REVIEW ARTICLE

Inhaled Liposomal Antimicrobial Delivery in Lung Infections

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Abstract

The management of difficult-to-treat acute and chronic respiratory infections (infections in cystic fibrosis, non-cystic fibrosis bronchiectasis, immunocompromised and mechanically ventilated patients) and difficult-to-treat pathogens (including multidrug-resistant strains) has become a challenge in clinical practice. The arsenal of conventional antibiotic drugs can be limited by tissue penetration, toxicities, or increasing antibiotic resistance. Inhaled antimicrobials are an interesting therapeutic approach for optimizing the management of respiratory infections. Due to extensive developments in liposome technology, a number of inhaled liposome-based antibiotic and antifungal formulations are available for human use and many products are undergoing clinical trials. Liposomes are biocompatible, biodegradable, and nontoxic vesicles able to encapsulate and carry antimicrobials, enhancing the therapeutic index of various agents and retention at the desired target within the lung. Liposomes reduce drug toxicity and improve tolerability, leading to better compliance and to decreased respiratory side effects. The aim of this article was to provide an up-to-date overview of nebulized liposomal antimicrobials for lung infections (with a special focus on liposomal amikacin, tobramycin, ciprofloxacin, and amphotericin B for inhalation), discussing the feasibility and therapeutic potential of these new strategies of preventing and treating bacteria, mycobacterial and fungal infections.

1 Introduction

Over recent years, there has been a worldwide increase in the prevalence of multidrug-resistant (MDR) and difficult-to-treat pathogens [1, 2]. This issue has forced clinicians to rediscover old drugs with suboptimal pharmacokinetics and toxicity issues and has resulted in significant research efforts, with few new molecules proposed for use in clinical practice. In addition, alternative novel therapies have been developed including monoclonal antibodies, vaccines, stem cells, bacteriophages, and liposomes [3]. Lung infections include a challenging spectrum of clinical conditions, ranging from acute to chronic infections, and new therapeutic approaches are warranted for optimizing treatment in difficult-to-treat infections, cystic fibrosis (CF), non-cystic fibrosis bronchiectasis (NCFB), and immunocompromised and mechanically ventilated patients.

Liposomes are safe and suitable carriers for a variety of drugs and have been used in a broad range of pharmaceutical applications [4]. The use of antibiotic liposomal delivery systems result in targeting of the antimicrobial agent at the site of infection to the infectious organism, increasing intracellular antibiotic concentrations, reducing drug toxicity, and improving tolerability [5].

The aim of this article was to provide an up-to-date overview of inhaled liposomal antimicrobials for lung infections, discussing the feasibility and therapeutic potential of these new strategies of preventing and treating bacterial, mycobacterial, and fungal infections.

2 Liposomal Antimicrobials for Lung Infections and Inhaled Drug-Delivery Systems

Liposome administration to humans has been principally used for drug delivery, vaccine adjuvants, medical diagnostics, and cosmetics. Liposomes, first discovered in the

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Key Points

Liposomes are biocompatible, biodegradable, and nontoxic vesicles able to encapsulate and carry drugs, and have been used in a broad range of pharmaceutical applications, including for nebulized antibiotic delivery

Use of inhaled liposomal antimicrobial treatment in lung Infections results in targeting of the antimicrobial agent at the site of infection to the infectious organism, increasing intracellular antibiotic concentrations, reducing drug toxicity, and improving tolerability

The most important liposomal antimicrobial drugs for inhalation include amikacin, tobramycin, ciprofloxacin, and amphotericin B

New avenues of research in the delivery of lung-targeted liposomal antimicrobials alone or in association with other treatment alternatives are being investigated

mid-1960s, are sphere-shaped vesicles (typically in the range of 20 nm–20 μm) consisting of one or more phospholipid bilayers of natural or synthetic origin enclosing an internal aqueous space. Liposomes are biocompatible, biodegradable, and nontoxic vesicles and are able to encapsulate and carry both hydrophilic and lipophilic drugs, allowing a precise release of the drug at the site of infection (Fig. 1) [6]. The liposomal encapsulation efficiency varies depending on the physicochemical characteristic of the drug (hydrophobic antibiotics can be intercalated in the phospholipid bilayer and hydrophilic antibiotics can be loaded in the aqueous core), the therapeutically feasible concentration of the drug into liposomes, the characteristics of the liposome vesicles (lipid composition, surface charge, size distribution, and lamellarity) and the preparation methods [5]. In addition, the size of liposomes plays an important role in the clearance.

