

Spotlight on inhaled ciprofloxacin and its potential in the treatment of non-cystic fibrosis bronchiectasis

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Abstract: Non-cystic fibrosis bronchiectasis (NCFB) is a severe chronic illness characterized by irreversible dilation of airways and thickening of bronchial walls, chronic inflammation, repeated infections, and progressive obstruction of the airways. In contrast to cystic fibrosis bronchiectasis (CFB), which is a well-defined genetic disorder, NCFB is a heterogeneous disease caused by many different medical entities. Inhaled antibiotics are effective for patients with CFB, but their efficacy in NCFB has not been proven. The main pathogens involved in the colonization of patients with bronchiectasis are *Haemophilus influenza*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. The latter is associated with increased morbidity and mortality. In addition, in NCFB, *P. aeruginosa* strains are frequently more resistant than those in CFB. At present, there are no approved inhaled antibiotic therapies for NCFB patients. Inhaled ciprofloxacin has been under investigation in the last few years. In two phase II randomized, double-blind, placebo-controlled trials, the use of inhaled ciprofloxacin was significantly associated with reduction in sputum bacterial density and greater eradication rates. In four phase III randomized, double-blind, placebo-controlled trials, the results regarding the time of the first exacerbation and the rate of exacerbations were inconsistent. Specifically, ORBIT-4 and RESPIRE-1 trials showed clinical benefit (prolongation of the time of the first exacerbation and reduced rate of exacerbations in the treatment group compared to the placebo group), whereas the ORBIT-3 and RESPIRE-2 failed to achieve their primary endpoints. The RESPIRE-1 was the first trial that examined the 14-days on/off course separate from the standard 28-days on/off regimen, which is based on CFB protocol treatments. The current data on the efficacy of inhaled ciprofloxacin are encouraging, but further evaluation is needed to determine the appropriate target group and the ideal duration of treatment.

Keywords: aerosolized antibiotics, ciprofloxacin, bronchiectasis, fluoroquinolone

Introduction

Non-cystic fibrosis bronchiectasis (NCFB) is an important health issue that is increasingly common and related to a considerably high mortality.¹ It has higher incidence in older patients and females. The increased incidence of NCFB during the last decades is partially attributable to early diagnosis with the use of high-resolution spiral-computed tomography.

The main causes of NCFB include infections, bronchial obstruction, allergic bronchopulmonary aspergillosis, immunodeficiency states, connective tissue disorders, idiopathic inflammatory disorders, and autoimmune diseases. The most common cause in the literature is post-infectious, although no underlying cause is identified

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in a substantial percentage of patients.² There is frequent, and often underestimated, coexistence of NCFB with COPD.^{2,3}

Inhaled antibiotics for patients with bronchiectasis

Treatment for NCFB has been based on the general principles of management of cystic fibrosis bronchiectasis (CFB), with inhaled antibiotics being an adjunctive part of the treatment.^{4,5} The main advantages of inhaled antibiotics are the maximization of drug delivery to the site of infection and the protection from systemic adverse events.⁶ Inhaled antibiotics have been used for prevention and treatment for patients with tracheobronchitis, especially in the intensive care unit. Several original investigations and meta-analyses of clinical trials have suggested the potential of antibiotics, such as colistin, for the prevention and treatment of lower respiratory tract infections in hospitalized patients.^{7–9}

There are commercially available inhaled antibiotics for patients with cystic fibrosis and colonization with *Pseudomonas aeruginosa*: two US Food and Drug Administration (FDA)-approved drugs, tobramycin (both as solution and dry powder) and aztreonam (solution), and two European Medicines Agency (EMA)-approved drugs, colistimethate (dry powder) and levofloxacin (solution).^{10–13} *P. aeruginosa* infection is related to a three-fold increase in mortality risk and a seven-fold increase in hospitalization risk.⁴ According to current data, eradication of *P. aeruginosa* leads to better clinical outcomes. The use of intravenous antibiotics in combination with inhaled antibiotics achieves greater rates of *P. aeruginosa* clearance, compared to monotherapy with intravenous antibiotics.¹⁴ However, despite the similarities between CFB and NCFB in terms of clinical presentation and microbiology, the clinical benefit of the use of inhaled antibiotics in NCFB, in contrast to that for CFB, is not well established.¹⁵ Inhaled antibiotics that have been studied in patients with NCFB include tobramycin, gentamicin, amikacin, aztreonam, colistin, levofloxacin, and ciprofloxacin. A meta-analysis of eight randomized trials showed that inhaled antibiotics were more effective than placebo or symptomatic treatment in the eradication of bacteria from sputum, in the reduction of sputum bacterial load, and in the prevention of acute exacerbations. However, neither the risk of unscheduled hospitalizations nor the health-related quality of life (QoL) were improved.^{16–18}

