Advances in the Management of Cystic Fibrosis: A Closer Look at the Roles of CFTR Modulation Therapy

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Objectives

• Assess newly approved and emerging CFTR-targeted treatment strategies according to their mechanism of action, efficacy, and safety
• Examine the role of CFTR modulation therapy in the treatment and management of cystic fibrosis
• Discuss the importance of genetic testing in suspected adult-onset CF
• Analyze optimal strategies to manage and monitor CFTR modulator-related adverse events in cystic fibrosis patients
• Explore strategies to employ a multidisciplinary approach to management of the CF patient, and communicate effectively with patients and their families about the role of genetic analysis

CF and CFTR

• Autosomal recessive disorder
  – ~1:4400 births
• >2000 sequence variants; disease liability of most is unclear
  – 70% of patients worldwide have at least one copy of F508del
  – Other pathogenic mutations: 5% or fewer
  – Updated diagnostic consensus in press
• Multi-organ expression and manifestations
  – Lungs, pancreas, liver, sweat gland, GI tract, vas deferens, others
• Median survival ~40 yrs in US
• Median age of death mid-20s
Pathogenic mechanisms of CF lung disease

Defective CF Gene Product
- Defective Ion Transport
- Airway Surface Liquid Depletion
- Defective Mucociliary Clearance

Obstruction → Inflammation → Infection

Molecular mechanisms of CFTR dysfunction

Most CF patients diagnosed during adulthood have mild CF mutations associated with pancreatic sufficiency.
Between the gene defect and end stage lung disease: “severe” phenotype

• Most infants with CF are healthy at birth
  - 15-20% rate of meconium ileus
• Malnutrition and pulmonary inflammation occur in the first weeks to months after birth

“Cystic fibrosis is not a disease. It is an inherited predisposition that becomes a disease if it is not treated properly.”

Warren Warwick, MD, around 1990
Without pancreatic enzyme replacement therapy, CF is fatal early in life

- Malnutrition/ vitamin deficiency related direct mortality
- “the nutritional state deteriorates with advance of the infection”

Early growth predicts childhood survival

Yen, Quinton and Borowitz
*J Pediatrics 2012*
The CF lung is nearly normal at birth

Early pulmonary inflammation in CF

- 16 CF infants (mean age 6 months) diagnosed by NB5 in Colorado; 11 disease controls (mean age 12 months)
- CF infants with increased markers of inflammation even when cultures negative

Small airways disease is present during the first months of life in CF infants diagnosed by NBS


Structural Airway Abnormalities in Cystic Fibrosis

Early pathophysiology of CF: summary and opportunity

- Infants with CF are healthy but have severe physiologic abnormalities that must be treated early to avoid a progressive decline in health
- The earliest possible diagnosis followed by disease modifying therapy is essential to prevent CF lung disease
- CFTR modulator therapies may be disease modifying, when given early in life, but clinical trials are just beginning:
Between the CFTR gene mutation and lung disease: “mild” phenotype

• CF may present in the second, third, fourth or later decade of life with sinopulmonary disease

• Illustrative case: “Ellen”
  - Became ill with dyspnea and cough at age 28 during her second pregnancy
  - Continued to have cough and sputum production after giving birth
  - Denied significant respiratory symptoms as a child
  - Spirometry with obstructive defect, FEV1 ~50% predicted
  - CT scan with bronchiectasis
  - Sweat chloride values 40 mEq/L
  - CFTR gene mutation panel: F508del, R117H/7T
  - In spite of having all recommended pulmonary treatments, FEV1 ~ 40% predicted at age 40

Importance of CFTR mutation testing

• Aids in diagnosis
  - Important for therapy and for monitoring of potential complications
  - Adults with CF at risk of
    • Infertility (men)
    • Reduced fertility (women)
    • Recurrent acute pancreatitis
    • CF related diabetes
    • Pulmonary complications prevalent in CF (ABPA, mycobacterial infections)
  - Increasingly, aids in therapy
Gene mutation testing in CF