The most common routes of liposomal drug delivery are oral, topical, and parenteral. In addition, inhaled drug delivery for treatment of respiratory diseases is an interesting alternative treatment option and has been used increasingly over the last few decades. Targeting antibiotics to the lungs via aerosolization can offer a way to achieve high exposure of antibiotics directly at the site of infection, including for antibiotics with poor lung penetration and tissue distribution (β-lactams, colistin, aminoglycosides, and glycopeptides). Optimal drug deposition is dynamic and is associated both with particle-related and with patient-related factors. Particle deposition patterns are critically dependent on size (ideally particles between 1 and 5 μm), proper viscosity (inversely proportional to the rate of aerosolization) and shape. Patient-related determinants include the diameter of

the large airways (relative to age), the quality of the inhalation technique in spontaneously breathing and mechanically ventilated patients, the presence of structural abnormalities (including mucus of the airways), and the ability of the lung [7]. Theoretically inhaled drugs may allow high drug concentration that exceed the minimal inhibitory concentration (MIC) for MDR pathogens as well as reduce the potential for development of drug resistance [8]. However, depending on the amount of drug inhaled and on the aerosol characteristics, a wide range of sputum concentrations exist throughout the lung with lower concentrations in the small airways and the risk of therapeutic levels below the MIC [9, 10]. Low concentrations below the MIC can lead to the development of high mutation rates and hence resistant subpopulations of bacteria that cannot be eradicated [10].
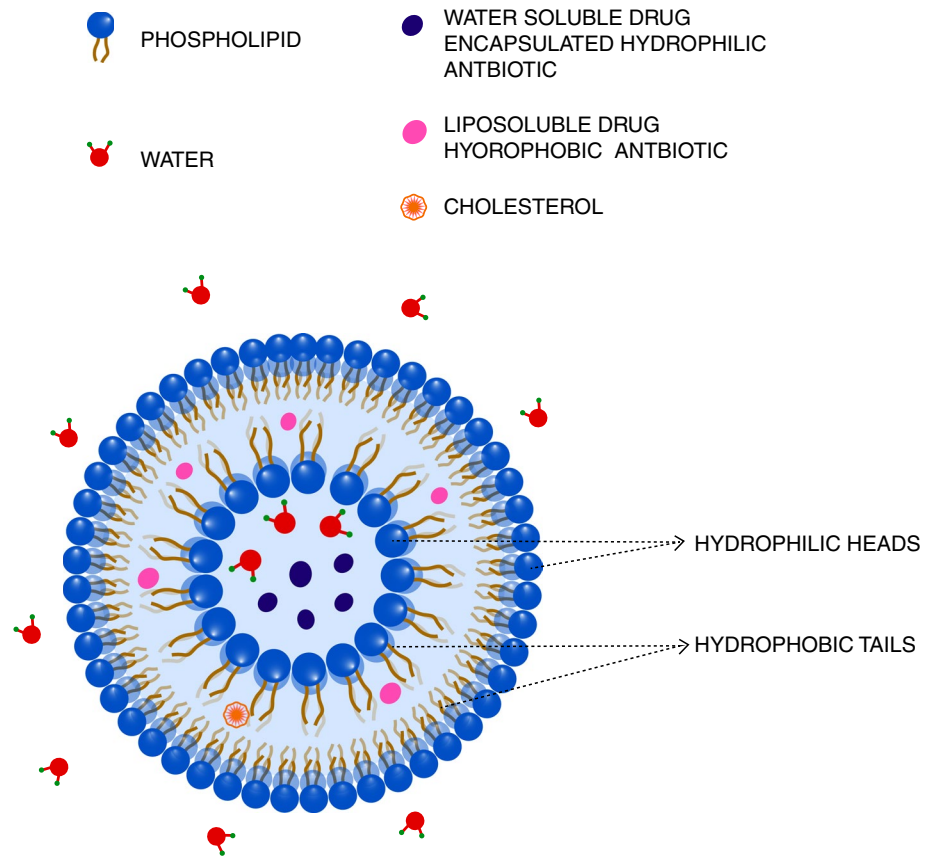
In addition, there are several factors that influence the clinical efficacy of inhaled antibiotics after delivery, especially for CF patients, although antibiotics may display activity against planktonic bacteria in vitro. Firstly, the antimicrobial aerosol particles need to dissolve in the epithelial lining fluid and in mucus. Secondly, the need for antibiotic diffusion toward the bacteria depends on the site, since in the case of CF with *Pseudomonas aeruginosa* chronic infections the location is most likely intraluminal within the mucus. Thirdly, microorganisms may have specific mechanisms to overcome antibiotic activity, including resistant mucoidal strains and increased biofilm production, and the environment of sputum-containing factors produced by the host and the microbes can reduce antibiotic activity [7, 11].