To date, there are no approved inhaled antibiotic therapies for patients with NCFB. The first international guidelines for adult bronchiectasis were published in September 2017 by the European Respiratory Society. Remarkably, most of

treatment recommendations were based on low or very low quality of evidence, except for pulmonary rehabilitation which was supported by high-quality evidence.¹⁹

Ciprofloxacin

Ciprofloxacin is a second-generation fluoroquinolone, a broad-spectrum antibacterial with excellent activity against pathogens relevant to NCFB, such as *P. aeruginosa*, available in oral and intravenous formulations. The pharmacokinetics and the antibacterial spectrum of ciprofloxacin make it a promising option for NCFB treatment.^{20,21} The potential of achieving greater pulmonary concentrations with inhaled ciprofloxacin, compared to oral or intravenous administration, makes inhaled formulations of the antibiotic worthy of investigation.

Two formulations of inhaled ciprofloxacin – liposomal (CFI, ciprofloxacin for inhalation) and dry-powder for inhalation (DPI) – have been under investigation for their efficacy and safety in the treatment of NCFB patients.³ The pulmonary deposition of DPI ciprofloxacin was assessed by quantitative scintigraphy in a phase I study that included 24 participants (six patients with NCFB, six with COPD, and 12 healthy volunteers). The results showed high and reproducible lung deposition (mean relative to nominal dose $53\% \pm 11\%$, range 38%–64% for NCFB patients; $51\% \pm 10\%$, range 34%–61% for COPD patients; and $51\% \pm 7\%$, range 40%–64% for healthy volunteers) and low-systemic exposure in all participants.²²

The objective of this review was to evaluate the current data on the efficacy and safety of inhaled ciprofloxacin in NCFB patients.

Clinical trials: current data

The characteristics of the main clinical trials on the clinical efficacy of inhaled ciprofloxacin in NCFB patients are shown in Table 1.

A phase II, randomized, double-blind, placebo-controlled, multicenter study included 124 (60 in the DPI group and 64 in the placebo group) stable NCFB patients with positive sputum culture for respiratory pathogens, including *P. aeruginosa*. DPI or placebo were administered twice daily for 28 days, with 56 days of follow-up. At Day 29 (end of treatment), the results showed a statistically significant reduction in sputum bacterial density and greater eradication rates in the DPI group as compared to the placebo group ($-3.62 \log_{10} \text{CFU} \cdot \text{g}^{-1}$ vs $-0.27 \log_{10} \text{CFU} \cdot \text{g}^{-1}$, $P < 0.001$ and 35% vs 8%, $P = 0.001$, respectively).²⁰

Another phase II, 24-week, randomized, double-blind, placebo-controlled, trial – Once daily Respiratory

Table 1 Characteristics of main clinical trials on the clinical efficacy of inhaled ciprofloxacin in NCFB patients

