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New Inhaled Antimicrobial Formulations for Use in the Cystic Fibrosis Patient Population

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Abstract

Objective: To review the current literature on inhaled antibiotic therapies currently in clinical trials for cystic fibrosis (CF) patients. **Data Sources:** A literature search was performed using PubMed (1975 to September 2015), International Pharmaceutical Abstracts (1970 to September 2015), and MEDLINE (1946 to September 2015) to identify studies for inclusion. The following search terms were used: *cystic fibrosis, inhaled amikacin, inhaled liposomal amikacin, inhaled vancomycin*, and/or *inhaled levofloxacin*. **Study Selection and Data Extraction:** All English-language phase II to III studies evaluating efficacy and/or safety, case reports, and retrospective studies of inhaled amikacin, inhaled vancomycin, and inhaled levofloxacin in CF patients were included. **Data Synthesis:** Currently available inhaled antibiotics, tobramycin and aztreonam, have demonstrated improvement in respiratory function of CF patients. Newer agents have shown potentially similar efficacy, with improvement in ease of use. Limited data suggest that inhaled liposomal amikacin and levofloxacin are both noninferior to tobramycin in terms of improvements in respiratory function. Inhaled levofloxacin has a lower rate of hospitalizations secondary to respiratory exacerbations and a reduction in the *Pseudomonas aeruginosa* sputum density compared with inhaled tobramycin. Inhaled vancomycin use has been documented in case reports and 2 small retrospective eradication trials, although data are limited to support its use. **Conclusions:** The horizon of inhaled antibiotic choices for CF patients is promising. The introduction of different drug classes and formulations to treat resistant Gram-negative and Gram-positive organisms increases the number of options for patients for both eradication and treatment of chronic colonization.

Keywords

inhaled antibiotic, cystic fibrosis, amikacin, levofloxacin, vancomycin

Introduction

The treatment of cystic fibrosis (CF) is constantly evolving with the advent of new therapeutic agents and modalities of drug delivery. Over the past several decades, the median age of survival has been steadily increasing, although the exact reason is likely multifactorial. Still, these patients suffer from a variety of chronic issues associated with their disease, including recurrent infections and respiratory exacerbations.[1]

Thick secretions in the lungs foster an environment for bacteria and other pathogens to flourish. Often, these bacteria are multidrug resistant and require antibiotic treatments with potentially harmful side effects. Inhaled antibiotics are most commonly used as chronic maintenance therapy to decrease secretions and eradicate or suppress the colonized organisms growing in the lungs. The goal is to prevent worsening respiratory function. These antibiotics are both associated with a significant improvement in forced expiratory volume percentage (FEV_1%) predicted from baseline.[2] When given via inhalation, these medications achieve high pulmonary concentrations and limit systemic absorption and adverse effects.[3]

Currently, there are 2 US Food and Drug Administration (FDA)-approved inhaled antibiotics, tobramycin, an aminoglycoside, and aztreonam, a monobactam. Tobramycin and aztreonam both have activity against Gram-negative

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bacteria that are common CF pathogens, in particular *Pseudomonas aeruginosa*. Each of these medications is given for 28 days followed by a 28-day drug holiday. Tobramycin is available in a dry powder inhaler and solution for nebulization, both dosed twice daily. Aztreonam is available via nebulization given 3 times daily. Colistin, a polymyxin antibiotic not approved for inhaled use in the United States, has been studied head to head with inhaled tobramycin, with similar changes in FEV_1% predicted, yet with a higher rate of drug-related adverse events and discontinuation.[4] The advantage of colistin is its broader spectrum of activity compared with tobramycin or aztreonam, which could be beneficial in a patient with a multidrug-resistant organism.