The properties of an inhaled antibiotic can be modified by use of liposomes, which enhance the therapeutic index of various agents, mainly through alterations in their pharmacokinetics and pharmacodynamics (PK/PD) enhancing drug delivery and retention at the desired target within the lung. Liposomes reduce drug toxicity and improve tolerability, leading to better compliance and to decreased respiratory side effects [12, 13].

Most inhaled antibiotics and antifungals have a short half-life in the lungs and require two- or three-times-daily administration. An important benefit of an inhaled liposome formulation is to provide a slow release of the antibiotic, which reduces the dosing frequency and continuously maintains high drug concentrations in the lung above the MIC.

Liposomes can also deposit drug within alveolar macrophages via phagocytosis to improve treatment of intracellular infections (although many chronic lung infections reside in the conducting airways of the lung lumen) and can have the ability penetrate biofilms to enhance activity against *P. aeruginosa* and other biofilm producer bacteria and fungi [14]. Previous studies have demonstrated that liposomes are stable in the presence of sputum and inhibitory factors, with the ability to protect the antibiotic from

Fig. 1 Liposomal antibiotic drug delivery

- PHOSPHOLIPID
- WATER
- WATER SOLUBLE DRUG ENCAPSULATED HYDROPHILIC ANTBIOTIC
- LIPOSOLUBLE DRUG HYOROPHOBIC ANTBIOTIC
- CHOLESTEROL

HYDROPHILIC HEADS

HYDROPHOBIC TAILS

inactivation, although the sputum may act as a barrier to larger liposomes [11].

Despite the advantages of a liposome vehicle for nebulized drug delivery, there are some additional factors that need to be considered. Liposome nebulization can lead to changes in their physical properties and deposition of liposomes within alveolar macrophages may affect their functions, although there is no evidence of changes in lipid content of pulmonary surfactant or lung immune response [15, 16]. With the current dearth of safety and tolerability data of liposomal inhaled antibiotics and antifungals, caution should be exercised, although the most common adverse events are local mild pulmonary effects [16, 17] (Table 1).

Modern technologies involving pulmonary drug delivery have employed new devices with liposomal formulations that should be aerosolized into particles that have a high fine particle fraction to achieve improved delivery throughout the lung.

There are four types of devices that are used for the pulmonary delivery of liposomes: pressurized metered-dose inhalers, dry powder inhalers, soft mist inhalers, and medical nebulizers [18].

Medical nebulizers are the most commonly used inhalation devices to deliver liposomes. Compared to other inhalation devices, nebulizers are particularly useful for diseases that require high pulmonary doses, with no need to perform drying procedures or to involve propellants, and are useful for patients who are unable to coordinate or achieve flow rates [18]. Nebulizers can be categorized into four general types: air jet, ultrasonic, vibrating mesh, and static mesh nebulizers [8]. The air jet type nebulizer is the most commonly used aerosolized delivery system in the world and is the best-established nebulizer for delivering liposomes. Vibrating mesh nebulizers have become increasingly popular, especially in pharmaceutical-sponsored studies, and have demonstrated excellent suitability in delivering vesicles in fine-particle fractions, including large liposomes and liposome aggregates [18]. Compared with jet nebulizers, vibrating mesh nebulizers are more efficient (less residual antibiotic in the nebulizer reservoir), but are more expensive to manufacture [19]. Vibrating mesh nebulizers have not been consistently shown to be superior to jet nebulizers in terms of pulmonary drug delivery, clinical outcome, and safety [20, 21]. The ultrasonic nebulizer has generally been shown to be the least suitable to deliver liposomes [19].

