Cystic Fibrosis 2015: Improving Survival Through Optimization of Care and Innovative Therapeutics

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Disclosure

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- Cystic Fibrosis Therapeutics
- The Cystic Fibrosis Foundation
- Children with Special Health Care Needs

Learning Objectives

At the end of this presentation the participant will be able to discuss the impact of
1. Newborn screening
2. Quality Improvement
3. New therapeutic technologies
on the survival of patients with cystic fibrosis

Some CF Basics

- Autosomal recessive disease-Chromosome 7
- Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)
  - Membrane spanning channel
  - Facilitates movement of Cl⁻ and HCO₃⁻ across the cell membrane
  - Ears, sinuses, respiratory tract, pancreas, intestines, liver, kidneys, reproductive tract, sweat glands
- Diagnosis based on sweat testing, nasal potential difference measurement, genetic testing, clinical stigmata

CF in the Gut: Clinical Manifestations

- Poorly hydrated secretions in the pancreas
- Obstruction of pancreatic ducts-impaired secretion of pancreatic enzymes
  - Malabsorption of fats, proteins, vitamins A,D,E, K
- Autodigestion of the pancreas
  - Impaired islet cell function-impaired insulin secretion
- Poorly hydrated intestinal secretions
  - Meconium ileus
  - Constipation
  - Distal Intestinal obstruction syndrome (DIOS)

The Pulmonary Manifestations of CF

- Inflammation
- Obstruction
- Progressive Bronchiectasis/Fibrosis
- Infection
  - MSSA, MRSA
  - Pseudomonas
  - Fungi
  - Viruses

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The median predicted age of survival has increased from 33.4 years in 2003 to 40.7 years in 2013.

62% of new CF diagnoses in 2013 resulted from newborn screening

History of Newborn Screening for CF

- 1985-1994 Wisconsin Randomized clinical trial of NBS
- Screening based on trypsinogen levels (IRT) and F508
- Results for “controls” blinded until 4 years of age
- Significantly earlier diagnosis (12 vs 72 weeks)
- Improved height, weight, FOC %ile at time of dx
- Better cognitive testing scores? Vitamin E supplementation
- 2004 CDC recommends CF NBS
- December 2009-Texas begins NBS

Texas IRT/IRT/ DNA NBS Algorithm

1st NB screen

Normal IRT

Elevated IRT

2nd NB Screen

Normal IRT

Elevated IRT

CFTR mutation analysis

2 mutations

1 mutation

0 mutations

Sweat Test

Improved Nutritional Outcomes

NEJM 1997; 337: 963-8

2013 North American Cystic Fibrosis Patient Registry
Impact on Infection

Benefits Extend Into Adulthood

Opportunities to Better Understand Disease Progression/Development

Opportunities for Better Survival

CF Quality Improvement History

The Dartmouth Microsystem Improvement Ramp
**CFF Initiatives**
- Learning and Leadership Collaboratives
- Nutrition
- Pulmonary Function
- Adherence to national guidelines
- Clinic encounters
- Screening for diabetes
- Implementation of infection control guidelines

**The impact of re-education of airway clearance techniques (REACT) on adherence and pulmonary function in patients with cystic fibrosis**
- QI team of providers and patient families
- Adherence survey
- Visualization of administration of therapies
- Re-education on techniques
- Monitor outcomes

**QI at UTHSCSA CF Center**
- 2003 NICHQ
  - Series of face to face meetings to teach the basics of PDSA cycles and QI
  - What did we do?
    - Nutritional status classified on every visit
    - Nutrition expectations clearly delineated to patients
    - Patients aggressively followed
    - Culture of good nutrition
    - Web based data entry system to track outcomes/run charts
    - Outcomes tracked annually through CF Registry data

**Here’s where we are now!**

**Current QI Collaboratives**
- OneCF (I and II)
- Concept of pediatric and adult programs as one CF Center
- Focus on transition
- FunLLC

**The FUN LLC**
*Theme: Understanding and improving the care and management of the pulmonary manifestations of cystic fibrosis.*
*Global Aim Statement: We aim to improve the treatment of Pseudomonas aeruginosa infections in the UTHSCSA CF Center.*
**New Therapies**

Up until 2012, all of the therapies we had fought the symptoms of the disease, but not the cause of the disease.

