Cystic fibrosis papers of the year 2008

Ian M Balfour-Lynn

Department of Paediatric Respiratory Medicine, Royal Brompton & Harefield NHS Trust, Sydney Street, London SW3 6NP

E-mail: i.balfourlynn@ic.ac.uk

DECLARATIONS

Competing interests
None declared

Funding
None

Ethical approval
Not applicable

Guarantor
IMB-L

Contributorship
IMB-L is the sole contributor

Acknowledgements
None

Introduction

The literature search was conducted using PubMed (www.ncbi.nlm.nih.gov/sites/entrez), entering the search term 'cystic fibrosis', for the period 13 November 2007 to 1 November 2008. There were 1380 papers identified, and when limits were set for 'clinical trial' and 'randomized controlled trial' this left 44 papers. In addition, three meta-analyses and three practice guidelines were identified. The papers selected for this review are a personal choice of studies with important or interesting clinical messages.

Clinical trials

PTC124

(1) Kerem E, Hirawat S, Armoni S, *et al*. Effectiveness of PTC124 treatment of cystic fibrosis caused by nonsense mutations: a prospective phase II trial. *Lancet* 2008;**372**:719–27

What is already known?

- A nonsense mutation, also known as a premature stop codon, is a single point alteration in DNA, which converts an amino acid-encoding codon to a translational stop codon (UAA, UAG, or UGA in the mRNA). Premature stop codons cause premature cessation of translation, hence result in truncated protein products, and when this results in loss of function or reduced activity, it can cause disease.
- When the protein product is Cystic Fibrosis Transmembrane Regulator (CFTR), cystic fibrosis ensues. The mutation leads to little functional CFTR so the CF phenotype is usually severe.
- Worldwide, about 10% of patients (estimated 7000 individuals) carry at least one CFTR nonsense mutation. Commoner in Ashkenazi Jews, it accounts for 50% of CF patients in Israel. The commonest of these gene mutations are G542X and W1282 X.
- Certain aminoglycoside antibiotics (e.g. gentamicin) can induce ribosomes to read through a premature stop codon in mRNA leading to continuation of translation and production of the complete protein. Topical application of gentamicin in the nose has been shown to lead to an increase in CFTR-mediated chloride transport.[1]
- PTC124 is an oral (non-aminoglycoside) drug that was identified via high throughput screening. It was produced specifically to induce ribosomes to read through premature stop codons but not normal stop codons. Mouse work showed it generated production of functional CFTR, and phase I studies established its safety profile.

Methods

- Four centres in Israel participated in a phase II open label prospective trial. Study sponsored by PTC Therapeutics and part funded by CF Foundation Therapeutics.
- Adults with at least one nonsense mutation were recruited. All had an $FEV_1 \geq 40$ % predicted and an oxygen saturation $\geq 92\%$.
- They were given PTC124 at a dose of 14 mg/kg/day (in three divided doses) for 14 days, and then had 14 days without. In the second cycle the dose was 40 mg/kg/day with the same timings.
- The primary outcomes were change in CFTR-mediated total chloride transport;

proportion of patients who responded to treatment; and normalization of chloride transport.

Results

- Twenty-three patients with median age 25 years were assessed in the first cycle and 21 in the second cycle. Median FEV_1 was 65% (range 41–117%).
- Mean total chloride transport increased in the first treatment phase, with a change of −7.1 (SD 7.0) mV ($p<0.0001$), and in the second, with a change of −3.7 (SD 7.3) mV ($p=0.032$). A response in total chloride transport (defined as a change in nasal PD of −5 mV or more) was recorded in 16/23 patients in the first cycle's treatment phase ($p<0.0001$) and in 8/21 patients in the second cycle ($p<0.0001$). Total chloride transport entered the normal range for 13/23 patients in the first cycle's treatment phase ($p=0.0003$) and for 9/21 in the second cycle ($p=0.02$).
- The drug was well tolerated, with constipation and mild dysuria the principle adverse effects.

Critique

- This is a potential major breakthrough for CF patients with nonsense mutations, as in many patients PTC124 shifted chloride transport into the normal range.
- However there was no dose response noted, although the authors suggest that may be because the lower dose may have been at the upper end of the dose response curve anyway.
- There was also no correction noted in sweat chloride concentrations.
- Phase III trials are now required to assess clinical outcomes, and these should include children. Cost effectiveness must also be considered.
- If these are successful, it is important the drug is made available soon and at an affordable price for the health services.

