Highlights of the North American CF Conference 2013

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SUMMARY

This is a personal selection of papers that were presented at the 27th North American Cystic Fibrosis Conference held in Salt Lake City in October 2013. The papers discussed in this review are thought to be of particular interest to CF caregivers in the UK.

INTRODUCTION

The 27th North American Cystic Fibrosis Conference took place at the Salt Palace Convention Center, Salt Lake City, Utah between the 17th and 19th October 2013. Around 4000 delegates from all over the world attended 3 plenary sessions, 8 short courses, 30 workshops, 25 caregiver sessions, 9 brown bag lunches, 21 symposia, 5 consultation clinics, and 99 round tables, and 670 abstracts were viewed.

It is impossible in a short presentation do justice to such a rich feast of cutting edge CF fare, so I have selected a few morsels that particularly impressed me and I think will be of the most interest to UK CF caregivers.

PLENARY SESSIONS I AND II

The US Cystic Fibrosis Foundation uses its plenary sessions to deliver what it considers to be state of the art advances in CF care and this conference was no exception. The first two of these majored on emerging gene product therapy and the journey towards finding CFTR modifiers that offer hope of a cure for the condition.

The first plenary session (Restoring CFTR Function, Road to a Cure [part I]) was given by Scott Donaldson (University of North Carolina) and looked at the effect of ivacaftor on those few G551D patients who benefit from it.

He introduced the GOAL (G551D Observational) study [1], a follow-on of 153 patients from 28 centres prescribed ivacaftor as part of their routine CF treatment. Core study measures included clinical outcome, sweat chloride, quality of life, and the collection of biomarkers. In addition, the effect on lung mucus and flora, intestinal pH, and sweat production were evaluated in subgroups of patients. Early results were produced from the study. Of interest was the effect ivacaftor had in improving the clearance of mucus from the lung, both centrally and peripherally, demonstrated by radionuclide scanning and muco-ciliary clearance indices. Furthermore, positive culture rates in those chronically infected with Pseudomonas aeruginosa decreased significantly at 6 months, suggesting that the reduction in sputum viscosity had allowed some patients to clear this organism: a potentially important finding. Unfortunately, markers of lung inflammation did not change significantly following ivacaftor in the small subset of patients studied. Intestinal pH was measured dynamically using a pass-through wireless motility capsule: ivacaftor corrected the abnormally low intestinal pH, implying that it may improve exogenous pancreatic enzyme efficacy thereby reducing GI symptoms and improving nutrition, and that its use early in life may ultimately preserve endogenous exocrine function since pancreatic bicarbonate production normalises intestinal pH. This also raises the interesting question of whether preserving exogenous pancreatic function may also help to preserve its endogenous function, since CF-related diabetes mellitus is increasingly common with age and is associated with a greatly increased treatment burden and clinical decline.

The second plenary session (Roadmap to a Cure [II], A Clinical Research Path Ensuring Benefit for All Patients with CF) was given by Bonnie Ramsey (University of Washington School of Medicine). She focussed on the pipeline of potential new therapies that might become available for the treatment of the different gene abnormalities that cause the CF condition. Treatment options depend upon the class of mutation (I, II and III severe; IV and V mild) coupled with the effect this has on CFTR utility [class I, II, V have reduced quantity, so will need corrector therapies; class III [gating] and IV [conductance] have reduced function [also V], so will need potentiators]. Furthermore, at least 30% of normal CFTR function needs to be achieved to have a clinical effect. Ivacaftor potentiates the effect of CFTR in patients with G551D and other class III gating mutations, as indicated by the normalisation of sweat chloride in G551D individuals, but these only make up

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5% of the US CF population (6% worldwide). A blinded placebo controlled crossover study of ivacaftor (KonaX); [2] in other gating mutations (G178R, S549N, S549F, G551S, G970R, G1244E, S1251N, G1349D, S1255P), has shown similar FEV1 improvement to that found in G551D at 8 and 24 weeks and FDA approval to extend the use of ivacaftor to these patients has recently been granted. Also, the original ivacaftor studies only looked at its effect from the age of 6 onwards: a two part open label study to evaluate its use in younger children (age 2-5) with any gating mutation (KIWI) is now fully enrolled and should report in the middle of 2014. Furthermore, a phase three multicentre randomized double blind placebo controlled study (KoDuct) of ivacaftor over 24 weeks in patients 6 years or older with at least one copy of R117H (where there is some residual CFTR function) is now fully enrolled and should report at the end of the year. If ivacaftor is useful in all these gating and residual function mutations, then approximately 8% of the CF population can look to a cure. The majority of the remaining CF population possess at least one copy of the class II F508-del mutation, associated not only with reduced production of CFTR but also its dysfunction. Lumacaftor increases the production of F508-del CFTR and helps move it to the cell surface: in vitro studies have shown that the addition of ivacaftor to lumacaftor improves F508-del CFTR functionality at the cell surface. Traffic and Transport (randomized, placebo-controlled double-blind Phase 3 studies in F508del homozygotes) are looking at two doses of lumacaftor combined with ivacaftor over a 24 week period: the studies are now fully enrolled and should report in the middle of 2014.