The CF Foundation has recommended chronic use of inhaled tobramycin in patients 6 years of age and older with moderate to severe lung disease and chronic *Pseudomonas* colonization.[2] For patients with mild lung disease and documented persistent *P aeruginosa*, the chronic use of antibiotics to improve lung function has a moderate benefit and is still recommended.[2] There are now similar recommendations for inhaled aztreonam use from the guidelines. For all other antibiotics, there is insufficient evidence to support a recommendation for chronic use.

With the limited drug classes represented with our current agents and the advent of further resistance to those agents, several new medications are entering the market with hopes of improving patient outcomes and satisfaction. This article will review the new inhaled antibiotics namely levofloxacin, amikacin, and vancomycin that the CF Foundation is following in the drug developmental pipeline.[5]

Data Sources

A systematic search was performed using PubMed (1975 to September 2015), International Pharmaceutical Abstracts (1970 to September 2015), and MEDLINE (1946 to September 2015). Combinations of the following search terms were used: *cystic fibrosis, inhaled amikacin, inhaled liposomal amikacin, inhaled vancomycin*, and *inhaled levofloxacin*. References from retrieved articles were manually searched for additional citations. Clinicaltrials.gov was searched for ongoing research.

Study Selection and Data Extraction

All English-language phase II to III studies assessing the efficacy and/or safety of inhaled amikacin, inhaled vancomycin, and inhaled levofloxacin in adult and pediatric CF patients were evaluated and included in this article. Randomized controlled trials, pharmacokinetic/pharmacodynamics studies, observational studies, and case reports were included. A total of 9 studies were included: a levofloxacin pharmacokinetic study, phase II and III open-label trial for levofloxacin, phase II and the open-label extension of the phase II trial for amikacin, and 2 retrospective reviews and 2 case reports for vancomycin. All studies including patient data are summarized in Table 1.

Levofloxacin

Levofloxacin is a third-generation fluoroquinolone with broad-spectrum Gram-negative and Gram-positive activity, including coverage against *P aeruginosa*. Compared with second-generation fluoroquinolones, such as ciprofloxacin, levofloxacin provides greater activity against Gram-positive organisms. The antimicrobial action of fluoroquinolones is mediated through the inhibition of 2 DNA topoisomerase enzymes: DNA gyrase and type IV topoisomerase. Inhibition of these enzymes interferes with DNA repair and replication, and ultimately leads to bacterial cell death.[6]

Levofloxacin has activity against a number of respiratory pathogens that are a concern in CF patients, including *P aeruginosa, Escherichia coli*, and *Haemophilus influenzae*.[7] Aerosol antibiotics can produce local drug concentrations that are associated with improved antibacterial efficacy of existing agents.[8] MP-376 and APT-1026 are two inhaled formulations of levofloxacin that have been developed for treatment of endobronchial infection in CF patients. Each is administered using a customized, vibrating, and perforated-membrane eFlow® nebulizer (PARI Pharma, Munich, Germany).[9]

Pharmacokinetics

Geller et al[9] completed a multicentered, single-blinded study that evaluated the pharmacokinetics of 2 concentrations of MP-376. A total of 10 CF patients 16 to 60 (mean age 32) years old were enrolled in this trial. Patients were to receive 180 mg (50 or 100 mg/mL) on day 1 followed by 7 days of daily treatment with 240 mg (100 mg/mL). On days when pharmacokinetic samples were obtained, patients rinsed their mouths and swallowed 15 mL of a suspension containing 400 mg magnesium hydroxide and 400 mg aluminum hydroxide 5 minutes before and after administration of the drug to minimize oral absorption of any swallowed levofloxacin. The authors reported that nebulized MP-376 produced higher concentrations of levofloxacin in the sputum with lower systemic concentrations. After administration of MP-376 180 mg (50 and 100 mg/mL formulations) and 240 mg (100 mg/mL), the mean sputum maximum plasma concentration (C_{max} 2563, 2932, and 4691 mg/L, respectively) was higher than the mean serum C_{max} (0.95, 1.28, and 1.71 mg/L, respectively). Additionally, MP-376 180 mg (50 and 100 mg/mL) and 240 mg produced a 24-hour sputum area under the concentration curve (AUC; 1891, 1961, and 4517 mg h/L, respectively) greater than the 24-hour serum AUC (8.1, 9.9, 16.9 mg h/L,

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Table 1. Summary of Evidence for Inhaled Antibiotics in Cystic Fibrosis Patients.