Nebulized aztreonam lysine – two studies

(2) Retsch-Bogart GZ, Burns JL, Otto KL, Liou TG, McCoy K, Oermann C, Gibson RL, for the AZLI Phase II Study Group. A Phase 2 Study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and *Pseudomonas aeruginosa* infection. *Pediatr Pulmonol* 2008;**43**:47–58

What is already known?

- *Pseudomonas aeruginosa* is the predominant pathogen infecting 80% of CF patients by 18 years, is associated with accelerated decline in lung function and is a significant predictor of mortality.
- Inhaled antipseudomonal antibiotics are widely used although choices are limited, principally to colomycin and tobramycin.
- Aztreonam is a monobactam with a wide spectrum of activity against aerobic gram negative bacteria, and has proved useful as an intravenous treatment for *P. aeruginosa*. The parenteral solution contains arginine, which causes airway inflammation after long-term use in CF patients.
- AZLI is the lysine salt of aztreonam and has been developed for aerosol use. A phase 1b study showed it to be safe in adults and adolescents with CF.[2]

Methods

- Double-blind randomized placebo controlled phase II study in 20 CF centres in USA. Study part sponsored by pharmaceutical company Gilead Sciences Inc.
- AZLI (or placebo) at a dose of 75 mg or 225 mg was given twice daily for 14 days using an eFlow® nebulizer.
- Adults and adolescents $\geq$13 years, with FEV_1 $\geq$40% predicted, oxygen saturation >90%, chronic *P. aeruginosa* infection and no antipseudomonal antibiotics for previous 56 days were recruited.

Results

- There was a total of 105 participants (78 adults, 27 adolescents) with mean age 26 years and mean FEV_1 77% predicted.
- There was a statistically significant reduction in sputum *P. aeruginosa* CFU density with both AZLI doses at 7 and 14 days, compared to placebo.

- No change in FEV_1 was demonstrated. Post hoc analysis implied an improvement in the higher dose group for those with baseline FEV_1 <75% predicted.
- Those using regular bronchodilators had a greater improvement in FEV_1 and greater reduction in *P. aeruginosa* density.
- The drug was generally safe and well tolerated. Commonest adverse event was cough, which was thought to be dose related. There was little risk of airway reactivity with continued AZLI administration.

Critique

- Early days still but encouraging that we may have a new nebulized antipseudomonal antibiotic to add to the armentarium.
- Nevertheless, beware claims made using post hoc analysis.
- Price will be important considering the high cost of TOBI especially compared with colomycin.

(3) McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis. *Am J Resp Crit Care Med* 2008;**178**:921–8

What is already known?

- See above.
- Tobramycin inhalation solution (TIS) is widely used to treat both chronic *P. aeruginosa* infections and acute *P. aeruginosa* exacerbations. Up to 6.5 one-month courses per year are recommended.

Methods

- Double-blind randomized placebo-controlled trial in 56 CF centres in USA. Study part sponsored by pharmaceutical company Gilead Sciences Inc.
- Following a 28-day course of TIS, AZLI (or placebo) at a dose of 75 mg was given twice or three times daily for 28 days using an eFlow® nebulizer. Patients took a bronchodilator before the study medication. Follow-up continued for a further 56 days after the treatment period.
- Adults and children $\geq$6 years, with FEV_1 between 25% and 75% predicted, oxygen saturation $\geq$90%, and $\geq$3 TIS courses within past year were recruited.
- Primary endpoint was time to need for additional inhaled or intravenous antipseudomonal antibiotics to treat a (defined) pulmonary exacerbation. Secondary endpoints included respiratory symptoms (CFQ-R scale), lung function and sputum *P. aeruginosa* density.

Results

- There were 211 participants with mean age 26 years (78% were aged $\geq$18 years) and mean FEV_1 55% predicted. Of these, 70% were on long-term azithromycin.
- AZLI increased median time for need of inhaled/intravenous antipseudomonal antibiotics for symptoms of an exacerbation by 21 days compared to placebo (92 vs 71 days, p=0.007).
- Compared to placebo, AZLI improved CFQ-R by 5 points (scored out of 100), p=0.02; improved FEV_1 by 6.3%, p=0.001; and reduced sputum PA density by a small but significant amount.
- There was no advantage taking AZLI three times a day compared to twice.
- The medication was well tolerated.