3 Inhaled Treatment for Acute and Chronic Infections and Possible Role for Liposomal Antimicrobials

Use of inhaled antimicrobials is an interesting therapeutic approach for optimizing respiratory tract infections in difficult-to-treat acute and chronic respiratory infections and for difficult-to-treat pathogens, including MDR bacteria, typical and atypical mycobacteria, and potential inhaled biowarfare agents. The possible role of liposomal inhaled preparations in different clinical settings is discussed below.

CF patients have a deficiency in mucociliary clearance, which makes the airways susceptible to infections that typically become chronic and lifelong [22]. CF registry data confirm that *P. aeruginosa* typically becomes the predominant organism cultured from the respiratory tract by adulthood and chronic *P. aeruginosa* infection is linked to progressive pulmonary function decline. The eradication and treatment of this organism from CF airways is particularly challenging. NCFB results from a permanent and progressive destruction of the airways leading to poor lung function, and is characterized by recurrent lung infection. Patients with NCFB and chronic infections with *P. aeruginosa* have a high risk of hospitalization, reduced quality of life, and increased mortality [23]. Current guidelines recommend inhaled tobramycin for individuals with CF and persistent *P. aeruginosa* infection who are aged 6 years or older [24]. Trials with long-term inhaled antibiotics in NCFB have indicated some benefits, but not in the way anticipated from trials in CF [25]. The new European Respiratory Society (ERS) guidelines for the management of bronchiectasis recognize the place of inhaled antibiotics, yet there is no international agency approval for NCFB [21, 26]. In these patients, the effectiveness of classical inhaled antibiotics is limited by poor penetration into infection sites, inactivation by sputum, non-penetration of biofilm, emergent resistance, bacterial phenotypic changes, and bacterial retention in mucous plugs. These limitations could be theoretically overcome with liposomal inhaled preparations and are discussed in the next paragraph with a focus on specific antimicrobials.

The global spread of MDR pathogens and limited efficacy of currently available intravenous antibiotics for the treatment of pneumonia in hospitalized and mechanically ventilated patients are also a growing cause for concern [13]. Despite lacking high-quality efficacy and safety data, and lack of international guideline recommendations, clinicians worldwide are increasingly using antibiotic nebulization for respiratory infections in critically ill adult patients. The role of liposomal antibiotics is yet to be defined in this setting [8, 21, 27, 28].

Aspergillus spp. is the most common cause of invasive fungal pulmonary infection in lung transplant recipients (LTR) and hematological patients, and despite the advances in antifungal drugs is associated with persistently high mortality. Inhaled antifungal agents have been investigated as antifungal prophylaxis and as adjunctive agents to systemic antifungals. In addition, inhaled antibiotics have been largely used off-label to prevent and treat bacterial in LTR, mainly in patients with devascularized anastomotic infections, history of MDR infections, and to prevent donor to host transmission [16, 29–31].

Use of nebulized antibiotics for tuberculous (TB) or nontuberculous mycobacterial (NTM) infections remains a very active area of research. Inhaled antibiotics for TB and NTM have the potential to reduce dosage (up to ten times less used for the standard oral treatment of care), to limit side effects, and to result in higher drug concentrations, potentially overcoming drug resistance [32]. Liposomal formulations have the ability to be more readily and effectively phagocytosed by alveolar macrophages within the airways and alveoli, with in vitro and in vivo therapeutic advantages for TB and NTM treatment [32, 33].

There are a number of other severe infections including melioidosis (endemic to South East Asia), potential inhaled biowarfare agents including *Francisella tularensis*, *Yersinia pestis,* and *Coxiella burnetiid*, and anthrax, which also do not have approved inhaled antibiotic therapies for prevention or treatment [34]. Limited data on the role of liposomal formulation are available in this setting but may improve treatment of intracellular infections [35].

4 Liposomal Antimicrobial Drugs for Lung Infections

Due to extensive developments in liposome technology, a number of liposome-based antibiotic and antifungal formulations are available for human use and many products are undergoing different clinical trials [12].