Study design	Patients and treatment	Endpoints	Outcomes	Treatment compliance
Phase II, randomized, double-blind, placebo-controlled, multicenter ²⁰	124 patients with NCFB and positive sputum culture for respiratory pathogens. Randomized to DPI ciprofloxacin (n=60) or placebo (n=64), administered twice daily for 28 days	Change in sputum predefined potential respiratory pathogens' bacterial density at Day 28 Time to first pulmonary exacerbation	Bacterial density at Day 28 in the CFI group $-3.62 \log_{10} \text{CFU} \cdot \text{g}^{-1}$ vs $-0.27 \log_{10} \text{CFU} \cdot \text{g}^{-1}$, $P<0.001$	>80% compliance was reached in 97% of subjects in the DPI ciprofloxacin group and 94% of subjects in the placebo group
ORBIT-2, Phase II, randomized, double-blind, placebo-controlled, multicenter ²³	42 adult bronchiectasis subjects with more than two exacerbations in the prior 12 months, with ciprofloxacin-sensitive <i>P. aeruginosa</i> at screening. Randomized to DPI ciprofloxacin (n=20) group or placebo group (n=22) in three treatment cycles of 28-days on/28-days off	Change in sputum <i>P. aeruginosa</i> bacterial density at Day 28 Time to first pulmonary exacerbation	<i>P. aeruginosa</i> bacterial density at Day 28 in the CFI group $-4.2 \log_{10} \text{CFU} \cdot \text{g}^{-1}$ vs $-0.08 \log_{10} \text{CFU} \cdot \text{g}^{-1}$ in the placebo group, $P=0.002$. Time to first pulmonary exacerbation in the DPI group at 134 days vs 58 days in the placebo group, $P=0.057$	Compliance 65% in the DPI ciprofloxacin group vs 41% in the placebo group
ORBIT-3, Phase III, randomized, double-blind, placebo-controlled trial, multicenter ²⁴	278 patients with NCFB and chronic <i>P. aeruginosa</i> lung infections. Randomized to CFI group (n=183) or placebo group (n=95), in six treatment cycles of 28-days on/28-days off	Time to first pulmonary exacerbation Frequency of exacerbations by Week 48	At least one pulmonary exacerbation by 48 weeks, 59% of patients in the CFI vs 57% in the placebo group, with a difference in median times of 78 days (median time to first exacerbation in the CFI group 214 days vs 136 days in the placebo group), HR 0.99, 95% CI 0.71–1.38, $P=0.974$ A 14.8% reduction in frequency of pulmonary exacerbations in the CFI group compared to the placebo group, 95% CI (–12.3 to 35.3), $P>0.05$	Study drug discontinuation in the CFI group 13.1% vs 9.5% in the placebo group
ORBIT-4, Phase III, randomized, double-blind, placebo-controlled trial, multicenter ²⁴	304 patients with NCFB and chronic <i>P. aeruginosa</i> lung infections. Randomized to CFI group (n=206) or placebo group (n=98), in six treatment cycles of 28-days on/28-days off	Time to first pulmonary exacerbation Frequency of exacerbations by Week 48	At least one pulmonary exacerbation by 48 weeks, 55% of patients in the CFI group vs 65% in the placebo group, with a difference in median times of 72 days (median time to first exacerbation in the CFI group 230 days vs 158 days in the placebo group), HR 0.71, 95% CI 0.52–0.97, $P=0.032$ A 36.9% reduction in frequency of pulmonary exacerbations in the CFI group compared to the placebo group, 95% CI 17.9–51.5, $P<0.001$	Study drug discontinuation in the CFI group 4.9% vs 7.1% in the placebo group
Countries that enrolled at least 10% of overall patients were UK (14.1%) and the USA (11.8%). Australia enrolled 8.6% of patients				
RESPIRE-1 Phase III, randomized, double-blind, placebo-controlled, multicenter ²⁷	416 patients with NCFB (idiopathic or post-infectious etiology), with at least two exacerbations in the previous 12 months and a positive sputum culture at screening for at least one of seven pre-specified pathogens (<i>P. aeruginosa</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i> , <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>S. maltophilia</i> , or <i>B. cepacia</i>)	Time to first exacerbation Frequency of exacerbations	14-days on/off regimen Time to first exacerbation in the DPI ciprofloxacin group >336 days vs 186 days in the placebo group, HR 0.53, 97.5% CI 0.36–0.80, $P=0.0005$ Reduction of frequency of exacerbations in the DPI ciprofloxacin group by 39% over 48 weeks, compared to the placebo group (incidence rate ratio 0.61, 97.5% CI 0.40–0.91, $P=0.0061$)	14-days on/off regimen • DPI ciprofloxacin group 94.4±8.4 days • Placebo group 91.8±10.3 days 28-days on/off regimen • DPI ciprofloxacin group 94.3±10.1 days • Placebo group 89.9±15.8 days

(Continued)

Table 1 (Continued)