- CFTR mutation panels
  - May test from 23 (ACOG panel) to 100s of mutations
  - Will miss rare mutations, deletions/ duplications
  - Currently less costly than sequencing

- CFTR gene sequencing
  - Finds any sequence variant in the CFTR gene
  - Still misses deletions/ duplications: need to order separately
  - Will find disease causing mutations, but also mutations of variable or unknown disease liability
  - Disease liability of rare mutations is being analyzed in CFTR2: [www.cftr2.org](http://www.cftr2.org)

- Essential to have appropriate genetic counseling when testing is performed for any genetic testing
  - Discuss false negative, identification of mutations of unknown significance
  - Discuss consequences on family members, notification of possible carrier status
  - Best done by a certified genetic counselor

CF care is multidisciplinary
A nutrient dense, liberal fat diet is associated with increased survival

- Survival compared between large CF Centers in Boston and Toronto (1972-1981)
- 10-20 year old patients in Boston were shorter than patients in Toronto. Toronto males weighed more than Boston males.
- Mean forced expiratory volume in one second (FEV₁) was not different
- Median age of survival: Boston 21 years, Toronto 30 years
  - the two curves showed a marked separation from age 10
- The only difference in care was diet: fat restriction in Boston, liberal fat in Toronto
- “The differences in growth and survival in these two patient groups, with similar age-specific pulmonary function, suggest further examination of nutritional guidance and intervention in CF, especially regarding the traditional restriction of dietary fat.”


Nutrition and pulmonary outcomes are correlated

“the nutritional state deteriorates with advance of the infection”
US children with CF have a normal BMI

![Graph showing BMI percentile]

Consistent practice improves BMI in CF children

- Multidisciplinary care teams support good nutrition in children and adults with CF
  - RD: dietary assessment and counseling, recommendations for supplemental tube feeding
  - Nurse: family counseling and support
  - Social worker: family counseling and support; referral to resources for food insecure families
  - Physician: support of diet, prescription of adequate pancreatic enzymes, diagnosis of comorbidities attributing to poor nutrition

Population FEV1 is improving

...but FEV1 is insensitive to early structural lung disease

Lung Clearance Index

- Multi-breath washout technique assesses:
  - Gas mixing
  - Airway patency/obstruction
- Tidal breathing; no effort
- Inert tracer gas:
  - $\text{SF}_6$: wash in and out
  - $\text{N}_2$: wash out with 100% $\text{O}_2$
- More diseased airways take longer to wash out
Lung Clearance Index


Targeting of Interventions

Multidisciplinary care for good pulmonary outcomes

- Respiratory and physical therapists
  - evaluate posture, teach airway clearance techniques and use of inhalational medications
  - collaborate with patients and physicians in making treatment decisions on maintenance therapies
- Social workers and psychologists
  - Screen for depression and anxiety and offer referrals, in accordance with recent practice guidelines
  - Refer to programs to offset high medication co-pays
- Nurses
  - Spend about half their time getting prior authorization for specialty medications!

Molecular mechanisms of CFTR dysfunction

- G551D and others
- F508del
- R117H
- ‘Severe’
- ‘Mild’
- NMD
- F508del
- CFTR gene
- CFTR transcript
- ribosome + polypeptide chain
- mature CFTR
- immature CFTR
- plasma membrane
- endosomal compartment
- TGN
- proteosome
- NMD
CFTR Mutations Reduce the Amount or Function of CFTR at the Cell Surface

**CFTR Mutations**

- Defect in CFTR Protein
- Reduced Quantity of CFTR at Cell Surface
- Reduced Function of CFTR at Cell Surface

