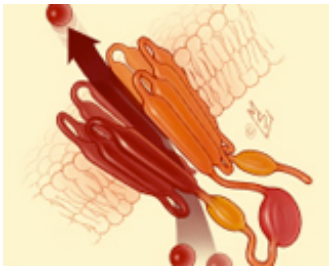
JOHNS HOPKINS MEDICINE eLITERATURE REVIEW
eCysticFibrosis Review
Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Supported by an educational grant from Gilead Sciences, Inc.



ecfs special edition

Special Edition #2: Highlights of the 35th European Cystic Fibrosis Conference

Welcome to Part 2 of this eCysticFibrosis Review Special Edition, our two-part series reporting on some of the key information presented at the European Cystic Fibrosis Society (ECFS) meeting in Dublin, Ireland June 6-9, 2012.

As a special feature, many of these reports include links to streaming video of eCysticFibrosis Review Program Director Peter Mogayzel, MD discussing the new data with the presenters.

Look for the to link to this feature.

In this Issue...

Investigators at the 35th European Cystic Fibrosis Society conference in Dublin, Ireland this past June presented research findings in virtually all areas of cystic fibrosis management.

In this issue we report on presentations focusing on:

- **Epidemiology:** Mortality in patients with poor lung function has been reduced by half since 1995, according to a retrospective analysis that showed a positive correlation with DNase therapy and improved nutrition.
- **Sodium Channel Blockers:** Research reports on the efficacy of new ENaC blockers.
- **Lung Clearance:** A study in neonates using the Lung Clearance Index (LCI) and HRCT looks to quantify lung abnormalities
- **Ivacaftor:** This *CFTR* potentiator may have utility in *CFTR* mutations other than Class III.
- **Ataluren:** The largest trial to date shows improved lung function and reduced pulmonary exacerbations in patients with Class I nonsense CF mutations.

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Identify therapies associated with long-term reductions in mortality
- Describe the "low volume" hypothesis relative to recent research in new sodium channel blockers.
- Discuss new findings describing the cystic fibrosis (CF) neonate lung based on measurement via Lung Clearance Index (LCI) and high-resolution computer tomography (HRCT.)

Program Information
CME/CE Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
Internet CME/CE Policy
Faculty Disclosures
Disclaimer Statement

Length of Activity
Physicians
1 hour
Nurses
1 contact hour

Release Date
November 27, 2012

Expiration Date
November 26, 2014

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- Explain the importance of residual chloride function in selecting patients suitable for treatment with ivacaftor.
- Summarize the effects of ataluren in lung function and rate of exacerbations in patients with nonsense mutations.

IMPORTANT CME/CE INFORMATION

Program Begins Below

ACCREDITATION STATEMENTS

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INTENDED AUDIENCE

This activity has been developed for pulmonologists, pediatric pulmonologists, gastroenterologists, pediatricians, infectious disease specialists, respiratory therapists, dieticians, nutritionists, nurses, and physical therapists.

LAUNCH DATE

This program launched on October 4, 2012, and is published monthly; activities expire two years from the date of publication.

HARDWARE & SOFTWARE REQUIREMENTS

Pentium 800 processor or greater, Windows 98/NT/2000/XP or Mac OS 9/X, Microsoft Internet Explorer 5.5 or later, Windows Media Player 9.0 or later, 128 MB of RAM Monitor settings: High color at 800 x 600 pixels, Sound card and speakers, Adobe Acrobat Reader.

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STATEMENT OF NEED
Based on a review of the current literature, including national and regional measures, detailed conversations with expert educators at Johns Hopkins, and a survey of potential program participants, this program will address the following core patient care gaps:

- Very recent developments in strategies for treating *P. aeruginosa*, using existing as well as new antibiotics, are only beginning to penetrate the awareness of clinicians who should be familiar with the most effective means of treating this dangerous pathogen.
- CF clinicians lack adequate clinical guidance in managing pulmonary exacerbations.
- CF clinicians are not aware of and/or are not implementing existing strategies for improving patient adherence to antibiotic medications.