In vitro studies with animal models are the first step to evaluate new drugs essentially based on acute infection models and reduction of bacterial loads. However, there are no good animal models available for chronic lung infections. Despite this limitation, in vitro and in vivo studies, pharmacokinetic and pharmacodynamic characteristics, clinical efficacy, and the safety profile of liposomal drugs for lung infections are discussed with regard to liposomal amikacin, tobramycin, ciprofloxacin, and amphotericin B. In addition, limited in vitro and animal model data have been published for the use of nebulized liposomal formulations of gentamicin [36], capreomycin [37, 38], streptomycin [39], polymyxin B [40], isoniazid [41], rifampicin, [42], pyrazinamide, and ethambutol [39].

Table 1 summarizes available treatment options.

Table 1 Liposomal antimicrobial drugs for inhalation

Product name (manufacturer)	Lipid composition encapsulation	Recommended preparation and administration	Target	Side effects
Amikacin (Arikayce™)	1,2-Dipalmitoyl-sn-glycero-3-phosphocholine + cholesterol liposome	Single-use 5 mL V vial of amikacin sulfate diluted in 1.5% saline (70 mg/mL) Nnebulization for about 13–15 min Once daily	MAC lung disease[a] CF NCFB Pseudomonas aeruginosa	Hypersensitivity pneumonitis, hemoptysis, bronchospasm, exacerbations of underlying pulmonary disease, ototoxicity, nephrotoxicity, neuromuscular blockade
Tobramycin (LipoBiEDT-TOB ™)	Liposomal bismuth-ethanedithiol-loaded tobramycin	Once daily	Pseudomonas aeruginosa Burkholderia cepacian	Hypersensitivity pneumonitis, hemoptysis, Bronchospasm, exacerbations of underlying pulmonary disease, ototoxicity, nephrotoxicity, neuromuscular blockade
Ciprofloxacin (Lipoquin™)	Hydrogenated soy phosphatidylcholine + cholesterol liposome	Once daily	CF NCFB Pseudomonas aeruginosa	Hypersensitivity pneumonitis, hemoptysis, Bronchospasm
Ciprofloxacin (Pulmaquin™)	Hydrogenated soy phosphatidylcholine + cholesterol liposome	Once daily 3 mL liposome encapsulated ciprofloxacin 135 mg and 3 mL free ciprofloxacin 54 mg	CF NCFB Pseudomonas aeruginosa MAC	Hypersensitivity pneumonitis, hemoptysis, bronchospasm
Amphotericin B (Ambisome™)	liposomes	*Prophylaxis after lung transplant* 25 mg (6 mL) thrice weekly for the first 60 days after lung transplant 25 mg once weekly between 60 and 180 days 25 mg once every 2 weeks thereafter, for life *Treatment* 25 mg (6 mL) very 24–48 h	Prophylaxis/treatment for IPA and pulmonary IFI in patients with high-risk hematologic malignancies or LTR	Bronchospasm, nausea, vomiting

CF cystic fibrosis, *IPA* invasive pulmonary aspergillosis, *LRT* lung transplant recipients, *MAC Mycobacterium avium* complex, *NCFB* non-cystic fibrosis bronchiectasis

[a]US Food and Drug Administration approved

4.1 Liposomal Amikacin for Inhalation

Liposomal amikacin for inhalation (LAI) (trade name Arikayce ™) is a unique formulation that encapsulates aqueous amikacin in charge-neutral liposomes composed of dipalmitoyl phosphatidyl choline and cholesterol, which is very similar to surfactant [43, 44]. These lipids have a neutral charge, shielding the positively charged amikacin from the characteristic negatively charged components of CF sputum [45]. In addition, the small diameter (~ 300 nm) and uniform size of the liposomes permits the molecule to penetrate the meshwork of *P. aeruginosa* biofilm in CF sputum.

The activity of LAI has been studied extensively both in vitro and in vivo. LAI has been shown to have deposition of higher local concentrations and a prolonged lung half-life of several hours relative to liposome-free antibiotics [46]. LAI reduced and eradicated *P. aeruginosa* in a rat lung model more effectively than inhaled free amikacin and has shown in a macrophage model significant activity against NTM (*Mycobacterium avium* complex, MAC, and *Mycobacterium abscessus*) [44], without being associated with macrophage defects in immune function [47, 48].

