Cystic fibrosis papers of the year 2007

Ian M Balfour-Lynn

Department of Paediatric Respiratory Medicine, Royal Brompton & Harefield NHS Trust, Sydney Street, London SW3 6NP, UK. E-mail: i.balfourlynn@ic.ac.uk

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Introduction

The literature search was conducted using PubMed (www.ncbi.nlm.nih.gov/sites/entrez), entering the search term 'cystic fibrosis', for the period 1 January to 13 November 2007. There were 1228 papers identified; when limits were set for 'clinical trial' and 'randomized controlled trial' 63 papers remained. In addition, three meta-analyses were identified. The papers selected for this review are a personal choice of studies with important or interesting clinical messages.

Randomised controlled trials

Growth hormone

Schnabel D, Grasemann C, Staab D, Wollmann H, Ratjen F; German Cystic Fibrosis Growth Hormone Study Group. A multicenter, randomized, double-blind, placebo-controlled trial to evaluate the metabolic and respiratory effects of growth hormone in children with cystic fibrosis. *Pediatrics* 2007;**119**:e1230–8.

What is already known?

- Growth in cystic fibrosis (CF) is affected by malnutrition from a number of causes (e.g. pancreatic insufficiency, increased energy requirements etc.).
- Chronically increased concentration of inflammatory cytokines (e.g. tumour necrosis factor-α, interleukins 1 and 6) also adversely affects production and secretion of growth hormone (GH).
- Many small, unblinded studies have been conducted, showing benefits in growth, nutritional status and lung function.

Methods

- Twelve German centres participated in a double-blind randomized placebo-controlled trial, using two doses of daily somatropin GH for 24 weeks followed by 24 weeks open label.
- All patients had body mass index (BMI) less than the tenth centile and/or weight less than the third centile; bone age was 8–18 years.

Results

- Sixty seven patients were enrolled with a mean age around 14 years, and height and BMI Z scores around −2.
- Height, growth velocity and growth factors (insulin-like growth factor 1 and insulin-like growth factor binding protein 3) increased significantly in both treatment groups.
- Weight did increase but weight gain was no different from placebo.
- Forced expiratory volume in 1 sec (FEV_1) did not change significantly, there was a trend to increase in forced vital capacity (FVC) in the higher dose group.
- Maximal oxygen uptake (VO_2max) during peak exercise increased significantly.
- No problems with glucose metabolism.

Critique

- GH had positive effects on metabolism but did not result in short-term improvement in lung function.
- An important study as this was a relatively large trial of GH and the first to be placebo-controlled. However 300 patients would have been required to show a significant difference in FEV_1. This illustrates the problem with clinical trials in CF that often require large subject numbers to prove significance.
- It is unlikely many CF teenagers would accept daily injections with GH simply to grow more.
- The authors suggest long-term studies in a larger cohort of patients are needed to clarify whether GH has a positive effect on lung function decline. I would suggest the time, money and effort are better spent studying other interventions.

Ibuprofen

Lands LC, Milner R, Cantin AM, Manson D, Corey M. High-dose ibuprofen in cystic fibrosis: Canadian safety and effectiveness trial. *J Pediatr* 2007;**151**:249–54.

What is already known?

- High dose ibuprofen can slow the rate of decline of lung function, especially in children.[1] However, the original study only included 49 children under 13 years, and 90% came from one CF centre.
- Concerns over safety of high dose ibuprofen and difficulties with the logistics of therapeutic monitoring (serum levels) have meant that the use of ibuprofen is limited, especially in the UK, but also in many US centres.
- Since the completion of this trial, there has been a publication of observational data from the CF Foundation Patient Registry looking at children with similar demographics to the trial (6–17 years with baseline FEV_1 >60%). They found a reduction in rate of decline over 2–7 years of FEV_1 in those taking ibuprofen (n=1365) compared to those not (n=8960).[2] Those taking it were more likely to have an episode of gastrointestinal bleeding requiring hospitalization (annual incidence 0.37% versus 0.14%).

Methods

- Twelve Canadian centres participated in a multicentre double-blind randomized placebo-controlled trial of high dose ibuprofen (20–30 mg/kg twice daily) for two years.

Results

- One hundred and forty-two patients were enrolled aged 6–18 years with a baseline FEV_1 >60% (i.e. they had mild lung disease).
- Treatment group had a significant reduction in rate of decline of forced vital capacity (FVC) (+0.07% versus −1.62% predicted).
- There was no change in FEV_1, chest radiograph scores or nutritional status.
- The therapy was well tolerated.

Critique

- Unfortunately the study was grossly underpowered: 142 enrolled instead of the 440 required from sample size estimates.
- Change in FVC may have been statistically significant but it was likely to be clinically insignificant.
- This study is unlikely to change practice.

Nebulized denufosol tetrasodium

Deterding RR, Lavange LM, Engels JM, *et al.* for the Cystic Fibrosis Therapeutics Development Network and the Inspire 08-103 Working Group. Phase II randomized safety and efficacy trial of nebulized denufosol tetrasodium in cystic fibrosis. *Am J Respir Crit Care Med* 2007;**176**:362–9.