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Reviewed & Approved by:
General Counsel, Johns Hopkins Medicine (4/1/03)
Updated 4/09

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IN THIS ISSUE

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Michael Konstan, MD discloses that he is a consultant/advisor to Abbott Aradigm, CSL-Behring, Genentech, Gilead, GlaxoSmithKline, Eli Lilly, Novartis, Savara, PTC Therapeutics, and Vertex. He also has received grant/research funding from Novartis PTC Therapeutics and Vertex.

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No other faculty has indicated that they have any financial interests or relationships with a commercial entity.

Unlabeled/Unapproved Uses

Drs. Konstan, Ratjen, Mogayzel and Binder have indicated that there will be reference to the following unlabeled or unapproved uses of drugs: ataluren and hypertonic saline.

Planning Committee Disclosures

MORTALITY WITH LOW LUNG FUNCTION

Workshop 3: Changing Epidemiology and Outcomes
Abstract WS3.7: Survival at low lung function in cystic fibrosis: cohort study from 1995 to 2010. Majdi Osman MD. Abstract from the 35 th European Cystic Fibrosis Congress; June 6-9, 2012; Dublin, Ireland

In the *Changing Epidemiology and Outcomes* workshop, Majdi Osman, MD from the Adult Cystic Fibrosis (CF) Unit of the University of Southampton, Southampton, UK described a retrospective analysis that examined mortality in patients with CF and low lung function as expressed by crude hazard ratios (a measure of relative risk of death over time).

"Improved survival was seen among patients with CF despite low lung function. The data reinforces the importance of airway clearance treatments and good nutrition in improving survival, " Dr. Osman explained.

Dr. Osman preformed a retrospective cohort study of patients with CF whose forced expiratory volume at 1 second (FEV_1) was first observed to be below 30% of predicted value between January and December 2009. He examined survival in 202 patients through December 2010, in sub-cohorts. Patients who had undergone lung transplantation were excluded, as censoring their survival at the date of their operation would have introduced variations in survival.

The 1995-1999 (39 male, 31 female; mean age of 24 ±9.8 years) sub-cohort, which exhibited FEV_1 of a mean (±SD) 24.3% ±4.7%, was as the reference population with a crude hazard ratio of 1. This group exhibited nearly 80% *P. aeruginosa* infection and 70% had a mean BMI of below 19. Nebulized antibiotics and DNase use, and diabetes were noted in 40%.

The 2000-2004 (31 male, 38 female; mean age of 23 ±9.8 years) sub-cohort, with FEV_1 of 25.9% ±3.7%, had a crude hazard ratio of 0.82 (0.52 to 1.24). This sub-cohort exhibited a similar level of *P. aeruginosa* presence in the lung, and BMI was <19 in approximately 70%. Nebulized antibiotics were used in almost twice as many patients as the previous cohort., DNase in over 50%, and diabetes was observed in 40%.

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NEWSLETTER ARCHIVE

The 2005-2009 (41 male, 22 female; mean age of 23.3 ±9.2 years) sub-cohort, which had FEV_1 values of 26.1% ±3.7%, had a crude hazard ratio of 0.55 (0.29 to 1.03). In this group, patients had 80% *P. aeruginosa* infection, and BMI was <19 in less than 60%. Nearly 80% had use of nebulized antibiotics, more than 50% use of DNase, and 60% had diabetes.

Dr. Osman observed that the use of recombinant DNase was significantly associated with a reduced risk of death (hazard ratio: 0.64, 95% CI: 0.41 to 0.99). DNase is an enzyme that breaks down the DNA that accumulates from decaying white blood cells in the mucus of patients with CF, reducing mucus stickiness and allowing better airway clearance.

Conversely, a significantly increased risk of death as associated with a BMI <19 (hazard ratio: 2.19; 95% CI: 1.35 to 3.53) and long-term home oxygen therapy (hazard ratio: 1.90; 95% CI: 1.15 to 3.94).