Reference	Study Design	Dosage Regimen	Nebulizer	Concomitant Antibiotic(s)	n (Mean Age, years)	Comments/Outcomes
Levofloxacin						
Geller et al[9]	Pharmacokinetics/ Safety	MP-376 180-mg dose (50 mg/mL or 100 mg/mL concentration) followed by 7 days of daily 240-mg dose (100 mg/mL concentration)	PARI eFlow®	None	10 (32)	Pharmacokinetics, safety, and tolerability were similar between the 2 formulations, advanced into late-stage clinical development
Geller et al[10]	Phase II, randomized, multicenter, double blinded	MP-376 120 mg daily, 240 mg daily, 240 mg twice daily, or placebo for 28 days	PARI eFlow®	Azithromycin	151 (28.7)	MP-376 inhalation (all doses) resulted in reduced sputum density of *Pseudomonas aeruginosa* compared with placebo ($P = 0.001$). Greatest decrease with 240-mg doses (placebo, 8%; MP-376 240 mg once a day, 32% [$P = 0.004$]; MP-376 240 mg inhaled twice a day, 36% [$P = 0.004$]).
Elborn et al[11]	Phase III, noninferiority trial	APT-1026240 mg twice daily or TIS 300 mg twice daily for three 28-day on/28-day off cycles	PARI eFlow®	None	282 (28)	Noninferiority was demonstrated with LIS compared with TIS (1.86% predicted mean FEV_1 difference [95% CI = −0.66 to 4.39%]). LIS was determined to be safe and well tolerated. Dysgeusia was the most common adverse event with LIS (46/186 [25.3%])
Liposomal amikacin						
Clancy et al[13]	Phase II	70, 140, 280, and 560 mg once daily ×28 days	PARI eFlow®	None	105 (21.9)	Significant improvement in FEV_1 in 280-mg and 560-mg dosages versus pretreatment values and placebo; 560-mg dosage experienced sustained increases through 56 days. Also significant reduction in sputum density with 560-mg dosage
Clancy et al[13]	Phase II open-label extension	560-mg Once daily ×28 days followed by 56 days off treatment	PARI eFlow®	None	49 (17.4)	Significant improvement and sustained response in FEV_1; 48 out of 49 patients reported adverse drug effects, yet <10% considered it to be contributed by medication
Vancomycin						
Doe et al[19]	Retrospective review	Nebulized vancomycin 200 mg 4 times daily + 2 oral antibiotics for 5 days	N/A	Fusidic acid, rifampicin, trimethoprim	37 (25.6)	81% Eradication rate at 6 months after first eradication course; nebulized vancomycin (n = 18; success rate 61%)
Solis et al[18]	Retrospective review	Nebulized vancomycin 4 mg/kg/dose 4 times a day for 5 days	N/A	Topical and/ or oral vancomycin	15 (median: 117 months)	Success rate: 10/18 episodes (55%); mean time MRSA-free: 12 months (6-36 months); FEV^1 did not change significantly (only able to be performed in 8 children); all strains sensitive to vancomycin
Máiz et al[20]	Case report	250 mg in 4-mL sterile water every 12 hours for 17 months	Venstream®	None	1 (10)	Lung function improved after 17 months of treatment (FEV^1 63% posttreatment vs 53% pretreatment); pulmonary exacerbations decreased; MRSA bacterial colony counts in sputum decreased
Hayes et al[21]	Case report	250 mg In 5-mL sterile saline twice daily for 6 months	PARI LC Plus®	None	1 (34)	Successful eradication of MRSA after 6 months of treatment

