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Review

Clinical papers of the year 2018 – Cystic fibrosis

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Educational aims

The reader will be:

- Up to date in important clinical literature published in 2018, in the field of cystic fibrosis.
- Able to adapt their clinical approach in light of contemporary evidence for best practice.

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ABSTRACT

This paper reviews the most important clinical papers in cystic fibrosis published in 2018, having searched all the literature on Pubmed. Focus is on CFTR modulator therapy, randomised controlled trials, and infection/microbiology issues.

INTRODUCTION

This review article discusses papers published in 2018, either electronically or in paper form. It focuses on clinical papers relevant to cystic fibrosis (CF) that will have a significant therapeutic impact and/or that have an important message for clinicians. Inevitably it is a personal choice and with limited space authors who do not see their name should not be offended. The online database PubMed (US National Library of Medicine, National Institutes of Health) was searched just using the term 'cystic fibrosis' from 1.1.18 to 31.12.18. This has become more time consuming over the years, with 2475 articles flagged in 2018 compared to 1573 a decade earlier in 2008.

CFTR MODULATORS

Inevitably we must start with articles pertaining to small molecule therapies, the CFTR (CF transmembrane conductance regulator) modulators, that have the potential to revolutionise CF care. This impact will be even greater if it is felt worldwide, and we must hope that every country will be able to afford to make them available to all people with CF. Of course, this is highly unlikely given some countries cannot provide basic drugs for treatments such as pancreatic enzyme replacement therapy, and many patients do not have access to a dietitian or physiotherapist. Even in the UK, currently only one of the three licensed CFTR modulator drugs is available within the nationalised health care system.

Ivacaftor

Ivacaftor (a CFTR potentiator) has had a huge impact on those with the relevant gating mutations receiving it [1]. The age of eligible patients has fallen from 6 years and above [2], to those above 2 years [3], and now it has been shown to be safe and effective in those aged 1–2 years and work is proceeding for even younger infants. The ARRIVAL study was a multicentre phase 3 single arm study in 1–2 year olds with at least one gating mutation [4]. They received ivacaftor at 50 mg twice daily or the same dose as given to 2–5 year olds – 75 mg twice daily. The first part was pharmacokinetic analysis over 3 days ($n = 7$) and the second part looked at safety over 24 weeks ($n = 19$). Pharmacokinetic data were the same as in 2–5 year olds and it was found to be safe, although there is a cautionary note over liver function, with 5 infants having liver enzymes measured at greater than 3 times the upper limit of normal, which included 2 in whom it rose greater than 8 times the upper limit at a time of concurrent infection. In terms of effectiveness, the sweat chloride fell impressively by an absolute mean of 74 mmol/L. In addition, the mean faecal elastase (a marker of pancreatic exocrine function) rose by 165 mcg/g, although results were variable for individuals; this is exciting and indicates that

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the earlier the drug is started, the greater the likelihood that some pancreatic function can be preserved or even improved to the point where pancreatic enzyme replacement therapy may not be required.

Long term data inevitably take a while to accumulate when a new drug is launched, and this becomes important for an expensive drug where health economic analysis is critical for health services when evaluating cost effectiveness. Ivacaftor was first available in the US in 2012 and in the UK in 2013. A joint US and UK study gathered 2014 CF Registry data for an observational analysis [5]. The mean ivacaftor use in UK was 1.3 years and the US 2.0 years for 1667 patients, who were compared to 8269 patients with comparable age, gender and genotype severity. In the US, compared with the control group, the risk of death was reduced (0.6% vs 1.6%), the risk (need) of transplant was reduced (0.2% vs 1.1%), and hospitalisations were reduced (28% vs 43%). All the US data were significant, but due to the smaller numbers ($n = 411$) on ivacaftor in the UK, whilst there was a significant reduction in hospitalisations, there was only a trend in reduction in death and transplantation. There were also fewer complications such as CF-related diabetes, CF liver disease, and bone/joint issues, with significantly less cultures of the classic pathogenic organism (*Pseudomonas aeruginosa, Staphylococcus aureus,* Aspergillus spp.). This certainly suggests that the drug is truly disease-modifying.