"The investigation showed improved survival associated with DNase and improved nutrition. The use of FEV_1 <30% predicted, as the most important factor for the timing of lung transplantation, is outdated. Other factors should be considered in referring patients for transplants, " he concluded.

back to top

SODIUM CHANNEL INVESTIGATIONS

Symposium 24: Enhancing *CFTR* functions- What's In The Pipeline

Blocking sodium channels. Marcus Mall, MD. Talk from the 35th European Cystic Fibrosis Congress; June 6-9, 2012; Dublin, Ireland

The imbalance of sodium absorption and chloride secretion is critical in the pathogenesis of CF lung disease, leading to airway surface fluid depletion, mucus plugging and the subsequent inflammation and infection characteristic of CF lung disease. In the *Enhancing CFTR Functions-What's In The Pipeline* symposium, Marcus Mall, MD of the Division of Pediatric Pulmonology, Translational Lung Research Center, University of Heidelberg in Germany, described on-going research.

"The low volume hypothesis suggests that dehydration of the airway surface liquid (ASL) in the lung is caused by an imbalance of both chloride and sodium ions. This imbalance leads to mucostasis in the airway lumen and provides an environment for bacterial colonization that allows chronic infections. The low volume hypothesis was validated in a mouse model, which showed increased sodium transport in the airways of mice with CF-like disease, which is very similar to what we see in children in early CF lung disease," he explained.

Based on this principle, a promising new class of potent human epithelial sodium channel (ENaC) blockers, which includes P643, is currently undergoing active research. These compounds are structurally distinct from amiloride, a potassium-sparing diuretic that blocks ENaC but did not show long term effectiveness in CF ENaC-Tg mice trials. Amiloride caused a mucolytic effect in the proximal and distal airways in neonatal ENaC-Tg mice, and an anti-inflammatory effect (reduced neutrophilia and interleukin 8), but without any effect on mucus obstruction and inflammation in adult ENaC-Tg mice.

By contrast, investigations using novel ENaC blockers revealed robust therapeutic effect, including reducing mucus obstruction and inflammatory cell reduction, in adult ENaC-Tg mice. P643 inhibited ENaC with IC_{50} of 30nM in human bronchial epithelial cells *in vitro,* as well as *in vivo* using a guinea pig model. In a sheep model, it also accelerated mucociliary clearance. P643 is about 50x more potent and more readily absorbed than amiloride; the effects translate into keeping fluid longer in the lumen of the airways, Dr. Mall said.

Similar effects in the active regulation if ENaC can be attained through manipulation of serine proteases and anti-proteases, he continued. "Normally, anti-proteases are diluted by high volume conditions, allowing membrane-bound proteases to activate the sodium channel and absorb the excess volume. Under low-volume conditions, however, the anti-proteases become concentrated and inhibit protease activity. This aggravates airway surface dehydration in CF airways."

Furthermore, chronic neutrophil inflammation increases the activity of neutrophil elastase, which further activates ENaC, thereby aggravating ENaC-medicated ASL depletion. This suggests that inhibitors, especially low molecular weight inhibitors of both channel activating protease and neutrophil elastase, may be viable approaches to hydrating the airways in patients with CF.

The channel activating protease (CAP) inhibitor camostat has been shown to inhibit ENaC function in airway epithelia, both *in vitro* and *in vivo* using a sheep model. CAP was also shown to enhance prolonged accelerated mucociliary clearance, in a dose dependent fashion, according to the early results using this approach.

"In addition to CAP inhibitors, there are also several small-molecule neutrophil inhibitors currently in development. These protease inhibitors may actually emerge as an alternative to ENaC blockers in the near future", Dr Mall said.

Dr. Peter Mogayzel and Dr. Marcus Mall, Division of the Pediatric Pulmonology, Translational Lung Research Center, at the University of Heidelberg in Heidelberg, Germany, discuss *Blocking Sodium Channels.*

back to top

MEASURING NEONATE LUNG INVOLVEMENT

Workshop 7: Lung Clearance Index in Real Life

WS7.5: Lung Function and Structure in CF Infants Diagnosed through Newborn Screening (NBS). L Thin, MD. Abstract from the 35 th European Cystic Fibrosis Congress; June 6-9, 2012; Dublin, Ireland.