Abbreviations: FEV_1, Forced expiratory volume in 1 s; LIS, levofloxacin inhalation solution; MRSA, methicillin-resistant *Staphylococcus aureus*; TIS, tobramycin inhalation solution.

respectively). The serum levofloxacin exposure from MP-376, 180- and 240-mg doses using the 100-mg/mL formulation was only 12% to 19% of the 24-hour serum AUC achieved in another study of CF patients dosed with 750 mg oral levofloxacin. This pharmacokinetic study demonstrated that the 100 mg/mL formulation produced similar sputum concentrations to those obtained by the 50 mg/mL dose and required less time for nebulization. The authors concluded that the aerosol administration of MP-376 produced sputum levofloxacin exposure that should maximize bacterial killing and minimize the development of resistance. It is theorized that lower systemic exposures with aerosol MP-376 should improve the safety and tolerability profile compared to that of either parenteral or oral administration of levofloxacin.[9]

Evaluation of Clinical Efficacy and Safety

Geller et al[10] conducted a randomized, double-blind phase IIb study to assess the efficacy and safety of MP-376. A total of 181 patients were screened, with 151 patients randomly assigned to receive 1 of 3 MP-376 inhalation dosing regimens (120 mg daily, 240 mg daily, and 240 mg twice daily) or placebo for 28 days. A sample size of 128 was estimated as providing 80% power to detect a difference between treatment arms using a 2-sided analysis of variance, with $\alpha = 0.05$. The primary efficacy end point of this study was change in sputum *P aeruginosa* density from day 1 to day 28. A total of 6 patients withdrew from the study as a result of adverse events; 1 patient withdrew consent; and 1 patient withdrew because of a hospitalization not related to the study drug, leaving 143 patients who completed the study.

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The baseline FEV_1% predicted was 52.3%, and the average age was 28.7 years. Patients were allowed to continue baseline respiratory medications throughout the trial: dornase alfa (78%; n = 118), azithromycin (74%; n = 112), and hypertonic saline (46%; n = 70). At baseline, only 38% of *P aeruginosa* isolates were susceptible to levofloxacin based on a minimum inhibitory concentration ≤2 μg/mL, the breakpoint used for systemic dosing with levofloxacin. The authors reported that mean sputum *P aeruginosa* density decreased from baseline at day 28 in patients using MP-376 but increased in patients in the placebo group ($P < 0.01$). The greatest decrease was seen in the 240-mg dosing groups (once or twice daily) (placebo, 8%; MP-376 240 mg once a day, 32% [$P = 0.004$]; MP-376 240 mg inhaled twice a day, 36% [$P = 0.004$]). In addition, more patients in the MP-376 treatment groups experienced a >10% increase in adjusted FEV_1% predicted on day 28 compared with the placebo group (placebo, 27%; MP-376 120 mg inhaled every day, 59%; MP-376 240 mg inhaled every day, 54%; MP-376 240 mg inhaled twice a day, 72% [$P < 0.001$ vs placebo]). A clinically and statistically significant reduction in risk for needing additional antibiotics was observed for the MP-376 120 mg inhaled every day (hazard ratio [HR] = 0.29; $P = 0.007$), 240 mg inhaled every day (HR = 0.39; $P = 0.021$), and 240 mg inhaled twice a day (HR = 0.21; $P < 0.001$) treatment groups.[10]

The percentage of patients reporting at least 1 adverse event was similar for placebo (73%; 27/37) and MP-376 (73.7%; 84/114) groups. During the study, adverse events reported with the highest frequency in the MP-376-treated patients were taste disturbance (45 patients; 40%), cough (18 patients; 16%), and headache (9 patients; 8%). The authors concluded that only 5 (3.3%) and 3 (2%) cough and headache episodes, respectively, were related to the study drug. A total of 4 serious adverse events occurred during the 28-day study period: 2 cases of acute pulmonary exacerbation in the placebo group, 1 occurrence of bronchitis in a placebo patient, and 1 case of appendicitis unrelated to the study drug in a patient administered MP-376, 120 mg every day. The authors concluded that MP-376 given for 28 days reduced *P aeruginosa* density and the need for other antibiotics and produced improvements in pulmonary function. MP-376 was well tolerated, with only 8 patients discontinuing the study. Adverse events were found to be mild-moderate in severity and did not increase in frequency or severity with increases in dose.[10]