Critique

- AZLI seems to be effective in patients already on inhaled tobramycin, so may have a role as an add-on therapy.
- In relation to the study's primary endpoint, it is not clear that every exacerbation was due to PA infection and needed antipseudomonal antibiotics, some of them may have been viral or due to other bacterial organisms such as *Staphylococcus aureus*.
- The work with this drug continues, and at the time of writing (November 2008) did not receive FDA approval.

Non-invasive ventilation

(4) Young AC, Wilson JW, Kotsimbos TC, Naughton MT. Randomised placebo

controlled trial of non-invasive ventilation for hypercapnia in cystic fibrosis. *Thorax* 2008;**63**:72–7

This was a small cross-over study assessing domiciliary nocturnal non-invasive ventilation (NIV) in the form of BiPAP, in eight adults who had hypercapnia while awake ($PaCO_2$ >5.85 kPa). Patients received six-week blocks of air, supplemental oxygen at 0.5 L/min via nasal cannulae or NIV with mean pressures 12/5 cms H_2O (with two-week wash-out periods). Mean NIV usage was 4.3 hours per night and one patient did not tolerate the NIV. Compared to placebo, the NIV led to improvement in chest symptoms, exertional dyspnoea, nocturnal hypoventilation and peak exercise capacity; there was no change in sleep architecture, lung function or awake $PaCO_2$. Longer larger studies are still required but will be very difficult to conduct.[3]

Case–control study

Acute renal failure

(5) Smyth A, Lewis A, Bertenshaw C, Choonara I, McGaw J, Watson A. Case-control study of acute renal failure in patients with cystic fibrosis in the UK. *Thorax* 2008;**63**:532–5

What is already known?

- CFTR is expressed in the kidney but its function is unknown and CFTR mutations are not associated with renal dysfunction.
- In the UK, the incidence of acute renal failure (ARF) in patients with CF is estimated to be 4.6–10.5 cases per 10,000 CF patients per year, which means approximately 3–7 new cases of ARF each year.[4] In children, there is a 100-fold greater risk of ARF in CF compared to normal children.

Methods

- ARF was defined as raised plasma creatinine for age with or without oliguria.
- Previous national survey identified 24 confirmed cases from 20 centres, and these were matched for age and gender with patients from the UK CF Trust national database to identify risk factors.

Results

- Of 24 patients with ARF, 21 (88%) had received an intravenous (IV) aminoglycoside at the time of their episode or in the previous week compared with 3/42 (7%) controls (odds ratio 82, 95% confidence interval 5–1427, p<0.001).
- In the year prior to the ARF, significantly more cases had received IV gentamicin 19/24 (79%) *vs* 1/42 (2%) controls, p<0.001.
- The numbers receiving IV tobramycin were similar: 9/24 (38%) cases *vs* 16/42 (38%) controls.
- A known risk factor for ARF was present in 18/24 (75%) cases *vs* 7/42 (17%) controls. These included prior renal disease, CF-related diabetes, acute dehydration or long-term treatment with nephrotoxic drugs.
- Any excess risk due to use of IV cephalosporin could not be calculated as all receiving it also had been given an aminoglycoside.
- There was no risk associated with the use of nebulized aminoglycosides or colistin.

Critique

- Original survey probably an underestimate of ARF so incidence may be even higher.
- This is clearly a significant problem and many more patients with CF may have subclinical renal impairment.
- Some methodological problems highlighted in accompanying editorial, particularly with only 42/96 controls being assessed.[5]
- Nevertheless highlights importance of identifying potentially reversible risk factors before using aminoglycosides.
- Should we stop using intravenous gentamicin? It is no longer our first-choice aminoglycoside at Royal Brompton Hospital paediatric CF Unit.
- Authors suggest an annual formal measure of glomerular filtration rate might be considered which sounds a good idea if logistics allow.

Epidemiological studies

Anaerobic bacteria

(6) 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

It is known that the flora inside CF lungs is multiple and varied, and that anaerobic conditions exist within the mucus. Sputum samples were collected from 50 stable adults with CF and bronchoalveolar lavage (BAL) fluid from 10 children with CF. Additionally, induced sputum was collected from 20 healthy adults. Specimens were analysed for presence of anaerobic bacteria. High numbers of anaerobes (*Prevotella*, *Veillonella*, *Propionibacterium* and *Actinomyces* genera) were isolated from 42/66 (64%) adult sputum samples, and similar numbers were found in the BAL samples of children. Although anaerobes were also isolated from 16/20 normal adults, they were present in much smaller numbers, and were generally different species to those in CF patients. Chronic infection with *P. aeruginosa* significantly increased the likelihood of finding anaerobes. All isolates were susceptible to meropenem. It is quite possible some of these anaerobes are causing infection and inflammation, and consideration should be given to including them in antibiotic regimens.