$P2Y_2$ agonists may be useful, as they activate an alternate chloride ion channel, inhibit sodium absorption and enhance airway clearance. This was a multicentre, double-blind, randomized, placebo-controlled phase II study of nebulized denufosol tetrasodium given three times daily for 28 days. Eighty-nine subjects aged 8–45 (median 14) years took part, with mild CF lung disease (baseline FEV_1 >75% predicted). The study found the drug significantly improved lung function, albeit by only small amounts, and was well tolerated.

Inhaled corticosteroids

de Boeck K, de Baets F, Malfroot A, Desager K, Mouchet F, Proesmans M. Do inhaled corticosteroids impair long-term growth in prepubertal cystic fibrosis patients? *Eur J Pediatr* 2007;**166**:23–8.

This was a multicentre, double-blind, randomized, placebo-controlled trial of high dose inhaled fluticasone propionate given twice daily for one year. Twenty-seven children were enrolled with mild disease (baseline FEV_1 around 90% predicted). There was no difference found in lung function. Importantly, however, longitudinal growth was significantly slower in those on inhaled corticosteroids – 3.96 versus 5.49 cm in one year – which resulted in a significant change in height standard deviation scores (−0.38 versus −0.01). There was no catch-up growth noted in the 1–2 years after the drug was discontinued. Given the lack of evidence for benefit of inhaled corticosteroids, this is a warning of potential harm.

Epidemiological studies

Infant care patterns

Padman R, McColley SA, Miller DP, *et al.* Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Infant care patterns at epidemiologic study of cystic fibrosis sites that achieve superior childhood lung function. *Pediatrics* 2007;**119**:e531–7.

What is already known?

- The Epidemiologic Study of Cystic Fibrosis (ESCF) is a multicentre longitudinal observational study of patients with CF in the USA and Canada that started in 1993. By the end of 1994, over 18,000 patients had been enrolled.
- A publication in 2003 showed that sites with the highest average lung function monitored patients more frequently (by clinical status, lung function and respiratory cultures) and also treated patients more aggressively, particularly with intravenous antibiotics.[3]

Methods

- Sites were divided into quartiles in terms of their median FEV_1, based on the best lung function measured during the year for children aged 6–12 years in 2003.
- Data was then taken for demographics, clinical characteristics and treatment patterns for patients who were aged 0–3 years in 1994–1999 at the sites in the upper quartile (UQ) and lower quartile (LQ) for lung function.

Results

- Of the 837 children in the lung function UQ and LQ cohorts, 525 (63%) were also included in the infant cohort. Median FEV_1 at UQ sites was 107% predicted and at LQ sites 89% predicted.
- The infant cohort consisted of 755 children from 12 UQ sites and 743 children from 12 LQ sites.
- Significant differences for UQ sites:
  - More white (non-Hispanic) patients.
  - More diagnosed by newborn screening, fewer by symptoms.
  - Less cough.
  - Less liver function abnormalities.
  - More sinusitis.
  - Airway cultures taken more often; more *Staphylococcus aureus* and less *Pseudomonas aeruginosa* isolated.
  - Higher weight and height for age centiles.
- Significant treatment differences for UQ sites are shown in Table 1
- No differences were found for use of intravenous, oral or inhaled antibiotics, inhaled corticosteroids, Pulmozyme and enteral nutrition.

Table 1
Significant treatment differences for UQ versus LQ centres in the Epidemiologic Study of Cystic Fibrosis

More	*Less*
Supplemental oxygen	Chest physiotherapy
Oral corticosteroids	Inhaled bronchodilators
Mast cell stabilizers	Oral calorie supplements
Mucolytics (excluding Pulmozyme)	Pancreatic enzymes

Critique

- Epidemiological studies can only identify associations, not cause and effect. Because chest physiotherapy was more prevalent in LQ centres, it does not follow that physiotherapy is bad for the patients. Equally, it would be wrong to jump to the conclusion that oral corticosteroids were good for infants; furthermore, mast cell stabilizers have never been shown to be of value in infants with CF.
- A limitation of the study is that two cross-sectional cohorts were used, it would have been more powerful if the infant cohort was followed until old enough to perform lung function. Only 525 of 1498 children (35%) from the infant cohort were included in those who had lung function. The study gives no information on treatment benefit in individuals, only on treatment in CF centres.
- Their conclusion that 'pulmonary function of older children may be improved through specific interventions during the first 3 years of life' may be correct but unfortunately this paper cannot tell us which interventions.

MRSA

Ren CL, Morgan WJ, Konstan MW, *et al.* The Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Presence of methicillin resistant *Staphylococcus aureus* in respiratory cultures from cystic fibrosis patients is associated with lower lung function. *Pediatr Pulmonol* 2007;**42**:513–8.

What is already known?

