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.1,4,5 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).4,5–9 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).5,6 Tobramycin given on alternate months improved forced expiratory volume in 1 s (FEV1) and reduced pulmonary exacerbations compared to placebo.11 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changes and a small advantage in favour of levofloxacin for time to next antibiotics.8 A longer phase II study, as yet unpublished, showed a small advantage in FEV1 (3–4%) for levofloxacin compared to placebo and no difference in frequency of pulmonary exacerbations.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
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.\textsuperscript{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 \textit{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 FEV\textsubscript{1}. 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 FEV\textsubscript{1} 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 FEV\textsubscript{1} 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, FEV\textsubscript{1} 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.\textsuperscript{13} This is a more sensitive measure than FEV\textsubscript{1} 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.\textsuperscript{14} On the microbiological side, profiling 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.\textsuperscript{15,16} 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 levofloxacin.

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