Preschool lung function

(7) Kozlowska WJ, Bush A, Wade A, *et al*. London Cystic Fibrosis Collaboration. Lung function from infancy to the preschool years after clinical diagnosis of cystic fibrosis. *Am J Respir Crit Care Med* 2008;**178**:42–9

The London CF Collaboration has followed 48 children with CF diagnosed from clinical symptoms and 33 healthy children from infancy through their preschool years. Raised volume technique was used during infancy and incentive spirometry at age 3–5 years. The diagnosis of CF itself accounted for a mean reduction in $FEV_{0.75}$ of 7.5% and in $FEF_{25–75\%}$ of 15%. Wheeze, recent cough and *P. aeruginosa* infection (even if apparently treated) were independently associated with further reductions. This makes gloomy reading and emphasizes the need for newer therapies that can be started in infancy. It should be stressed though that these children were not diagnosed by newborn screening so it is not clear whether the findings are truly primary, or secondary to infections the infants may have suffered prior to their CF diagnosis.[6]

Lung function in screened infants

(8) Linnane BM, Hall GL, Nolan G, *et al*. Lung function in infants with cystic fibrosis diagnosed by newborn screening. *Am J Respir Crit Care Med* 2008;**178**:1238–44

This cross-sectional Australian study assessed 68 infants aged 6 weeks to 30 months who had been diagnosed with CF by newborn screening (at a median age of 6 weeks) and compared them with 49 healthy infants. They had lung function measured by the standard raised volume thoracoabdominal technique. The CF infants also had a bronchoalveolar lavage performed 48 hours after the lung function measurements. Median age at first test for CF patients was 59 weeks (range 6–131 weeks). The lung function of the CF infants was no different to the healthy infants while aged <6 months, but in those older than 6 months the mean $FEV_{0.5}$ Z score was 1.15 lower ($p<0.001$). The deficit in mean $FEV_{0.5}$ Z score increased by 0.77 per year of age. This deficit was not accounted for by pulmonary inflammation, as markers were no different for those less than compared to those over 6 months of age. Lung function was no different in those with positive microbiology compared to this with no organisms isolated. This study implies that even with early diagnosis and initiation of CF therapies in specialist centres, lung function deteriorates within the first 6 months.

Cochrane systematic reviews – new or substantially amended in 2008

(9) Fernandes BN, Plummer A, Wildman M. Duration of intravenous antibiotic therapy in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD006682. DOI: 10.1002/14651858.CD006682.pub2; first published 16 April 2008

This review found no trials to assess the optimal duration of intravenous antibiotic therapy for treating chest exacerbations in people with cystic fibrosis.

(10) Houston BW, Mills N, Solis-Moya A. Inspiratory muscle training for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD006112. DOI: 10.1002/14651858.CD006112.pub2; first published 8 October 2008

Although this review could include six studies, they were not able to combine results. They therefore can not make any recommendation on the usefulness or not of inspiratory muscle training for patients with CF.

(11) Waters V, Ratjen F. Combination antimicrobial susceptibility testing for acute exacerbations in chronic infection of Pseudomonas aeruginosa in cystic fibrosis. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD006961. DOI: 10.1002/14651858.CD006961.pub2; first published 16 July 2008

This review was only able to include one trial so there was insufficient evidence to determine the effect of combination antibiotic susceptibility testing for CF patients chronically infected with *P. aeruginosa*.

Consensus statements

(12) Farrell PM, Rosenstein BJ, White TB, *et al*. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation Consensus Report. *J Pediatr* 2008;**153**:s4–s14

The CF Foundation has published guidelines for diagnosing CF at all ages. It includes an algorithm for newborn screening, which is practised in almost all states in the US currently, and should cover the whole country by the end of 2009. However there are several methods used throughout the US. Sweat chloride testing remains the gold standard although can still be inconclusive. There are now over 1500 mutations of the CFTR gene identified but they do not all cause CF disease. The presence of clinical symptomatology still remains an important factor.