Initial Phase I and Phase II studies in CF patients with chronic *P. aeruginosa* infections demonstrated that LAI was a safe drug with no clear dose-dependent pulmonary adverse events. In addition, LAI resulted in significant improvements in lung function after 14–28 days of treatment [14, 15]. Phase III studies of LAI compared to tobramycin inhalation solution in CF patients with *P. aeruginosa* infection did not demonstrate its superiority over conventional tobramycin inhalation, showing a comparable increase in forced expiratory volume in 1 s (FEV 1) at the end of three cycles [49].

In addition, LAI has other potential applications in the management of difficult-to-treat pulmonary infections including NTM. In the COVERT trial, LAI has proven statistically significant improvement in bacterial clearance when added to guideline-based therapy (GBT) therapies in refractory MAC patients, leading to increased sputum conversion (29% vs. 9%) [33]. Although current evidence for efficacy is limited to microbiological outcomes, LAI has received US Food and Drug Administration (FDA) approval for adult patients with MAC lung disease refractory to conventional therapy and with limited or no alternative treatment options. Furthermore, the CONVERT and extension trials are ongoing, with final results awaited to establish clinical benefit [50].

4.2 Liposomal Tobramycin for Inhalation

Many studies have described the efficacy of inhaled tobramycin (TOB) in lowering *P. aeruginosa* pulmonary infection in CF patients and the CF guidelines recommend chronic use of inhaled TOB in patients 6 years of age and older with moderate to severe lung disease and chronic *Pseudomonas* colonization [24]. The high dose required and the prolonged use of tobramycin has raised investigators' concerns about its toxicity.

In vitro studies show that encapsulation of TOB in liposomes enhances bacterial killing and increases efficacy against both *P. aeruginosa* and *Burkholderia cepacia* complex when compared with the corresponding conventional form [51, 52]. Bismuth-ethanedithiol (BiEDT) has been shown to inhibit the exopolysaccharide, lipopolysaccharide, and alginate production by *P. aeruginosa* and has been incorporated into a liposome-loaded tobramycin formulation (LipoBiEDT-TOB). A study on rats chronically infected with *P. aeruginosa* showed that the MIC of LipoBiEDT-TOB was 16-fold lower than the MIC of tobramycin alone and fourfold lower than the MIC of free BiEDT-TOB. In addition, LipoBiEDT-TOB has been shown shown to reduce the production of quorum-sensing molecules and virulence factors [53, 54]. There are limited data and no randomized clinical trial ongoing on the in vivo role of liposomal TOB for inhalation. In contrast, research has focused on tobramycin formulated as a dry powder (tobramycin inhalation powder or TIP), which is currently being investigated [55].

4.3 Liposomal Ciprofloxacin for Inhalation

Liposomal ciprofloxacin is prepared using negatively charged liposomes (liposome surfaces coated with polyethylene glycol or PEG) and is delivered by inhalation or intravenous routes. In preclinical studies liposomal ciprofloxacin has shown great promise in the treatment of *P. aeruginosa* and MAC lung infections, since it was able to infiltrate established biofilms and penetrate infected macrophages [56–58]. The in vivo release profile after intratracheal instillation in mice confirmed that the liposomal formulation satisfied the requirement for sustained levels of ciprofloxacin in the lung for a duration of 24 h, having a lung clearance half-life after inhalation of approximately 12 h (compared with 1 h for free ciprofloxacin).

There are two types of liposomal ciprofloxacin formulation commercially available: rapid-release formulations (Lipoquin™ or ARD-3100) and slow release formulations CF (Pulmaquin™ or ARD-3150). Lipoquin™ consists of ciprofloxacin active-loaded in a liposomal formulation, while Pulmaquin™ is a dual-release ciprofloxacin formulation for inhalation containing Lipoquin™ mixed with a solution of free ciprofloxacin for inhalation in order to provide an initially high peak of ciprofloxacin in the lung. In a clinical Phase II trial involving 22 adult CF patients, Lipoquin™ was shown to be safe and well tolerated when administered once daily for 14 days at a 300 mg dose [59]. It was the remarkable tolerability in CF that encouraged the exploration of Lipoquin™ in NCFB patients colonized with *P. aeruginosa*,

since this population of patients historically failed to show a positive clinical response to inhaled antibiotics, in contrast to CF patients [60].