Due to increasing concern that spirometry and chest radiography are inadequate to detect abnormalities at the mild/moderate stages of cystic fibrosis, the lung clearance index (LCI) has risen in relevance as a sensitive predictor of lung function abnormalities.

As described by Lena Thia, MD of University College and Institute of Child Health, London, UK, in an observational cohort study conducted in association with the London Cystic Fibrosis Collaboration, UK investigators observed raised LCI in 16% of newborns using the multiple breath washouts technique (MBW). In addition, lung abnormalities, including gas trapping and parenchymal changes, were seen in roughly 40% of these newborns using high-resolution computer tomography (HRCT).

The study tested 60 infants who were diagnosed with CF by newborn screening (NBS), at a mean age at diagnosis of 4 weeks. Ninety percent were either homozygous or heterozygous for the F508del mutation, and 92% were pancreatic insufficient.

The study newborns underwent pulmonary function testing using plethysmography, raised volume rapid thoracoabdominal compression, and MBW at 1 year of age. The lung function tests were followed (within 2 weeks) by volumetric inspiratory (PIP=25cm H20) and expiratory (PEEP=0) HRCT scans of the chest, under general anaesthesia. CT scans were anonymized and scored using Brody-II CT scoring. Normal Children (n=35), recruited as controls, were matched for background characteristics and did not undergo CT scans.

Sixteen percent of infants with CF had elevated LCI, 15% had elevated plethysmographic lung volume, and 17% showed diminished forced expiratory volume or flow. While the abnormalities detected were low-grade, 42% of infants with CF had at least one lung function abnormality 55% (33/60) had completely normal lung function.

The mean difference between newborns with CF and healthy controls in LCI was 0.9 ($p<0.001$); in functional residual capacity (FRC pleth) z-score 0.9 ($p<0.001$); in FRC 0.8 ($p<0.001$); and in FEV 0.5 z-score -0.5 ($p<0.05$).

HRCT of the chest is increasingly used as a sensitive measure of early lung disease in children with CF, and investigators have found a correlation between Brody-II CT scores and PFT and LCI (with the greatest correlation seen in LCI), the investigators found no significant correlation between HRCT and lung function tests in patients in early adults in previous investigations.

The CT scans in the infants studied revealed: 5% mucus plugging, 5% wall thickening, 8% bronchial dilation, 25% gas trapping (however only 2% had significant involvement), 40% parenchymal changes, and 55% normal scans.

Dr. Thia reported weak correlations between gas-trapping scores and LCI and FRC z-scores, and no correlation between any other CT subscore and lung function. The gas-trapping sub-score revealed a significant but weak correlation with LCI (Spearman correlation, R-0.3)

"In trying to relate structure and function, the results have been somewhat disappointing", Dr. Thia observed. "The majority of our infants with CF still have what we would consider normal lung function, with z-scores at the upper limit of normal."

Recent evidence indicates the appearance of abnormalities like trapped gas, bronchiectasis and parenchymal changes as early as three months in the lungs of newborns diagnosed with CF. A correlation between these lung abnormalities and LCI would aid physicians in detecting early disease in infants in CF.

"We hope to come up with a better way to quantify these abnormalities in this group of infants, whereby one would expect mild changes only. Although CT has proven to be a sensitive measure in older children and adults, its usefulness in infants requires further validation. Our longitudinal cohort study is in progress," Dr. Thia concluded.

back to top

IVACAFTOR

Workshop 14: Early Stage Therapies

Kick-Starting the Stop-Mutations; Michael Wilschanski MD. Talk from the 35 th ECFS; June 6-9, 2012; Dublin, Ireland.