Lumacaftor/ivacaftor (Orkambi)

Orkambi combines the CFTR corrector lumacaftor with the CFTR potentiator ivacaftor. The drug has had less of an impact as it is not as effective for those with homozygous Phe508del as ivacaftor is for those with a gating mutation; nonetheless it has led to significant benefit in some patients.

The original trials were in 12 years and above [6], this was then extended to 6–11 year olds [7]. There has now been an open label safety study in 60 children aged 2–5 years that was presented at the European CF Society conference 2018 and published in 2019 [8]. This has led to a further extension of licensing down to 2 years of age.

The original trials in those over 12 years did not study changes in sweat chloride. This has subsequently been done in 53 people with CF, and they found median sweat chloride fell by 18 mmol/L, and the changes did not correlate with changes in Forced Expiratory Volume in 1 s (FEV_1) or Body Mass Index (BMI) [9]. This change in sweat chloride can be compared with that in 6–11 year olds (median 20 mmol/L) [7], and 2–5 year olds (median 32 mmol/L) [8]. In the 12 year olds and above, they also found improvement in Nasal Potential Difference to a level of 10% normal CFTR function, although figures remained in the CF range, and Intestinal Current Measurement improved to 18% of normal CFTR function [9].

Tezacaftor/ivacaftor (Symdeko in US, Symkevi in Europe)

Tezacaftor is another CFTR corrector. The publications for the 3rd modulator combining tezacaftor with ivacaftor, were published in 2017, for 12 years and above who had either the homozygous Phe508del mutation or heterozygous Phe508del and a residual function mutation [10,11]. A further (unpublished to date) study of 6–11 year olds in North America and Canada led to an application to the FDA (US Food and Drug Administration) to extend the licence. A phase 3 study has been conducted in 6–11 year olds in Europe and Australia which included measurement of lung clearance index as well as safety data. Presentation of results and publication are awaited, but a Vertex press release (February 2019) suggested it was positive and application to EMA (European Medicines Agency) will happen later in 2019.

Triple therapy

Triple therapy refers to a combination of tezacaftor and ivacaftor with one of two newer CFTR corrector drugs, known as Vx659 and Vx445. The phase 2 studies were published in 2018 looking at adults aged 18 years and above with FEV_1 40–90% predicted. Triple therapy with Vx659 was studied in 48 centres outside the USA [12]. 29 people with homozygous Phe508del mutation received the study drug or the tezacaftor/ivacaftor combination. After one month, the FEV_1 % predicted rose a further 9.7 points compared to those on tezacaftor/ivacaftor and the mean sweat chloride fell by 42 mmol/L. In 63 people heterozygous for Phe508del with a minimal function mutation, after one month, the FEV_1 rose by 10.2–13.3 points compared to placebo, and the mean fall in sweat chloride was 44–51 mmol/L, depending on the dose given. There was an acceptable safety profile in all groups, similar to existing CFTR modulators.

Triple therapy with Vx445 was studied in 38 worldwide centres (excluding the UK) [13]. 28 people with homozygous Phe508del mutation received the study drug or the tezacaftor/ivacaftor combination. After one month, the FEV_1 % predicted rose a further 11.0 points compared to those on tezacaftor/ivacaftor and the mean sweat chloride fell by 40 mmol/L. In 98 people heterozygous for Phe508del with a minimal function mutation, after one month, the FEV_1 rose by 11.1–13.8 points compared to placebo, and the mean fall in sweat chloride was 33–39 mmol/L, depending on the dose given. There was an acceptable safety profile in all groups.

These phase 2 studies are most exciting and suggest effective therapy will in theory be available for approximately 90% of people with CF, and further studies will most likely bring the age range down to young children. Clearly the younger the drugs are started the more likely chronic infection with airway inflammation and irreversible lung damage will be avoided. There is also hope that some pancreatic function can be retained. The phase 3 studies are on-going and will be presented at the North American CF Conference in autumn 2019. Initial pre-specified one month results have been the subject of Vertex press releases in November 2018 and March 2019 and seem to be encouraging. Again though, the big question is, will these drugs be affordable to health care systems outside the USA?