Study design	Patients and treatment	Endpoints	Outcomes	Treatment compliance
RESPIRE-2 Phase III, randomized, double-blind, placebo-controlled, multicenter ³¹	Randomized to the 14-day on/off regimen (DPI ciprofloxacin group [n=137] and placebo group [n=68]) and the 28-day on/off regimen (DPI ciprofloxacin group [n=141] and placebo group [n=70])		28-day on/off regimen Prolongation of time to first exacerbation and reduction of exacerbation rate in the DPI ciprofloxacin group compared to the placebo group, but not statistically significant (HR 0.73, 97.5% CI 0.50–1.07, P=0.07 and HR 0.98, 97.5% CI 0.64–1.48, P=0.89, respectively)	
	Patients with NCFB (idiopathic or post-infectious etiology), with at least two exacerbations in the previous 12 months and a positive sputum culture at screening for at least one of the seven pre-specified pathogens (<i>P. aeruginosa</i> , <i>H. influenzae</i> , <i>M. catarrhalis</i> , <i>S. aureus</i> , <i>S. pneumoniae</i> , <i>S. maltophilia</i> , or <i>B. cepacia</i>)	Time to first exacerbation within 48 weeks after start of treatment (FDA)	14-days on/off regimen Time to first exacerbation in the DPI ciprofloxacin vs placebo group, HR 0.87, 95% CI 0.62–1.21, P=0.39	14-days on/off regimen • DPI ciprofloxacin group 96.2±8.2 days
		Frequency of exacerbations during the 48-week study (EMA)	28-days on/off regimen Time to first exacerbation in the DPI ciprofloxacin vs placebo group, HR 0.71, 99.9% CI 0.39–1.27, P=0.05	• Placebo group 96.2±9.9 days 28-days on/off regimen • DPI ciprofloxacin group 95.8±10.8 days
	Randomized to the 14-day on/off regimen (DPI ciprofloxacin group [n=176] and placebo group [n=88]) and the 28-day on/off regimen (DPI ciprofloxacin group [n=171] and placebo group [n=86])		14-days on/off regimen Reduction of frequency of exacerbations in the DPI ciprofloxacin group by 17% over 48 weeks, (incidence rate ratio [IRR] 0.83, 95.1% CI 0.59–1.17, P=0.2862), (IRR 0.55, 99.9% CI 0.30–1.02, P=0.0014) 28-days on/off regimen Reduction of frequency of exacerbations in the DPI ciprofloxacin group by 45% over 48 weeks (IRR 0.55, 99.9% CI 0.30–1.02, P=0.0014) Number of exacerbations, 0.6±0.8 for ciprofloxacin DPI 14-days on/off compared with 0.7±1.0 in the matching placebo arm and 0.4±0.6 for ciprofloxacin DPI 28-days on/off vs 0.7±1.1 in the matching placebo arm	• Placebo group 96.3±8.9 days

Abbreviations: NCFB, non-cystic fibrosis bronchiectasis; CFU, liposomal, ciproxin for inhalation; CFU, colony forming unit; DPI, dry-powder for inhalation; FDA, US Food and Drug Administration; EMA, European Medicines Agency; *P. aeruginosa*, *Pseudomonas aeruginosa*; *H. influenzae*, *Haemophilus influenzae*; *M. catarrhalis*, *Moraxella catarrhalis*; *S. aureus*, *Staphylococcus aureus*; *S. pneumoniae*, *Streptococcus pneumoniae*; *S. maltophilia*, *Stenotrophomonas maltophilia*; *B. cepacia*, *Burkholderia cepacia*.

Bronchiectasis Inhalation Treatment (ORBIT-2) – examined the efficacy of dual-release CFI in 42 (20 in the CFI group and 22 in the placebo group) NCFB adults with two or more exacerbations in the last year and ciprofloxacin-sensitive *P. aeruginosa* at screening. CFI or placebo was administered once daily in three treatment cycles of 28-days on/28-days off. The results showed significant reductions in *P. aeruginosa* bacterial density on Day 28 in the CFI group, compared to the placebo group ($-4.2 \log_{10} \text{CFU} \cdot \text{g}^{-1}$ vs $-0.08 \log_{10} \text{CFU} \cdot \text{g}^{-1}$, $P=0.002$). Moreover, CFI delayed time to first pulmonary exacerbation in the studied population (134 days vs 58 days, $P=0.057$), although the study was not adequately powered for this endpoint.²³

The phase III, 48-week multinational, randomized, double-blind, placebo-controlled trials, ORBIT-3 (278 patients, 75.5% experienced 2–3 pulmonary exacerbations in the 12 months prior to screening, 69.8% women, 30% men, mean age 65.1 [range 21–87] years, 183 in the CFI arm, 95 in the placebo arm) and ORBIT-4 (304 patients, 79.6% experienced two pulmonary exacerbations in the 12 months prior to screening, 64.8% women, 35.2% men, mean age 63.6 [range 18–90] years, 206 in the CFI arm, 98 in the placebo arm) were designed to examine the efficacy of CFI in patients with NCFB and chronic *P. aeruginosa* lung infections.^{24,25} CFI or placebo were administered once daily for six cycles of 28-days on/off treatment. The primary endpoint of both studies was the increase in the median time to first pulmonary exacerbation and the secondary endpoints were the frequency of exacerbations, the number of severe (treatment with intravenous antibiotics or/and hospitalization) pulmonary exacerbations, and the change in the Respiratory Symptoms Domain Score for QoL.²⁴