In the *Early Stage Therapies* workshop, Fredrick Van Goor, PhD, Head of Biology, CF Research Program at Vertex Pharmaceuticals described as *in vitro* study using ivacaftor on *CFTR* mutations other than the Class III G551D mutation.

"Ivacaftor is a broad acting *CFTR* potentiator *in vitro.* It shows promise as a CFTR potentiating agent for multiple mutant CFTR forms with residual CFTR function beyond G551D. These data suggest we may be able to define a class of patients, based on the molecular and functional phenotype, for clinical study," he explained.

His investigation normalized mutant CFTR syntheses by using host Fisher rat thyroid (FRT) cell lines with a single integration site, resulting in cells with very similar levels of mutation expression. In these cell lines, he found a wide range of baseline chloride transport in the absence of ivacaftor.

Using the CFTR2 database, Dr. Van Goor plotted the sweat chloride levels associated with the individual mutations against those from the *in vitro* system and saw a good qualitative relationship between *in vivo* measures of CFTR function (sweat chloride) and the baseline chloride transport, suggesting it was a reasonable system to evaluate baseline chloride transport in responses to CFTR modulators.

After acute addition of ivacaftor, the great majority of the mutant CFTR forms tested responded from baseline by at least 10%, a potentially therapeutic level of change in chloride transport that has been associated with milder disease forms. While some mutant CFTR forms had little or no response to ivacaftor, those that exhibited a good response had either a processing defect or normal amounts of CFTR at the cell surface.

Dr. Van Goor synthesized P67L (class IV conductance mutation) and A455E (Class V reduced CFTR synthesis mutation) cell lines, observing an overall 6-10% of residual baseline chloride transport. These mutant forms responded to ivacaftor by at least 10% from baseline.

Cells with Class IV mutations have CFTR protein at the cell surface but a decreased (in the 30-70% range) level of channel conductance, with sweat chloride levels consistent with residual CFTR function and a lower PI rate. The R347A mutation showed, in spite of a low chloride transport of 5% at baseline, a 10% response to ivacaftor. Other Class IV mutation cell lines, such as R334W, had higher sweat chloride levels consistent with minimal CFTR

function, higher rates of PI, a lower level of baseline chloride transport *in vitro*, and a smaller increase in response to ivacaftor.

In Class II mutations (i.e. F508del) very little or no mature CFTR reaches the cell surface, resulting in higher level of sweat chloride values, a higher incidence of PI and no or minimal measurable chloride transport. The effect of ivacaftor on chloride transport on Class II *CFTR* cell line mutations was low.

Mutant CFTR forms are a heterogeneous group associated with multiple different molecular defects and a range in the disease phenotype, according to Dr. Van Goor, who continued by explaining, "This is different from the very homogeneous mutant group associated with Class III mutations, in which all of the defects are related to channel gating. The mutant CFTR forms all had minimum chloride transport in the absence of ivacaftor and all had a significant response on a similar level to ivacaftor, as G551D did."

back to top

ATALUREN

Workshop 22: Late Breaking Science
Results of the Phase 3 Study of Ataluren in Non-sense Mutation Cystic Fibrosis (nmCF); Michael Konstan MD.
Workshop 6.1: Efficacy of hypertonic saline in infants and young children: the ISIS study
Inhaled Hypertonic Saline in Infants and Children Younger Than 6 Years With Cystic Fibrosis: the ISIS Randomized Controlled Trial; Margaret Rosenfeld, MD, MPH; Felix Ratjen, MD, PhD; Lyndia Brumback, PhD; Stephen Daniel, PhD, et al; for the ISIS Study Group JAMA. 2012; 307(21):2269-2277
Symposium 24: Enhancing *CFTR* Functions - What's in the Pipeline?
Kick-Starting the Stop-Mutations; Michael Wilschanski MD.
Talk from the 35 th ECFS; June 6-9, 2012; Dublin, Ireland.

Presentations in two separate sessions-- the *Late Breaking Science* workshop and the *Enhancing CFTR Function - What's in the Pipeline* symposium--discussed the use of ataluren in patients with Class I, nonsense *CFTR* mutations (nmCF). The nmCF mutation is characterized by a pre-mature stop codon insertion with mRNA, which stops ribosomes from translating the mRNA responsible for full-length protein production, resulting in truncated proteins.

