planned clinical trials.

We speculate that government and philanthropic investment in product development will be the most likely route for inhaled TB drugs entering the clinic. In considering development activities, health economic assessments that take into account total savings accrued from pulmonary drug targeting (i.e. the overall cost saving and benefit in disease management) should be considered, not simply setting the cost of the inhaler product against a tablet. Inhalers can be manufactured and supplied at the same or lower cost as syringes and needles, but they will never be as inexpensive as tablets (71). However, it should be noted that treatment of MDR-TB and XDR-TB accounts for the majority of the total costs of TB treatment and management (72). The addition of inhaled drugs to orally delivered drug combinations to effectively treat the fraction of TB cases that are MDR-TB or XDR-TB would require a relatively modest expense compared to the savings that would accrue from reducing the overall expense of these cases going untreated or relapsing from suboptimal regimens of oral therapy. For inhaled drugs that prove effective in treating the serious emerging problem of drug resistant NTM infections, product repurposing could be an alternate path to introducing inhaled TB drugs into the clinic (32, 73).

Discussion

While new drug discovery is ongoing, we need to consider alternatives that will increase life expectancy and quality of life for TB patients. Inhaled therapies for TB represent a potentially useful strategy, which need to be evaluated in clinical studies. Why wait? Based on in vivo animal and human studies described above, inhaled capreomycin, aminoglycosides and colistin (Table 1) could immediately be moved forward. In addition, clofazimine and linezolid, which are second-line TB drugs with significant toxicities, deserve evaluation in pre-clinical inhalation studies. Inhaled delivery of these drugs could lower systemic doses while achieving higher lung doses and efficacy. Inhaled therapies with existing TB drugs could relatively quickly become a new option for the TB clinical tool kit.

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Abbreviations

COPD	Chronic Obstructive Pulmonary Disease

DPI	dry powder inhalers
NTM	non-tuberculous mycobacteria
MDR	multidrug drug resistant
POA	pyrazinoic acid
PAEs	pyrazinoic acid esters
PDP	pyrazinoic acid/ester dry powder
XDR	extensively drug resistant

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Table 1.

Old and new drugs to treat TB delivered by inhalation.

Drug	Summary
Colistin	Widely used in cystic fibrosis to treat *Pseudomonas aeruginosa* (26, 27) – Preliminary studies in MDR-TB patients showed safety and promising results in a preliminary transmission study (E.A. Nardell, personal communication). In addition, inhaled colisitin was included in successful treatment of an XDR patient with a highly complex case of TB (28).
Capreomycin	In *Mtb* infected animals, the inhaled dose was efficacious (29, 30) and in a clinical Phase I single-dose, escalating study high dose inhaled capreomycin exceeded the MIC and was well tolerated (31).
Amikacin/kanamycin/ gentamycin	Inhaled aminoglycosides are proving safe and effective on patients with non-tuberculous mycobacteria (NTM) infections (32–35) and they were used on refractory pulmonary TB cases, as an adjunctive salvage therapy (36, 37)
Streptomycin	Clinical use of inhaled streptomycin to treat TB (11, 20). In a small study, inhaled streptomycin in combination with steroids had effects on patients with endobronchial TB(38).
Pyrazinoic acid ester (PAE) and Pyrazinoic acid/ester Dry Powder (PDP)	In *Mtb* infected animals, the inhaled dose was efficacious (39). Inhaled PDP resolved necrotic granulomas better than other therapies tested (40).
Spectinamides	In *Mtb* infected animals, intrapulmonary administration of spectinamide-1599 was efficacious (41).
Rifampicin	In *Mtb* infected animals, inhaled rifampicin was efficacious (42–44).
Clofazimine	In *Mtb* infected animals, inhaled clofazimine was efficacious (45).
Isoniazid	In *Mtb* infected animals, inhaled isoniazid was efficacious (29). In a small study, inhaled isoniazid had effects on patients with endobronchial TB (46).
PA-824 (Pretomanid)	In *Mtb* infected animals, inhaled PA-824 was efficacious (47).