In ORBIT-4, the median time to first pulmonary exacerbation was 230 days in the CFI group vs 163 days in the placebo group ($P<0.05$), and there was a 37% reduction in the frequency of pulmonary exacerbations in the CFI group ($P<0.001$). In ORBIT-3, the median time to first pulmonary exacerbation was 221 days vs 136 days in the placebo group ($P=0.84$), and there was a 13% reduction in the frequency of pulmonary exacerbations in the CFI group ($P=0.31$). The pooled results showed a 27% reduction in the frequency of exacerbations (RR 0.73, 95% CI 0.60–0.88, $P<0.001$). No statistically significant differences were found between the two groups in either trial, with regard to the number of severe exacerbations or QoL assessed by the Respiratory Symptoms Domain Score.²⁴

The baseline demographic characteristics of included patients in each study were balanced. However, in ORBIT-3,

the percentage of patients with serious adverse events was higher than in ORBIT-4, which could partially be attributed to the indices of severity of the disease not measured, as well as to the differences in etiology of NCFB – information that was not collected by the researchers. Moreover, the rates of premature discontinuation were higher in the CFI group compared to the placebo group in ORBIT-3, whereas the opposite was noticed in ORBIT-4.²⁴ The results of the ORBIT studies have not been fully published yet.

The RESPIRE program consists of two phase III, 48-week, randomized, multicenter placebo-controlled trials of the same design that examined the efficacy and safety of DPI in NCFB. They represent the largest clinical trial program conducted in NCFB. The two trials differed by the enrolling countries and the statistical analysis of the data.²⁶ The RESPIRE-1 study included countries of Europe, North and South America, Australia, and Japan, whereas the RESPIRE-2 included countries of Asia and Eastern Europe. The primary endpoints of both studies were the efficacy of DPI in prolonging the time to the first exacerbation (analysis plan for FDA) and reducing the frequency of exacerbations (analysis plan for EMA). Secondary endpoints were microbiology parameters, QoL, and pulmonary function. In both trials, DPI or placebo was administered twice daily in cycles of 14-days on/off (12 cycles) or 28-days on/off (six cycles) for 48 weeks. The patients were followed for 8 weeks after the last dose.^{26,27}

The RESPIRE-1 trial included 416 patients, randomized to the 14-days on/off regimen treatment (137 in the DPI group, 68 in the placebo group) or to the 28-days on/off regimen treatment (141 in the DPI group, 70 in the placebo group). The frequency of pulmonary exacerbations, in the DPI 14-days on/off group vs the matching placebo, was significantly reduced by 39% over 48 weeks (RR 0.61, 95% CI 0.40–0.91, $P=0.006$) and the time to first exacerbation was significantly prolonged in the DPI group vs placebo group (HR 0.53, 95% CI 0.36–0.80, $P<0.001$). Furthermore, prolongation of time to the first exacerbation and reduction of exacerbations were seen in the DPI 28-day on/off group vs the matching placebo, but the results were not statistically significant (HR 0.73, 95% CI 0.50–1.07, $P=0.07$ and HR 0.98, 95% CI 0.64–1.48, $P=0.89$, respectively).²⁷ In the RESPIRE-2 trial, no significant improvement was found with regard to the primary endpoints between the DPI and the placebo group, neither in the 14-days on/off nor in the 28-days on/off regimen treatment. The discrepancy between the results of the two studies reflects, possibly, the ethnic and geographic heterogeneity of the disease.²⁸

Adverse events

The most common adverse events of inhaled antibiotics include bronchospasm, cough, throat irritation, and abnormal taste, whereas the current data for systemic toxicity are favorable. However, the major concern remains – the emergence of antibiotic-resistant pathogens.⁶

According to a meta-analysis of seven trials with 526 patients, the most common adverse event was bronchospasm, which occurred in 10% of patients treated with inhaled antibiotics and 2.3% in the control group (RR 2.96, 95% CI 1.30–6.73, $P=0.01$, I^2 0%).¹⁸ The results of the subgroup analysis showed that inhaled ciprofloxacin and colistin were not significantly related to the occurrence of this adverse event, contrary to inhaled aminoglycosides (ciprofloxacin, two trials with 166 patients, RR 1.07, 95% CI 0.25–4.56, $P=0.93$; colistin, one trial with 144 patients, RR 4.86, 95% CI 0.58–40.59, $P=0.14$; aminoglycosides, four trials with 216 patients, RR 4.78, 95% CI 1.55–14.76, $P=0.007$).