A recent noninferiority study conducted by Elborn et al[11] evaluated the safety and efficacy of levofloxacin inhalation solution (LIS) versus tobramycin inhalation solution (TIS) in stable CF patients. A phase 3, open-label, active comparator trial was conducted at 125 CF centers in Europe, the United States, and Israel form February 2011 to August 2012. CF patients ≥12 years old with chronic *P aeruginosa* airway infections who had received at least three 28-day courses of inhaled tobramycin solution were enrolled in the study. Patients were randomized to receive three 28-days-on 28-days-off cycles of either LIS 240 mg (2.4 mL of 100 mg of levofloxacin per mL) twice daily or TIS 300 mg (5 mL) twice daily. LIS was delivered via the PARI investigational eFlow nebulizer, and TIS was delivered via the PARI LC Plus nebulizer.[11]

A total of 282 patients were enrolled; 182 received LIS and 90 received TIS. The primary end point was the relative change in FEV_1% predicted at day 28 from baseline. *P aeruginosa* was isolated in 93% of patients with no difference in susceptibility patterns between the 2 groups. Noninferiority was demonstrated with LIS compared with TIS (1.86% mean FEV_1 predicted difference [95% CI = −0.66 to 4.3%]). There was no significant difference in time to first exacerbation in the LIS group compared with the TIS group. Additional antibiotics were administered earlier in the TIS group compared to the LIS group (median time; 110 days and 140 days respectively [$P = 0.04$]). A lower proportion of patients in the LIS group required hospitalization during the 168-day trial period for respiratory exacerbations compared with the TIS group ($P = 0.04$). The reduction in *P aeruginosa* sputum density and the increase in the levofloxacin minimum inhibitory concentration of *P aeruginosa* isolates were similar for both groups.[11]

During the study, 1 patient in the TIS group withdrew from the study as a result of adverse events, and 6 patients in the LIS group withdrew as a result of adverse events. Also, 1 patient in the LIS group discontinued the study drug because of the adverse event of costochondritis that resolved following discontinuation of the study drug. The authors also reported that 1 LIS patient had symptoms consistent with tendonitis; however, they did not specify whether this patient discontinued the study drug. The incidence of at least 1 adverse event was similar between the TIS and LIS groups: 90 patients (100%) and 180 patients (98.9%) respectively. There was a higher incidence of dysgeusia (taste disorder) in the LIS group compared with TIS (46/182 patients [25.3%] vs no patients [0%], respectively). The authors concluded that LIS is noninferior to TIS in CF patients for the treatment of chronic *P aeruginosa* infections over 28 days. There was no difference observed in the occurrence of pulmonary exacerbations between the 2 groups. However, the incidence of hospitalizations caused by pulmonary exacerbations was significantly less with LIS. The safety profiles are similar between the 2 groups. Taste distortion was the only notable difference in adverse events between TIS and LIS, but this did not appear to have an impact on adherence.[11]

Liposomal Amikacin

Amikacin is an aminoglycoside antibiotic with primary activity against Gram-negative bacteria, including

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P aeruginosa. P aeruginosa grows in small colonies and tends to form a biofilm that is difficult to penetrate. Aminoglycosides work by inhibiting protein synthesis through binding at the 30S ribosomal subunit but struggle to penetrate this barrier because of electrostatic interactions.[12] The currently available inhaled aminoglycoside on the market in the United States—namely, tobramycin—is delivered via nebulization as aqueous medication, yet it is a small molecule that is rapidly removed from the lungs following inhalation. Arikace™, the proposed brand name for an investigational inhaled liposomal formulation of amikacin composed of dipalmitoyl phosphatidylcholine and cholesterol, has demonstrated the ability to penetrate mucus and biofilms.[13] Through slow and sustained release of medication, drug is localized to the lungs and allows for once-daily dosing with similar efficacy.[12,13]