RANDOMISED CONTROLLED TRIALS

OPTIMISE – Azithromycin for early Pseudomonas infection

We know that long term oral azithromycin reduces the risks of pulmonary exacerbations in those with and without *Pseudomonas aeruginosa*, even though it is not bacteriocidal against *Pseudomonas*. This trial set out to determine whether azithromycin would reduce the risk of a pulmonary exacerbation and delay recurrence of infection with *Pseudomonas aeruginosa* in patients who had the organism for the first time or a new infection after being free for 2 years [14]. This multicentre USA study looked at 221 children aged 6 months to 18 years. At the time of their *Pseudomonas aeruginosa* eradication with 28 days nebulised tobramycin, they started oral azithromycin 3 times a week for 18 months. Eradication was repeated if they cultured *Pseudomonas aeruginosa* after 21 days or if a culture (taken every 3 months) was positive. The study was stopped early as it reached its pre-specified endpoint – the risk of a pulmonary exacerbation requiring antibiotics was reduced by 44% in those having azithromycin, with the greatest reduction seen in those under 3 years. There was however, no difference in *Pseudomonas aeruginosa* eradication rate in the 1st quarter (about 75%), nor a difference in its recurrence rate (about 40%). This would suggest that it was the milder non-

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Pseudomonas exacerbations that were affected, and although the time to exacerbation was prolonged, the actual number occurring was not different. Lung function was not improved between the groups, but weight gain was significantly higher in the azithromycin group. There were no safety issues (audiology and QTc interval) and no negative interactions with tobramycin. Concerns do remain though over long term use of azithromycin and macrolide-resistance (especially for *Haemophilus influenzae* and *Staphylococcus aureus*) and acquisition of *Mycobacterium abscessus*.

PRESIS – Hypertonic saline in infants as prevention

Hypertonic saline is a well-recognised therapy in older children and adults. The main infant study (ISIS) did not show significant differences [15] although there was a signal of improvement in LCI in a subset of 27 infants [16]. This was a trial in 42 infants aged under 4 months (mean 3 months) conducted in Germany [17]. Children were given nebulised 6% hypertonic saline or 0.9% saline placebo twice daily for one year. It was well tolerated and a parental diary suggested adherence was 77–100%, although it would have been better to collect data directly from the nebulisers. There was a significant improvement in LCI of −0.6 compared to −0.1 in the placebo, with a baseline LCI of 7.2–7.5. Growth was also improved (mean difference 500 g and 1.5 cms). There were no changes in lung MRI scanning, nor pulmonary exacerbation rate. The remaining question is whether the burden of twice daily hypertonic saline is worth a change in LCI of −0.5 over a year in essentially well infants. Certainly the trial proved that LCI and MRI scanning could be used successfully as outcome measures for drug trials in infants.

INFECTION ISSUES

CF-SpIT – sputum induction vs cough swabs vs bronchoalveolar lavage

Respiratory microbiological sampling is a critical part of CF care; this is carried out routinely as well as when a patient is symptomatic. Many children do not expectorate sputum, even when unwell with a wet cough. This Welsh study recruited 124 patients aged 6 months to 18 years [18]. There were 200 sputum inductions carried out using 8 ml nebulised 7% hypertonic saline and these were compared with standard cough swabs. Sputum induction had an 84% success rate, with no differences in those under 6 years *vs* older children, asymptomatic *vs* symptomatic, and with or without a wet cough. Of the 167 paired samples, pathogens were isolated in 38% sputum induction samples *vs* 14% cough swabs. In the second part, 35 patients had 41 paired samples of sputum induction and bronchoalveolar lavage (BAL); the BALs were taken from either one, two or six lobes. Overall, 39 pathogens were identified – 69% from sputum induction, 56% from single lobe (right middle) BAL, 72% from two lobed (right middle and lingula), and 85% from six lobed. Interestingly there were some organisms isolated that were missed on BAL, and the authors suggest they come from the large intrathoracic airways. It would be a usual practice to suction any secretions from those airways during a clinical bronchoscopy, so they ought not be missed outside of a study with a rigid BAL protocol. Certainly use of sputum induction has cut down the number of bronchoscopies we carry out at our large CF centre.

Cross infection

This is an important issue and a source of great concern for people with CF and their families. It is already known that *Pseudomonas aeruginosa* is aerosolised during coughing and remains viable within droplets for extended durations [19]. It has now been demonstrated by an Australian group that during voluntary coughing into an Andersen Cascade Impactor, gram negative organisms (*Achromobacter*, *Stenotrophomonas maltophilia* and *Burkholderia* species) and *Staphylococcus aureus* travel up to 4 m and are viable within droplets for up to 45 min, similar figures to that found with *Pseudomonas aeruginosa* [20].