- Prevalence of methicillin-resistant *S. aureus* (MRSA) is increasing in the general population and CF patients. ESCF data has shown prevalence of MRSA-positive respiratory cultures was 0.1% in 1995 and 7.3% in 2001; large scale data for UK CF patients has not been published.
- A previous small case-controlled study in UK children showed MRSA did not significantly

effect lung function but did result in worse chest radiograph scores, adversely affect growth and lead to greater use of intravenous antibiotics.[4]

Methods

- ESCF data for 2001 analysed, which included 20,451 patients in 194 CF centres.
- The study compared patients positive only for *S. aureus* – methicillin resistant versus *S. aureus* – methicillin-sensitive (MSSA).

Results

- 1834 (7.5%) patients were positive for *S. aureus* only: 11% MRSA, 89% MSSA.
- Patients with MRSA had significantly lower FEV_1 than MSSA; for adults 61 versus 70% predicted, for children 81 versus 89%.
- Presence of MRSA was associated with increased hospitalization and intravenous, oral and inhaled antibiotic use.

Critique

- This is the largest study to look at the impact of MRSA and clearly there are additional adverse effects on lung function compared to MSSA.
- Increased hospitalizations may be due to the fact that oral antibiotic choice is more limited for MRSA.
- The nature of the study can not determine whether MRSA led to a reduction in lung function or whether MRSA is simply a marker of more severe lung disease.
- The study also provides no information on the interaction of MRSA with *P. aeruginosa*.

Cochrane systematic reviews – new or substantially amended in 2007

Oral anti-pseudomonal antibiotics

Remmington T, Jahnke N, Harkensee C. Oral anti-pseudomonal antibiotics for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2007;**3**: CD005405. DOI: 10.1002/14651858.CD005405 .pub2.

The review found no conclusive evidence that an oral anti-pseudomonal antibiotic regimen is more or less effective than an alternative treatment for either exacerbations or long-term treatment of chronic infection with *P. aeruginosa*.

CFTR gene replacement

Lee T, Southern KW. Topical cystic fibrosis transmembrane conductance regulator gene replacement for cystic fibrosis-related lung disease. *Cochrane Database of Systematic Reviews* 2007;**2**:CD005599. DOI: 10.1002/14651858. CD005599.pub2.

The review concluded that there is currently no evidence to support the use of CFTR gene transfer reagents as a treatment for lung disease in people with CF.

Oral calorie supplements

Smyth R, Walters S. Oral calorie supplements for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2007;**1**:CD000406. DOI: 10.1002/ 14651858.CD000406.pub2.

The reviewers stated that oral calorie supplements do not confer any additional benefit in the nutritional management of moderately malnourished children with CF over and above the use of dietary advice and monitoring alone. While nutritional supplements may be used, they should not be regarded as essential.

Reviewed papers

- De Boeck K, De Baets F, Malfroot A, Desager K, Mouchet F, Proesmans M. Do inhaled corticosteroids impair long-term growth in prepubertal cystic fibrosis patients? *Eur J Pediatr* 2007;**166**:23–8
- Deterding RR, Lavange LM, Engels JM, *et al.*for the Cystic Fibrosis Therapeutics Development Network and the Inspire 08-103 Working Group Phase II randomized safety and efficacy trial of nebulized denufosol tetrasodium in cystic fibrosis. *Am J Respir Crit Care Med* 2007;**176**:362–9
- Lands LC, Milner R, Cantin AM, Manson D, Corey M. High-dose ibuprofen in cystic fibrosis: Canadian safety and effectiveness trial. *J Pediatr* 2007;**151**:249–54
- Padman R, McColley SA, Miller DP, *et al.* Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Infant care patterns at epidemiologic study of cystic fibrosis sites that achieve superior childhood lung function. *Pediatrics* 2007;**119**:e531–7
- Ren CL, Morgan WJ, Konstan MW, *et al.* The Investigators and Coordinators of the Epidemiologic Study of Cystic Fibrosis. Presence of methicillin resistant *Staphylococcus aureus* in respiratory cultures from cystic fibrosis patients is associated with lower lung function. *Pediatr Pulmonol* 2007;**42**:513–8
- Schnabel D, Grasemann C, Staab D, Wollmann H, Ratjen FGerman Cystic Fibrosis Growth Hormone Study Group. A multicenter, randomized, double-blind, placebo-controlled trial to evaluate the metabolic and respiratory effects of growth hormone in children with cystic fibrosis. *Pediatrics* 2007;**119**:e1230–8

References

1 Konstan MW, Byard PJ, Hoppel CL, Davis PB. Effect of high-dose ibuprofen in patients with cystic fibrosis. *NEJM* 1995;**332**:848–54

2 Konstan MW, Schluchter MD, Xue W, Davis PB. Clinical use of ibuprofen is associated with slower FEV_1 decline in

children with cystic fibrosis. *Am J Respir Crit Care Med* 2007;**176**:1084–9

3 Johnson C, Butler SM, Konstan MW, Morgan W, Wohl ME. Factors influencing outcomes in cystic fibrosis: a center-based analysis. *Chest* 2003;**123**:20–7

4 Miall LS, McGinley NT, Brownlee KG, Conway SP. Methicillin resistant *Staphylococcus aureus* (MRSA) infection in cystic fibrosis. *Arch Dis Child* 2001;**84**:160–2