Michael Konstan, MD of University Hospital's Rainbow Babies and Children's Hospital in Cleveland, Ohio, USA reported on a 48-week, double blind, randomized, placebo controlled trial conducted at 36 sites in 11 countries. Of the 238 patients, 116 were heterozygous/homozygous for nmCF, and were at least 6 years old with an FEV_1 of 40-90% predicted. The patients were randomized to ataluren 3x/day (10 mg/kg morning, 10 mg/kg midday, 20 mg/kg evening).

At Week 48, the treatment difference in FEV_1 (primary endpoint) between the ataluren and placebo groups was 3% (p=0.124), in favor of ataluren, but was not considered statistically significant. However, FEV_1 averaged over all post-baseline visits revealed a difference of 2.5% (p=0.0478), which did show statistical significance.

Further, a statistically significant treatment difference of 6.7% (p=0.013) was noted in FEV_1 between patients who did not receive inhaled chronic antibiotics at the trial. Patients who used inhaled antibiotics hardly experienced any treatment effect with ataluren. Further exploration of this subgroup showed that (a) the most frequent antibiotics used were aminoglycosides (tobramycin), colistin, and aztreonam, and that (b) a statistically significant treatment difference of 5.7% was observed between patients who specifically received aminoglycosides and those who did not.

Dr. Konstan reported a large reduction in the exacerbation rate (secondary endpoint) of 23% (p=0.0992). Interestingly, when calculated without patients on chronic inhaled antibiotics, the decrease was 43% (p=0.014).

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"Larger differences in primary and secondary endpoints were seen among patients who were not using inhaled antibiotics. Much of this specifically related to the use of inhaled aminoglycosides. Tobramycin is known to bind to the ribosome and interfere with the effect of ataluren," Dr. Konstan explained.

In his *Kick-Starting the Stop-Mutations* presentation, Michael Wilschanski, MD, Director of the Pediatric Gastroenterology Unit, Hadassah University Hospitals, Jerusalem, Israel, noted that: "10% of people with cystic fibrosis have Class I mutations. Ataluren promotes ribosomal read-through of all 3 types of premature nonsense codons: UGA, UAG, and UAA. Ataluren, which was designed to overcome nonsense mutations, is bioavailable and not related to aminoglycoside compounds."

Dr. Wilschanski reported that the outcomes of this current study mirrored those shown in previous ataluren studies, which found a dose-dependent ribosomal read-through of premature stop codons, although not of normal stop codons. He also noted ataluren-related changes in mean nasal trans-epithelial chloride secretion, with improved chloride transport of about 2.5mvolt/cycle (2 week cycles ataluren/washout). Furthermore, immunostaining provided evidence of ataluren-mediated increases in epithelial cell-surface CFTR.

"Patients with nonsense mutations CF tend to have a severe disease phenotype, despite use of available therapy. This phase 3 study provides long term natural history of data of nonsense mutations. Patients who completed this trial were able to continue on open label ataluren for another year, which is ongoing," said Dr. Wilschanki.

Dr. Peter Mogayzel and Dr. Michael Konstan of University Hospital's Rainbow Babies and Children's Hospital in Cleveland, Ohio, USA discuss *Results of the Phase 3 Study of Ataluren in Non-sense Mutation Cystic Fibrosis (nmCF).*

Dr. Peter Mogayzel and Dr. Felix Ratjen, Professor of Peadiatrics, Senior Scientist in Physiology & Experimental Medicine at the Research Institute, the H.E Seller's Chair in Cystic Fibrosis and Division Chief, Respiratory Medicine at the Hospital for Sick Children at the University of Toronto, Canada, discuss *Efficacy of hypertonic saline in infants and young children: the ISIS study.*

back to top

Presented by JHUSOM and IJHN in collaboration with DKBmed.

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