Ciprofloxacin dry powder inhaler in
cystic fibrosis

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Inhaled antibiotics are the backbone of care for people with cystic fibrosis (CF) who have lung infection due to *Pseudomonas aeruginosa*. They have significantly contributed to the improved quality of life (QOL) and increased survival in people with this disease.¹ The systematic application of antibiotic eradication therapy for new or recurrent infections with *P. aeruginosa* and for long-term use of inhaled antibiotics in people with CF is now standard of care.^{1–3} There are currently two inhaled antibiotics licensed in the USA (tobramycin and aztreonam lysine) and four in Europe (tobramycin, aztreonam lysine, colistimethate sodium and levofloxacin).^{4–9} One of the current challenges of using inhaled antibiotics in CF is that tobramycin is licensed for use on alternate months, though clinical practice assessed from registries suggests that the majority of physicians when using tobramycin suggest a second antibiotic for the alternating months.¹⁰

Tobramycin inhalation by inhalation solution or dry powder has been available for 15 years and colistimethate sodium dry powder and has recently been licensed by the European Medicines Agency (EMA).^{5–7} Tobramycin given on alternate months improved forced expiratory volume in 1 s (FEV₁) and reduced pulmonary exacerbations compared to placebo.⁹ Colistimethate sodium has only been tested in a head-to-head active comparator study against tobramycin and demonstrated non-inferiority in patients. It has not been studied in a large placebo-controlled trial.

Levofloxacin as an inhalation solution, though approved for over 18-year-olds in Europe, is not yet available to clinicians for use.⁸ This fluoroquinolone demonstrated good activity against *P. aeruginosa* and improvement in FEV₁ compared to placebo in a phase II study. In a non-inferiority, phase III active comparator trial against nebulised tobramycin there was no difference in FEV₁ changes and a small advantage in favour of levofloxacin for time to next antibiotics.⁸ A longer phase II study, as yet unpublished, showed a small

advantage in FEV₁ (3–4%) for levofloxacin compared to placebo and no difference in frequency of pulmonary exacerbations.

The addition of further inhaled antibiotics is likely to make a valuable contribution to management of people with CF and so it is disappointing to see a negative study of dry powder inhaled ciprofloxacin in this study published in *BMJ Open Respiratory Research*.¹¹ This was a well-designed and powered, dose finding study in people with CF using a well-designed dry powder device, with between 90 and 100 patients in each of the two dose groups and a placebo comparator. The study failed to meet its primary end point of change in FEV₁ from baseline to the end of inhaled treatment at 29 days. There was a modest antimicrobial effect with a reduction of around 1.5 log CFU/g at day 14 though this was not sustained to day 29 where the difference was not significant compared to placebo. There was a trend in improvement in QOL scores and there were no major safety concerns.

There are a number of reasons why the ciprofloxacin may have been ineffective in this clinical trial. First, the authors suggest, this was a cohort of patients with relatively advanced disease. This, however is very similar to the cohort described in phase III levofloxacin, placebo-controlled trial where there also was only a small change in FEV₁ of around 4% predicted.⁸ In the ciprofloxacin study the difference compared to placebo is also in this range at 1–2% predicted.

The changes in the sputum density of *P. aeruginosa* were also similar for levofloxacin and, ciprofloxacin. Ciprofloxacin, in common with other fluoroquinolones, rapidly induces resistance and the microbiology data suggests that the antimicrobial effect of dry powder inhaled ciprofloxacin was attenuated after 30 days. This may have been due to the induction of resistance and contributed to the lack of improvement in FEV₁. However, other recent studies changes in FEV₁ do directly relate to changes in microbial load.¹⁰ It is also possible that the

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dose used and the distribution and delivery of drug or inhaler was insufficient for a major antimicrobial effect though the significant reduction microbial burden at 2 weeks would argue against this.

In contrast to this study in people with CF, dry powder ciprofloxacin demonstrated a positive effect in a phase II study of patients with bronchiectasis and is currently in phase III trials to assess longer term outcomes in this patient group.¹² It may be more successful in patients with bronchiectasis because of the lower microbial load and perhaps less lifetime exposure to fluoroquinolones and therefore less likely to develop resistance. These data also strongly suggest that it is not the inhaler device and drug delivery that accounts for the lack of efficacy in CF.

We can learn a number of lessons from this and other recently published studies of inhaled antibiotics in CF. Sputum density of *P. aeruginosa* tells us about antimicrobial effect of the drug but a positive effect on CFU/g does not necessarily translate into clinical benefit. Optimally treated patients on inhaled antibiotics (64% in the study) may not demonstrate much further significant improvement in FEV₁. However, there was a trend in benefit in exacerbations (both total events and time to next) in favour of treated patients though this study was not powered for exacerbations. Reducing exacerbations, however, is a more important clinical outcome than improving FEV₁ as the former is closely related to decline in lung function and survival.