The US Cystic Fibrosis Foundation infection control guideline 2013 suggested that all people with CF (regardless of their respiratory tract culture status) should wear surgical masks when entering a hospital and only take them off in their clinic or hospital room [21]. The same Australian group above looked at 25 adults with chronic *Pseudomonas aeruginosa* and found 76% produced pseudomonas-positive droplets at 2 m in an Andersen Cascade Impactor with uncovered forced voluntary coughing [22]. When those 76% wore surgical or N95 masks or put their hands over their mouths when coughing, there was a significant reduction in *Pseudomonas aeruginosa* aerosol load. With the surgical mask, 11% produced positive aerosols at 2 m, 21% whilst wearing the N95 mask, and 68% if they coughed into their hand or elbow. Talking only (without coughing) produced aerosols at 2 m in just 4% patients. The surgical masks were more comfortable than the N95 masks, although inevitably some preferred the latter and a third had no preference between the two; they still tended to prefer no mask at all however. This provides some evidence of effectiveness of masks (at least over 10 min), but the concept has not been universally accepted, particularly outside the US, mostly due to concerns of stigmatising patients in public hospital areas. Furthermore, how effective will they be when worn for over an hour in clinic when they will inevitably become moist, and what about children who do not expectorate sputum? The Australian group looked to answer the first query in 25 adults and 10 healthy volunteers [23]. The people with CF rated masks less comfortable than the controls at all times up to 40 min and those with better lung function were more tolerant. The masks were still effective at reducing *Pseudomonas aeruginosa* aerosol load at 40 min, and although some clearly retained water (with weight gain of up to 20 g) they still worked. The debate continues, with interesting editorials and correspondence following these papers about masks. This debate is likely to be intensified with the screening of the Hollywood film 'Five feet apart' about two young people with CF who meet in hospital and fall in love.

Lung transplantation for chronic Mycobacterium abscessus infection

Finally, a small case series of 4 transplanted adults with chronic *Mycobacterium abscessus* infection is worth highlighting as most transplant centres quote this as an absolute contraindication [24]. Two had *Mycobacterium* subspecies *abscessus*, and two had subspecies *bollettii*. One died after 3 days from bleeding complications, but three were doing well at 16–28 months post-transplant with no evidence of local or disseminated Mycobacterial disease.

MISCELLANEOUS

Protein pump inhibitors

Antacids, and especially proton pump inhibitors (PPIs) are used extensively in paediatric CF practice, *e.g.* US registry 2016 data showed PPIs were prescribed to 51% patients. They are used for both gastro-oesophageal reflux and to aid efficacy of pancreatic enzyme replacement therapy in those requiring high doses. However PPIs have been associated with community-acquired pneumonia in adults and children. A retrospective study looked at children with a mean age of 10.5 years in a single US centre and compared 126 who had taken PPIs for at least 6 months with 49

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who had never received them [25]. They found 60% of the PPI group *vs* 25% had at least one pulmonary exacerbation over the year of study. Furthermore, a Dutch CF Registry 2009–14 study looked at 545 children aged 5 years or more with a mean age of 12 years, and found 26% were on PPIs [26]. Using a multivariate model, they found PPI use to be associated with annual decline in FEV_1 and a risk factor for future exacerbations (odds ratio 1.6). These studies prove association only, and cannot state categorically PPIs are causative. However, it is an important message that PPIs should only be used when absolutely necessary and their use should be reviewed in each patient. Reflux usually improves with age, and perhaps taking more enzyme (as long as doses are kept within recommended margins) may be safer than long term PPIs.

Survival data

And finally, for anyone else baffled by survival statistics, this guide to interpreting them is excellent and easy to understand, and will help clinicians explain data to parents and patients [27]. Up to date and projected estimates for the UK are then given in the accompanying paper [28]. It is suggested that Phe508 del homozygous babies born today will have a median survival of 65 years for men and 56 years for women, a figure that will be changed for certain, if and when successful CFTR modulators are available to all.

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