Pharmacokinetics

Inhaled liposomal amikacin is delivered via an investigational eFlow® nebulizer system. This system produces aerosols with a high density of drug as well as droplet size precision by way of a vibrating, perforated membrane.[14] Once administered, the liposomal formulation permits a slow and controlled release of medication that allows effective concentrations in the target tissue without resultant elevated systemic trough levels. The pharmacokinetics and pharmacodynamics of this medication have been researched in parallel with phase II safety and efficacy studies. In a dose-ranging placebo-comparator study,[15] 69 patients received the study drug for 28 days via a nebulizer. Serum, sputum, and urine were collected on days 1, 14, and 28; serum was collected just prior to the dose and 6 to 8 hours following the dose, sputum prior to dosing and 0 to 1 hour following the dose, and urine at 12-hour intervals for up to 24 hours. The pharmacokinetics were described as zero-order for absorption to the lungs, a first-order process for distribution to a central compartment, and a first-order renal elimination process ($r^2 = 0.965$). The authors found that following the administration of all dosages, concentrations of drug were much higher in the sputum than in the serum, confirming high lung penetration and low systemic exposure. The concentration in the sputum as well as the serum increased along with increased dose.[15]

The authors also performed analyses on pharmacokinetic-pharmacodynamic relationships. When comparing the relationship between dose or day 1 AUC and the relative change in FEV_1 and predicted change in FEV_1, there was a modest yet significant correlation: $r_s = 0.211$ to 0.419, $P \leq 0.033$. This relationship remained significant at days 7, 14, 21, 28, and 56 suggesting the importance of dose and drug concentration in clinical efficacy and durability. The authors found that the sputum samples obtained had significantly higher amikacin concentrations than serum concentrations, demonstrating a concentrated antibiotic presence in the lungs with little systemic exposure. Of note, the models predicted estimated improvements in change in FEV_1% predicted with 560 mg of inhaled amikacin of 9.94%, which is higher than that seen in previous CF patients treated with tobramycin and comparable to that in previous patients treated with inhaled aztreonam.[15]

Evaluation of Clinical Efficacy and Safety

There is only 1 phase II study that has been published to date detailing the safety and efficacy of liposomal amikacin in CF patients. Clancy et al[13] randomized 105 participants to either placebo or once-daily liposomal amikacin at various doses (70, 140, 280, and 560 mg).[13] Patients were included from the United States and Europe if they had a CF diagnosis, were ≥6 years old, had an FEV_1 ≥40% predicted, had chronic *P aeruginosa* colonization, and had clinical stability off inhaled or intravenous antibiotics for at least 28 days. The initial 19 participants in the United States started with lower doses (70 and 140 mg), but all doses were increased to 560 mg based on evidence from the parallel European cohort and on recommendation from a prespecified Data Safety Monitoring Board. Tolerability was defined as experiencing a reduction in FEV ≥15% within 30 minutes of administration. The authors reported no significant difference in frequency of adverse events between all the doses and placebo. Liposomal amikacin was deemed to have better tolerability (2.8% vs 11.1%), and fewer patients reported adverse events: 55.6% in the 560-mg group versus 61.1% in the placebo arm. Respiratory adverse events and pulmonary exacerbations were reported more often in the liposomal amikacin group (25% vs 17%).