If the remaining gating potentiators and the combination treatment outlined above for F508-del mutations work, then around 20% of CF patients will still be left unserved by gene product therapy. Many of these are nonsense mutations, where abnormal stop codons prevent the formation of effective CFTR protein. Ataluren (PTC Pharmaceuticals), a novel molecule discovered by high throughput screening, has been shown to correct this defect in a dose dependent fashion in mouse models, and in a placebo controlled phase 3 trial in CF patients with nonsense mutations ameliorated some of the loss of FEV1 over a 48 week period. However, aminoglycosides can inhibit ataluren, so a Phase 3 efficacy and safety trial in patients not receiving inhaled aminoglycosides will be initiated in 2014 by PTC Pharmaceuticals.

If all these gene therapy products are successful, up to 10% of CF patients with still remain untreated. For this group, the UK CF Gene Therapy Consortium double blind, placebo controlled multidose trial in 123 patients of nebulised CFTR+liposome in 5 ml 0.9% saline versus saline alone, which is due to report at the end of 2014, may prove helpful.

**MYCOBACTERIUM ABBESSUS AND INFECTION CONTROL**

Always a perennial flyer at any CF conference is an update on infection, the main cause of morbidity and mortality in CF patients.

Following the reports of two outbreaks of Mycobacterium abscessus in CF patients last year from the USA [3] and UK [4], a further outbreak was reported from a small adult centre in Honolulu [5], where 9 of 19 patients became cross infected, probably in the pulmonary function department, from an index case who was strongly sputum positive. Alteration in infection control measures seemed to have limited further spread. This apparent increase in the incidence of non-tuberculous mycobacteria (NTM) prompted the symposium entitled “From Guidelines to QI to Improving Clinical Care: New Guidelines for Infection Prevention & Control & for Non-tuberculous Mycobacteria (Care).” In this, Charles Howarth (Papworth Hospital, UK) gave an overview of proposed NTM treatment in CF from the ECFS/CFF NTM Guidelines Group [6]. He discussed the problems of making a diagnosis of significant NTM in CF, where uninfected patients often already have many of the criteria on which the international definition depends due to their underlying CF lung disease. Draft guidelines suggest that NTM treatment should be divided into that for *M. avium intracellulare* and *M. abscessus* (MABSC), with that for the latter being more intensive and problematic. In both cases, treatment would involve a combination of often toxic antimicrobials for a prolonged period and ongoing surveillance for months after apparent cure. Treatment for MABSC may need to be lifelong.

In the same symposium Lisa Saiman (Columbia University Medical Center) gave an update on the existing 2003 infection control recommendations for patients with CF (Infection Control and Hospital Epidemiology; May 2003) [7] consisting of 10 adjustments [8]. These included general education, audit and hand hygiene measures for both healthcare providers and users, and the assumption that all CF patients might harbour organisms that were transmissible. CF patients should be aware of cough hygiene: containing their respiratory secretions and disposing of them safely immediately. As regards segregation, the previous advice indicating a one metre infection “cough droplet” transmission distance was increased to 2 metres, and CF patients should avoid all other CF patients unless they live in the same household. Although procedures which included the active expression of respiratory secretions (e.g. chest physiotherapy) should still involve gowning, gloving and masking of healthcare professionals, this was not extended to use at other times. Somewhat controversially the new guidelines will recommend that CF patients should wear a surgical mask at all times when in the hospital environment other than in their own room if hospitalized, the examination room in clinic, or when undertaking pulmonary function measurement.

The Conference ended with the traditional dinner dance in the Grand Ballroom, and delegates travelled home to await the next international CF gathering, the 37th European Conference in Gothenburg, Sweden in June 2014.

**CONFLICT OF INTEREST**

I can confirm that I have no conflict of interest and that this work is not under consideration for publication elsewhere.

**References**