Further Phase II clinical trials (ORBIT-1 for Lipoquin™ and ORBIT-2 for Pulmaquin™) to evaluate the efficacy and safety of liposomal ciprofloxacin in adults with chronic *P. aeruginosa* lung infection by ciprofloxacin-sensitive strains and CF/NCFB have proven that a once-daily inhaled dose had strong antipseudomonal microbiological efficacy, was well tolerated, and delayed the risk *P. aeruginosa* exacerbation [59, 61]. Based on the totality of the preclinical and clinical evidence, 6 mL of once-daily Pulmaquin™ was selected for the Phase III program in NCFB, with the ORBIT-3 and ORBIT-4 trials [57]. Pulmaquin™ led to a significantly longer median time to first pulmonary exacerbation compared with placebo in ORBIT-4, but not in ORBIT-3 or the pooled analysis. Inconsistency between the trials and disappointing results suggest the need for further research, but could support the rationale for the use of inhaled ciprofloxacin in this specific setting [62].

4.4 Liposomal Amphotericin B for Inhalation

Amphotericin B has broad activity against various yeasts, molds, and dimorphic fungi, including Aspergillus species.

The first stage in the pathogenesis of *Aspergillus* spp. disease includes inhalation of spores, colonization of *Aspergillus* spp. in the airways, and its proliferation. In patients with altered local or systemic defense mechanisms, colonization may cause invasive pulmonary aspergillosis (IPA).

Several types of nebulized amphotericin B preparations are available. The unique particle structure and size of each amphotericin B product is inversely related to the aerosolized particle size. To achieve aerosolization, the large molecules of the various intravenous amphotericin B formulations—deoxycholate (AmBd), liposomal (L-AmB), colloid dispersion (ABCD), and lipid complex (ABLC)—result in small-aerosolized particle sizes ranging from 0.90 to 2.43 μm. The variable sizes of these different aerosolized amphotericin B formulations influence the extent of alveolar distribution and the half-life of the drug in the lungs [63].

Current clinical evidence for the use of liposomal aerosolized delivery in preventing fungal infections is limited to L-AmB, with few data on ABLC [64, 65]. Other publications have reported good tolerance to n-LAB and an optimal safety profile with no evidence of significant systemic absorption, effects on respiratory function, or changes in lipid content of pulmonary surfactant, permitting long-term administration [16, 66]. After comparing nebulized L-AmB and nonliposomal amphotericin B deoxycholate, rates of IPA were low and comparable between the two treatment groups, but the liposomal form was better tolerated and had a longer half-life. In addition drug concentrations after nebulized L-AmB remained high and adequate for *Aspergillus* spp. prophylaxis over 14 days, a convenient administration interval [67].

Current clinical evidence for the use of aerosolized delivery is limited to amphotericin B products for prophylaxis against IPA in patients with LTR, but rigorous randomized controlled trials evaluating their use after transplant have not been conducted [68]. Moreover, prophylactic inhalation of L-AmB has been proven to also significantly reduce the incidence of IPA in hematological patients with chemotherapy-induced prolonged neutropenia (≥ 10 days) [16, 69].

L-AmB may serve also as an alternative method of treatment for patients with pulmonary fungal infections either used alone or in combination with systemic treatment. Nebulized L-AmB has been used as adjunctive treatment in devascularized anastomotic infections in LTR and for fungal infections other than aspergillosis [70]. Furthermore, L-AmB may have a place in the treatment of patients with corticosteroid-dependent allergic bronchopulmonary aspergillosis [71].

5 Conclusions

The potential use of liposomal compounds for the treatment of acute and severe infections has recently emerged. Liposomes are safe and suitable for delivery of variety of antibiotics and antifungals to improve the therapeutic index of encapsulated agents and reduce drug toxicity. The combination of specifically designed drug formulations and modern, high efficiency delivery devices has the potential to overcome current challenges with aerosolized treatment. Their effects on infected macrophages and biofilms have promising applications in CF, NFCF, and pulmonary NTM infections. However, the promise of liposomal aerosol formulations has partially fulfilled the developed expectations. New avenues of research in the delivery of lung-targeted liposomal antimicrobials alone or in association with other treatment alternatives are needed.

Compliance with Ethical Standards

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