FEV_1 significantly increased with the 280- and 560-mg doses as compared with pretreatment values and placebo. For the 280-mg dose group, FEV_1 change relative to placebo was 0.101 L as compared with 0.011 L ($P = 0.009$) but returned to pretreatment values by 56 days. The 560-mg dosage demonstrated a significant increase in FEV_1 (0.081 vs 0.011 L, $P = 0.033$) that was sustained through 56 days (0.093 vs −0.032 L, $P = 0.003$). In addition, there was a significant reduction in sputum density in the 560-mg group when compared with placebo and pretreatment values ($P = 0.007$ and 0.021, respectively).[13]

Following this study, 49 patients were enrolled in an open-label extension that included 6 cycles of liposomal treatment for 28 days followed by 56 days off treatment.[13] FEV_1 was significantly improved from baseline after 6 cycles of treatment (7.9%, $P < 0.0001$) and demonstrated a sustained response 56 days posttreatment (5.7%, $P = 0.0001$). In addition, the density of the *P aeruginosa* was significantly reduced from baseline over all 6 cycles. Although 48 of the 49 patients reported adverse drug reactions, most of these were mild, and <10% were considered to

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be contributed by the medication. The authors conclude and suggest that based on the results of these trials, liposomal antibiotics may provide significant benefits as compared with nonliposomal formulations.[13]

Vancomycin

There is no current consensus on the management of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in CF patients. A recent *Cochrane Database Systematic Review* was unable to identify any randomized or quasi-randomized controlled trials for inclusion. However, they did identify 3 ongoing trials.[16] Inhaled vancomycin has been utilized for both eradication (or decolonization) of initial isolation and management of persistent MRSA infection. Different combination strategies, including oral, IV, and/or inhaled antibiotics have been reported.[17-19] Previous data have included a compounded solution of nebulized vancomycin from the IV formulation in doses ranging from 125 to 500 mg twice daily. Vancomycin inhalation powder (AeroVanc™) delivered by a capsule-based device is currently under investigation for both eradication of newly cultured MRSA and treatment of persistent MRSA lung infection. The product is currently being tested at doses of 32 and 64 mg twice daily. A phase II trial in 87 CF patients with persistent MRSA infection has recently been completed, with results pending.

Solis et al[18] completed a 12-year retrospective study of 12 children with CF and MRSA colonization to evaluate the efficacy of an eradication protocol that included oral, topical, and nebulized vancomycin and antistaphylococcal hygiene. The protocol was successful in 10 of 18 episodes (55%) of MRSA colonization. Success was defined as remaining MRSA free for a minimum of 6 months after discontinuation of the protocol. In addition, 7 of the patients achieved complete MRSA eradication. Although this study does demonstrate the success of an eradication protocol, it was conducted in a small patient population with a low prevalence of MRSA colonization (6.5%) and only consisted of pediatric patients 6 to 13 years old; also, the contribution of nebulized vancomycin to the results is difficult to extrapolate because of the combination strategy utilized.

Doe et al[19] reported the results of a successful infection control policy and MRSA eradication strategy over a 10-year period (1998-2008) in 37 adult CF patients. Patients had to have at least 1 positive MRSA culture and were treated with a combination or oral and inhaled antibiotics. After 6 months of treatment, 81% of patients achieved successful eradication (defined as 3 consecutive negative sputum and peripheral cultures over 6 months). Nebulized vancomycin was formally added to the protocol in 2005 (200 mg 4 times daily with bronchodilator). The authors report that it was only used 18 times; however, it resulted in successful MRSA eradication 11 times (61%). The primary adverse effect of inhaled vancomycin was chest tightness. Three patients were unable to complete the treatment course. Again, this was a small study and the intervention involved both nonpharmacological and pharmacological strategies, so the effect of nebulized vancomycin alone is unknown.

There have been 2 published case reports on the use of aerosolized vancomycin in CF. Máiz et al[20] report the case of a 10-year-old boy with CF who was chronically colonized with MRSA and received aerosolized vancomycin for 17 consecutive months. On completion of therapy, his clinical condition and FEV_1% predicted had improved; the number of moderate pulmonary exacerbations had decreased (1 since vancomycin initiated compared with 4 the year prior); and bacterial counts of MRSA in the sputum had decreased. Unfortunately, the investigators were not able to eradicate the MRSA colonization from the lower airways.