It is possible, therefore, that inhaled ciprofloxacin could reduce pulmonary exacerbations in a phase III study but the lack of a significant effect on FEV₁ and bacterial density has resulted in the programme not being progressed in CF. Pulmonary exacerbation is arguably the most important end point in trials in CF as it is powerfully related to future QOL, FEV₁ and survival. Bacterial density in phase II trials does not predict an effect on exacerbations and perhaps we need to reconsider appropriate primary outcome measures in phase II programmes.

What might these be? Cystic Fibrosis Transmembrane conductance Regulator (CFTR) potentiators, hypertonic saline and DNase all improve lung clearance index measured by multiple breath washout.¹³ This is a more sensitive measure than FEV₁ of lung physiology improvement in CF and has some predictive value for pulmonary exacerbations. It has yet to be tested as an outcome measure in a long-term inhaled antibiotic study but has shown some encouraging trend in a short-term intravenous antibiotic study.¹⁴ On the microbiological side pyrosequencing using 16S Ribosomal RNA has led to a deeper understanding of the lung microbiome. Changes in the microbiome are associated with disease compared to healthy lungs and in CF the microbiome diversity narrows with disease severity.^{15–18} We have few data yet on the effect of inhaled antibiotics on the microbiome but this may be a more relevant microbiological outcome than single organism sputum density.

New antimicrobial therapies are needed in CF and other chronic lung diseases associated with infection. We

also need better short-term end points for early phase development or we will lose potentially effective drug because we have inappropriate end points in early phase development. These should predict long-term impact on QOL, future exacerbations and survival.

Competing interests JSE is the consultant for Raptor Pharmaceutical who own laevofloxacin.

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REFERENCES

- Waters V, Smyth A. Cystic fibrosis microbiology: advances in antimicrobial therapy. *J Cyst Fibros* 2015;14:551–60.
- Döring G, Flume P, Heijerman H, et al. Consensus Study Group. Treatment of lung infection in patients with cystic fibrosis: current and future strategies. *J Cyst Fibros* 2012;11:461–79.
- Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al. Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. *Am J Respir Crit Care Med* 2013;187:680–9.
- McCoy KS, Quittner AL, Oermann CM, et al. Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. *Am J Respir Crit Care Med* 2008;178:921–8.
- Retsch-Bogart GZ, Quittner AL, Gibson RL, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. *Chest* 2009;135:1223–32.
- Assael BM, Pressler T, Bilton D, et al. Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: a comparative efficacy trial. *J Cyst Fibros* 2013;12:130–40.
- Schuster A, Haliburn C, Döring G, et al. Safety, efficacy and convenience of colistimethate sodium dry powder for inhalation (Colobreathe DPI) in patients with cystic fibrosis: a randomised study. *Thorax* 2013;68:344–50.
- Stuart Elborn J, Geller DE, Conrad D, et al. A phase 3, open-label, randomized trial to evaluate the safety and efficacy of levofloxacin inhalation solution (APT-1026) versus tobramycin inhalation solution in stable cystic fibrosis patients. *J Cyst Fibros* 2015;14:507–14.
- Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med* 1999;340:23–30.
- Dasenbrook EC, Konstan MW, VanDevanter DR. Association between the introduction of a new cystic fibrosis inhaled antibiotic class and change in prevalence of patients receiving multiple inhaled antibiotic classes. *J Cyst Fibros* 2015;14:370–5.
- Dorkin, et al. Ciprofloxacin DPI: Randomised, Placebo-controlled, Phase IIb, Efficacy and Safety Study in Cystic Fibrosis. *BMJ Open Resp* 2015;2:e000100. doi:10.1136/bmjresp-2015-000100
- Wilson R, Welte T, Polverino E, et al. Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis: a phase II randomised study. *Eur Respir J* 2013;41:1107–15.
- Subbarao P, Milla C, Aurora P, et al. Multiple-breath washout as a lung function test in cystic fibrosis. A Cystic Fibrosis Foundation Workshop Report. *Ann Am Thorac Soc* 2015;12:932–9.
- Sonneveld N, Stanojevic S, Amin R, et al. Lung clearance index in cystic fibrosis subjects treated for pulmonary exacerbations. *Eur Respir J* 2015;46:1055–64.
- Tunney MM, Field TR, Moriarty TF, et al. Detection of anaerobic bacteria in high numbers in sputum from patients with cystic fibrosis. *Am J Respir Crit Care Med* 2008;177:995–1001.
- Smith DJ, Badrick AC, Zakrzewski M, et al. Pyrosequencing reveals transient cystic fibrosis lung microbiome changes with intravenous antibiotics. *Eur Respir J* 2014;44:922–30.
- Zemanick ET, Harris JK, Wagner BD, et al. Inflammation and airway microbiota during cystic fibrosis pulmonary exacerbations. *PLoS ONE* 2013;8:e62917.
- Chmielek JF, Aksamit TR, Chotirmall SH, et al. Antibiotic management of lung infections in cystic fibrosis: part I. The microbiome, MRSA, gram-negative bacteria, and multiple infections. *Ann Am Thorac Soc* 2014;11:1298–306.