**Normal**

Class I/II

Class III/IV/V

Courtesy of Vertex Pharmaceuticals

Approach to Identify and Improve CFTR Potentiators and Correctors

**Potentiator HTS**

Screened >300,000 Compounds

Synthesized >5,000 Compounds

Optimized Potency and Efficacy

VX-770

**Corrector HTS**

Synthesized >5,000 Compounds

Optimized Potency and Efficacy

VX-809

cells expressing F508del-CFTR

Cultured human airway epithelia isolated from CF patients

Courtesy of Vertex Pharmaceuticals
VX-770 effects in human bronchial epithelial cells

Ivacaftor phase 3 clinical trial (> 12 years)

- FDA approved for G551D mediated CF in 2012
- Similar trial results seen in subjects with 8 “non-G551D gating mutations”; FDA approval for expanded use in 2014
- Approved for R117H mediated CF with lung disease in 2015
- Label extended to 2-5 year olds
- 0-24 month study in progress

Sawicki GS et al. Sustained benefit from ivacaftor demonstrated by combining clinical trial and CF patient registry data. AJRCCM 2015; 192:938-42.
Ellen

- Participated in the extension and open label follow-on trials of ivacaftor in CF patients with the R117H mutation
- Improvement in FEV1 and exercise tolerance
- Reduced exacerbations
- Example of severe “mild” disease and positive effect of a modulator effective for her specific gene mutation

Ivacaftor therapy in CF

- Marked efficacy
- Well tolerated
- Expensive
- Indicated for ~6% of the population with CF
Nearly half of US CF patients are homozygous for the F508del mutation.

Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR


Functional Additivity of VX-809 and VX-770 in Human Airway Cultures Isolated from F508del CF Patients

Using chamber studies of cAMP-stimulated Cl- flux in F508del-HBE (normalized to non-CF HBE)
Combined therapy results age 12+

Exacerbation reduction is not predicted by FEV1 improvement

McColley SA et al, North American Cystic Fibrosis Conference 2015
Lumacaftor-ivacaftor combination therapy has a disease modifying effect

- Similar to ivacaftor, ongoing treatment with lumacaftor-ivacaftor reduces the rate of lung function decline in F508del homozygotes, compared to untreated F508del homozygotes in the Cystic Fibrosis Foundation patient registry
- These data are being presented at the North American Cystic Fibrosis Conference 10/27/16-10/29/16
- A graph of these data will be displayed at the time of this presentation

Lumacaftor-ivacaftor approved for 6-11 year olds

- Lumacaftor-ivacaftor recently approved for 6-11 year olds
  - Based on open label safety study
  - Open label study results being presented at the North American CF Conference 10/27-10/29/16
  - Placebo-controlled study with efficacy measures underway
  - Additional slides will be displayed at the time of this presentation
Monitoring for toxicities and assessing efficacy in individual patients

- All patients taking ivacaftor or lumacaftor-ivacaftor should have transaminases monitored every 3 months for 12 months after initiating therapy
- Dose reductions recommended for moderate to severe liver disease (Child-Pugh Classification)
- Children < 12 years old should have an eye exam prior to starting therapy due to the occurrence of cataracts in exposed rat pups
  - Ocular safety study has been recently completed, not yet reported
- Chest tightness (“respiration abnormal”) occurs in some patients when initially starting lumacaftor-ivacaftor therapy
  - Mechanism unknown
  - Rarely leads to discontinuation of drug
- Monitoring efficacy can be difficult in patients with milder disease
  - Disease modification and exacerbation reduction benefit
Summary

• Onset of CF lung disease is a post-natal event
• Nutritional and pulmonary abnormalities occur very early in life
• Lung disease is present even when FEV1 is normal
• Genetic testing is important in diagnosis and, increasingly, for therapeutic considerations
• Analyze optimal strategies to manage and monitor CFTR modulator-related adverse events in cystic fibrosis patients
• Multidisciplinary care is essential
• CFTR modulation therapy has an increasing role treatment and management of cystic fibrosis
• Modulator therapy may reduce morbidity/ mortality over time