Hayes et al[21] report the case of a 34-year-old man with CF who presented with an acute illness 4 months following a bilateral sequential lung transplant. MRSA was repeatedly colonized from the sputum despite aggressive intravenous antibiotic therapy with linezolid. In an effort to eradicate the MRSA colonization, aerosolized vancomycin was administered for 6 months. Broncheolar lavage fluid cultures obtained from each allograft 3 and 6 months after initiation of therapy showed successful eradication of MRSA. Two additional broncheolar lavage cultures from multiple lobes obtained 6 and 12 months following discontinuation of inhaled vancomycin were negative for MRSA. In addition, the patient's FEV_1 improved from baseline to 75% predicted.

Discussion

While the medical community waits for curative treatment for the CF population, the pathogens that colonize and cause respiratory exacerbations continue to become more resistant to our current therapies. Patients and their families need therapies that can suppress the bacterial burden in an effective, efficient, and safe manner. FDA-approved inhaled tobramycin and aztreonam as well as other inhaled antibiotics such as colistin have demonstrated benefit to this effect. New therapies include inhaled levofloxacin, liposomal amikacin, and vancomycin. Although the data supporting these therapies are sparse and forthcoming, the initial results have shown promise.

Levofloxacin offers a third class of antibiotics available via inhalation. It has potent activity against several Gram-negative respiratory pathogens and has demonstrated a reduction in the need for other antipseudomonal antibiotics. In direct comparison studies with tobramycin, levofloxacin was deemed noninferior. Those patients treated with levofloxacin had a lower rate of hospitalizations secondary to respiratory exacerbations and a reduction in the *P aeruginosa*

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sputum density. In both phase II and phase III studies, patients in the levofloxacin group reported a higher incidence of taste disturbances, potentially leading to long-term nonadherence. Liposomal amikacin has demonstrated efficacy versus placebo and may have the advantage of once-daily dosing compared with tobramycin. Unpublished phase II and III data suggest that amikacin is noninferior to tobramycin in terms of change in FEV_1, and it demonstrated a sustained and superior improvement in patient satisfaction scores. With growing resistance rates to bacteria such as *P aeruginosa*, these therapies will offer alternative options to currently available agents.

Although only retrospective in nature, inhaled vancomycin has been used for MRSA eradication in a small number of pediatric and adult CF patients, with promising results. In 2 case reports, patients treated for MRSA in the sputum completed therapy, with an improvement in their clinical condition, the number of pulmonary exacerbations, and FEV_1% predicted. Data, however, are limited and MRSA eradiation was only seen in one of the case reports. Results of the recently completed phase II trial of the investigational inhalation vancomycin powder are highly anticipated; however, further study is required to determine the place in therapy of inhaled vancomycin.

The notion of inhaled antibiotics producing high concentrations at the site of infection while reducing systemic levels and effects is an attractive concept. Although dose-finding studies have demonstrated dosages that may be effective, sputum drug concentration may be unreliable as a marker for efficacy.[3] Inhaled antibiotics have generally been perceived as safe in phase II studies, but long-term studies in a larger population will be necessary to establish safe use in this population.

The horizon of antibiotic options for CF patients is promising. Several new inhaled antibiotics have demonstrated the potential for benefit similar to current therapies on the market. The addition of different medication classes to the armamentarium increases the number of options for patients who are colonized with different bacteria or develop resistance to the current agents. Once-daily dosing of the new inhaled antibiotic formulations may be associated with increased adherence to the regimen and decrease the complicated multidrug inhaled medication strategy for these patients. Until more curative therapies aimed at the disease state become readily available, reducing respiratory exacerbations and, thus, improving patients' quality of life remain the goals of therapy. Continued research and publication is necessary for the introduction of these inhaled antibiotics for use in the CF population.

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