Editorial

(13) Aurora P, Spencer H, Moreno-Galdó A. Lung transplantation in children with cystic fibrosis: a view from Europe. *Am J Respir Crit Care Med* 2008;**177**:935–6

Special mention to a superb editorial that rebuts the startling and widely publicized 2007 *New England Journal of Medicine* paper by Liou *et al*.,[7] from the US, that called for a halt to lung transplantation programs due to their reporting that only five out of 514 CF children listed for transplant received a survival benefit from their procedure. Their finding contrasted to the one previous paediatric study, from Great Ormond Street Hospital London, that showed a highly significant survival benefit associated with lung transplantation in 124 children with CF. This European perspective suggests that the paper's survival predictions were poor and that children in the US are listed too soon.

Reviewed papers

- Kerem E, Hirawat S, Armoni S, *et al*. Effectiveness of PTC124 treatment of cystic fibrosis caused by nonsense mutations: a prospective phase II trial. *Lancet* 2008;**372**:719–27
- Retsch-Bogart GZ, Burns JL, Otto KL, Liou TG, McCoy K, Oermann C, Gibson RL, for the AZLI Phase II Study Group. A Phase 2 Study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and Pseudomonas aeruginosa infection. *Pediatr Pulmonol* 2008;**43**:47–58
- McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway *Pseudomonas aeruginosa* in cystic fibrosis. *Am J Resp Crit Care Med* 2008;**178**:921–8
- Young AC, Wilson JW, Kotsimbos TC, Naughton MT. Randomised placebo controlled trial of non-invasive ventilation for hypercapnia in cystic fibrosis. *Thorax* 2008;**63**:72–7
- Smyth A, Lewis A, Bertenshaw C, Choonara I, McGaw J, Watson A. Case-control study of acute renal failure in patients with cystic fibrosis in the UK. *Thorax* 2008;**63**;532–5
- 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
- Kozlowska WJ, Bush A, Wade A, *et al*.; London Cystic Fibrosis Collaboration. Lung function from infancy to the preschool years after clinical diagnosis of cystic fibrosis. *Am J Respir Crit Care Med* 2008;**178**:42–9

- Linnane BM, Hall GL, Nolan G, *et al*. Lung function in infants with cystic fibrosis diagnosed by newborn screening. *Am J Respir Crit Care Med* 2008;**178**:1238–44
- Fernandes BN, Plummer A, Wildman M. Duration of intravenous antibiotic therapy in people with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD006682. DOI: 10.1002/14651858.CD006682.pub2; first published 16 April 2008
- Houston BW, Mills N, Solis-Moya A. Inspiratory muscle training for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No.: CD006112. DOI: 10.1002/14651858.CD006112.pub2; first published 8 October 2008
- Waters V, Ratjen F. Combination antimicrobial susceptibility testing for acute exacerbations in chronic infection of Pseudomonas aeruginosa in cystic fibrosis. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD006961. DOI: 10.1002/14651858.CD006961.pub2; first published 16 July 2008
- Farrell PM, Rosenstein BJ, White TB, *et al*. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic Fibrosis Foundation Consensus Report. *J Pediatr* 2008;**153**:s4–s14
- Aurora P, Spencer H, Moreno-Galdó A. Lung transplantation in children with cystic fibrosis: a view from Europe. *Am J Respir Crit Care Med* 2008;**177**:935–6

References

1 Wilschanski M, Yahav Y, Yaacov Y, *et al*. Gentamicin-induced correction of CFTR function in patients with cystic fibrosis and CFTR stop mutations. *N Engl J Med* 2003;**349**:1433–41

2 Gibson RL, Retsch-Bogart GZ, Oermann C, *et al*. Microbiology, safety, and pharmacokinetics of aztreonam lysinate for inhalation in patients with cystic fibrosis. *Pediatr Pulmonol* 2006;**41**:656–65

3 Noone PG. Non-invasive ventilation for the treatment of hypercapnic respiratory failure in cystic fibrosis. *Thorax* 2008;**63**:5–7

4 Bertenshaw C, Watson AR, Lewis S, Smyth A. Survey of acute renal failure in patients with cystic fibrosis in the UK. *Thorax* 2007;**62**:541–5

5 Goss CH. Should we stop using intravenous gentamicin in patients with cystic fibrosis?. *Thorax* 2008;**63**:479–80

6 Davis SD, Ratjen F. Reduced lung function in cystic fibrosis: a primary or secondary phenotype?. *Am J Respir Crit Care Med* 2008;**178**:2–3

7 Liou TG, Adler FR, Cox DR, Cahill BC. Lung transplantation and survival in children with cystic fibrosis. *N Engl J Med* 2007;**357**:2143–52