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**High Throughput Screening**

Screening for pharmacologic agents that

- Increase protein kinase A regulated chloride channel gating of CFTR
  - **Potentiators**: Increase the flow of chloride and bicarbonate through the activated CFTR (Kalydeco)
  - **Small molecules that “chaperone”/“rescue” misfolded CFTR**
  - **Correctors**: Improve the processing of CFTR and delivery of CFTR to the cell surface (lumacaftor)

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**Potentiators: Kalydeco (Ivacaftor/VX770)**

161 patients ≥12 years VX770 150 mg twice a day or placebo for 48 weeks in pts with G551D

- 55% less likely to have pulmonary exacerbation
- NEJM 2011; 365:1663-72

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**VX770 in 6-11 year olds**

52 patients 6-11 years old with G551D

- FEV1 40-105%
- Body weight > 15 kg
- 150 mg VX770 twice a day vs placebo for 48 weeks

- 12%
- 2.8kg

AMJRCM 2013;187:1219-1225
Further evidence of beneficial effects

- GOAL Study (153 pts, ≥6yrs, 6 months of use)
  - Sustained ↑FEV1*
  - ↑Weight and BMI
  - ↓Sweat Chloride
  - ↓Rate of Hospitalization,
  - ↓Rate of Pseudomonas + culture
  - ↑Prevotella + cultures
  - ↑intestinal pH
- European CF Conference 6/11-6/14/14
  - In patients > 6 years, ↓decreased rate of lung decline by 50% over 3 years (0.81%/year vs 1.73%)

Kalydeco for other mutations

- Approved for several other gating mutations
  - G551D, G551S
- Class IV mutation: R117H
  - 150 mg tablets BID (> 6 years of age)
  - 50 mg and 75 mg granules BID(2-6 years of age)
  - Examination for cataracts and monitoring liver function recommended

Class 2 Mutations-ΔF508

- 48% patients in US ΔF508 x2, 40% with ΔF508x1
- NBD 1 misfolding=degradation in ER
- NBD1-MSD2 binding facilitated by F508=key to opening anion channel
- Little protein reaches the cell membrane and even less of it works!

Attempts to Correct F508

Potentiators: Kalydeco alone
Correctors: Lumacaftor -Stabilization of NBD-MSD assembly

VX770 (Ivacaftor) + VX809 (Lumacaftor)

CFTR folding-TRAFFIC and TRANSPORT
Phase 3 studies
  - 1108 pts, ≥12 years, ΔF508 x2
  - 600mg once a day or 400 mg twice a day VX809+ 250 mg VX770 vs placebo
  - 24 weeks with 96 week extension
  - Mean baseline FEV1 81%

<table>
<thead>
<tr>
<th>ΔFEV1</th>
<th>&gt;5%</th>
<th>&gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumacaftor/Ivacaftor</td>
<td>36-48%</td>
<td>24-27%</td>
</tr>
<tr>
<td>Placebo</td>
<td>22%</td>
<td>13%</td>
</tr>
</tbody>
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NEJM 2015; 373(33) 220-31
Lumacaftor + Ivacaftor = ORKAMBI™

- Approved by FDA 7/3/15
- Dosing: Lumacaftor 400 mg/Ivacaftor 250 mg twice a day
- Pts >12 years of age with F508x2
- Most common side effects
  - Chest tightness, respiratory dyscomfort
  - Elevated liver function
  - GI disturbances

VX661 + VX770 - The Next Generation

- March 2015: 12 week Phase 2 study 39 people >18 years, ΔF508 x2
  - VX661 (various doses) + VX770 or placebo x28 days
  - VX661 (100 mg) + VX770 (150 mg) BID
  - 4.4% and 3% ↑ FEV1
  - 38% with pulmonary exacerbation vs 44% placebo
  - 33% with cough vs 39% placebo
- 4 Phase 3 studies: VX-661 + VX770:
  - ΔF508 x2 (550 pts)
  - ΔF508 + gating (200 pts) (4/15)
  - ΔF508 + residual function (300 pts) (5/15)
  - ΔF508 + minimal function mutation (120 pts) (Mid 2015)

Class 1 Mutations

- Need correctors that help to read through the stop codon to allow for full gene synthesis
- PTC 124 (Ataluren)
  - Promotes ribosomal read-through of premature stop codons/production of full length CFTR
  - Early studies showed improvement in nasal potential difference

PTC 124 - Ataluren

- Phase 3 study:
  - 238 patients ≥6 years with nonsense mutation
  - Ataluren TID (10 mg/kg, 10 mg/kg, 20 mg/kg) x 48 weeks
  - No change in BMI, sweat chloride, or reduction in pulmonary exacerbations
  - AE: Elevated creatinine

The Issue of Drug Interactions

- Readthrough activity of ataluren decreased with co-exposure to aminoglycosides
- Ataluren has no effect on antibacterial activity of tobramycin
- Study patients not on inhaled tobramycin
  - 5.7% increase in lung function
  - 40% decrease in exacerbations

A look towards the future.....