Development of microbial drug resistance

The use of antibiotics for extended periods may decrease the symptoms and number of exacerbations, but it may result in the appearance of multi-drug resistant bacteria. There are data from recent studies which show that these bacteria have a considerable impact on exacerbations and community-acquired pneumonia in NCFB patients.²⁹

P. aeruginosa, one of the main pathogens, and its isolates have a different phenotype compared to those of CFB. There is a high prevalence of hyper-mutable and wild strains with worse prognosis in NCFB than in CFB patients. According to the results of a recent meta-analysis that evaluated the efficacy and safety of inhaled antibiotics in NCFB, the risk of *P. aeruginosa* resistance did not differ between treatment and control groups (sub-analysis of five studies, RR 1.35, 95% CI 0.61–2.96, $P=0.46$).³⁰ However, in the RESPIRE-1 trial, the data showed that, at any time point, at least one isolate from sputum with an elevated minimum inhibitory concentration (as defined by the systemic ciprofloxacin breakpoints) was found in 54% of patients in the DPI 14-days on/off group and 53.9% of patients in the DPI 28-days on/off group vs 36.2% of patients in the placebo group.³¹ In ORBIT-3 and ORBIT-4, the percentage increase of ciprofloxacin-resistant *P. aeruginosa* isolates in the CFI group by the end of the study was 23% and 31%, respectively, whereas no percentage increase was observed in the placebo group.²⁴

Critical evaluation of the available data

The ORBIT-4 showed clinical benefit (statistically significant prolongation of the time of the first exacerbation and lower rate of exacerbations) for the CFI group vs the placebo group, which was contrary to ORBIT-3 despite their almost identical design.

The same pattern was observed in the RESPIRE-1 and RESPIRE-2 studies. The RESPIRE-2 trial did not meet the primary endpoints, whereas RESPIRE-1 showed significant reduced rate of exacerbations and increased time to the first exacerbation in the DPI group vs the placebo group in the 14-days on/off, but not in the 28-days on/off, regimen treatment. The RESPIRE-1 was the first trial that examined the 14-days on/off course apart from the standard 28-days on/off regimen, which is based on CFB protocol treatments. The results were encouraging and may be the beginning of a new dosing strategy in NCFB patients.

The long-term use of antibiotic treatment may be associated with the risk of emergence of ciprofloxacin-resistant pathogens. However, to appropriately evaluate this risk in clinical practice, a follow-up period longer than 8 weeks is essential. Moreover, an issue of great importance is the lack of evidence of QoL improvement of studied patients, which was a secondary endpoint of the conducted trials. The differences between CFB and NCFB with regard to the treatment response reflect the differences that exist in terms of pathophysiology. CFB is an inherited autosomal recessive disease, caused by mutations in the gene of cystic fibrosis that codes for a protein transmembrane conductance regulator (CFTR). The severity of the disease is different for each patient because of the poor penetrance of the mutated gene. However, the underlying mechanism is the same. Instead, NCFB is an heterogeneous disease, caused by multiple causes with many clinical phenotypes.^{21,32} Future clinical trials should stratify patients based on specific characteristics, such as the underlying cause, the severity of the disease, and the presence or absence of *P. aeruginosa*.

Conclusion

Despite the progress in the field of inhaled antibiotics in NCFB in the last few decades, there are three major unresolved issues that require further investigation: the appropriate target group of patients, the ideal duration of therapy, and the true associated risk of antibiotic resistance. More multicenter randomized-controlled studies are needed to answer these questions and clarify the most effective treatment of patients with this chronic illness.

Disclosure

Matthew E Falagas participated in advisory boards of AstraZeneca, Infectopharm, Tetrphase, Shionogi, and Xellia; received lecture honoraria from Cipla, Merck, and Pfizer; and received research support from Shionogi, Tetrphase, and Helperby. The authors report no other conflicts of interest in this work.

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