Pharmacological Management of Cystic Fibrosis - Exploring the Therapeutic Advancements in Cystic Fibrosis

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Pharmacological Management of Cystic Fibrosis: Exploring the Therapeutic Advancements in Cystic Fibrosis

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Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation.
Objectives

- Describe the pathophysiology of cystic fibrosis (CF)
- Discuss updates in therapeutic management for patients with acute and chronic CF
- Formulate appropriate counseling points for a CF patient
What is Cystic Fibrosis?

- Progressive, genetic disease that causes persistent lung infections & limits the ability to breathe over time
- Characterized by early colonization & infection of the airways
- Produces buildup of mucus in the lungs, pancreas & other organs
Epidemiology

- More than 30,000 people in the United States living with CF
- ~1,000 new cases are diagnosed each year
- More than half the population is over the age of 18
- Frequently occurs in those of northern European ancestry
- Lung disease is the major cause of morbidity and mortality in patients with CF
Pathophysiology

- Autosomal recessive genetic disorder
- Caused by mutations in the gene encoding for the CFTR protein on chromosome 7
- Absence or dysfunction of the CFTR results in dehydrated, thickened secretions that obstruct epithelium lined ducts resulting in tissue damage
- Affects all exocrine glands

Pathophysiology

Inflammation

Mucus retention

Infection

CFTR Regulator Function

- Largely expressed in the apical membranes of epithelial cells that line the cylindrical structures of tissues that secrete fluids rich in mucus & other proteins
- Belongs to family of transmembrane proteins called adenosine triphosphate (ATP) binding cassette transporters
- 1° role is to transport anions through the apical membrane of epithelial cells creating an osmotic gradient for fluid secretion
- Function is to regulate:
  - Chloride channel in apical membranes
  - Epithelial sodium channels
  - $\text{HCO}_3^-$

CFTR Mutations

- ~2,000 mutations have been identified in the CFTR gene since its discovery in 1989
  - ~242 mutations have been confirmed to cause CF
  - Mutation F508del accounts for 70% of all mutations
    - ~50% of patients worldwide are homozygous & 40% are heterozygous

- Mutations can be broadly classified into 6 categories
### CFTR Mutations

<table>
<thead>
<tr>
<th>Normal</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
<th>V</th>
<th>VI</th>
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<tbody>
<tr>
<td><img src="image1" alt="Diagram" /></td>
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<td><img src="image3" alt="Diagram" /></td>
<td><img src="image4" alt="Diagram" /></td>
<td><img src="image5" alt="Diagram" /></td>
<td><img src="image6" alt="Diagram" /></td>
<td><img src="image7" alt="Diagram" /></td>
</tr>
</tbody>
</table>

- **Normal**
  - Mature functional CFTR
  - Nascent CFTR
  - Endoplasmic reticulum
  - Full-length CFTR RNA
  - CFTR DNA

- **I**
  - Absent functional CFTR
  - Absent nascent CFTR
  - Endoplasmic reticulum
  - Unstable truncated RNA
  - Nucleus

- **II**
  - Absent functional CFTR
  - Endoplasmic reticulum
  - Full-length CFTR RNA
  - CFTR DNA
  - Nucleus

- **III**
  - Defective channel regulation
  - Nascent CFTR
  - Endoplasmic reticulum
  - Full-length CFTR RNA
  - CFTR DNA
  - Nucleus

- **IV**
  - Defective CFTR channel
  - Nascent CFTR
  - Endoplasmic reticulum
  - Full-length CFTR RNA
  - CFTR DNA
  - Nucleus

- **V**
  - Scarce functional CFTR
  - Scarce nascent CFTR
  - Endoplasmic reticulum
  - Correct RNA
  - Incorrect RNA
  - CFTR DNA
  - Nucleus

- **VI**
  - Decreased CFTR membrane stability
  - Nascent CFTR
  - Endoplasmic reticulum
  - Full-length CFTR RNA
  - CFTR DNA
  - Nucleus

- **CFTR defect**
  - No functional CFTR protein

- **Type of mutations**
  - Nonsense; frameshift; canonical splice
  - Missense; aminoacid deletion
  - Missense; aminoacid change
  - Missense; aminoacid change
  - Splicing defect; missense
  - Missense; aminoacid change

- **Specific mutation examples**
  - Gly542X
  - Trp1282X
  - Arg553X
  - 621+1G→T
  - Phe508del
  - Asn1303→ys
  - Ile507del
  - Arg560Thr
  - Gly551Asp
  - Gly178Arg
  - Gly551Ser
  - Ser543Asn
  - Arg112His
  - Arg347Pro
  - Arg117Gys
  - Arg334Trp
  - 3849+10kbc→T
  - 2789+5G→A
  - 3120+1G→A
  - 5T
  - 4326delTC
  - Gln1412X
  - 4279insA

Diagnosis of Cystic Fibrosis

- Prenatal Screening
- Newborn Screening
- Sweat Test
Prenatal/Newborn Screening

- **Prenatal Screening**
  - The American College of Obstetricians and Gynecologists recommends that pregnant women be offered screening for CFTR mutations
  - Prenatal diagnostic tests include chorionic villus sampling & amniocentesis

- **Newborn Screening**
  - Florida Statute 383.14(5)
  - All newborn screening programs rely on elevations of immunoreactive trypsinogen

Sweat Test

“Woe is the child who tastes salty from a kiss on the brow, for he is cursed, and soon must die.”

- **Gold standard**

- Measurement of sweat Cl⁻ by quantitative pilocarpine iontophoresis

- A sweat Cl⁻ concentration ≥ 60 mmol/L indicates a diagnosis of CF

- A concentration of < 30 mmol/L indicates that CF is unlikely


Clinical Presentation

- **Manifestations of Cystic Fibrosis**
  - Gastrointestinal system:
    - Malnutrition
    - Meconium ileus
  - Endocrine system:
    - Cystic fibrosis-related diabetes
  - Reproductive system:
    - Azoospermia in males
    - Reduced fertility in females
  - **Respiratory system**
Respiratory system

- Impaired mucociliary clearance resulting in thick sputum
- Respiratory compromise characterized by copious hyperviscous & adherent pulmonary secretions
- Development of polyps in the sinus cavity
- Chronic infections
- Digital clubbing
Respiratory system

- The dominant pathology in the lung is inflammation generated by failure to clear microorganisms & generation of a toxic pro-inflammatory local microenvironment.

- Airway secretions contain a complex bacterial flora:
  - *Staphylococcus aureus*, *Haemophilus influenzae*, & *Pseudomonas aeruginosa*
Pharmacological Treatment

- **Goals of therapy:**
  - Improve symptoms
  - Minimize loss of lung function
  - Minimize adverse drug reactions due to acute treatment

- Effective airway clearance involves the use of a bronchodilator, a mucolytic medication & chest percussion

- Therapies directed towards the chronic infection in CF should reduce inflammation
PHARMACOTHERAPY: MUCOCILIARY CLEARANCE

Dornase Alfa (Pulmozyme®)
Hypertonic Saline
Dornase Alfa (Pulmozyme®)

- MOA: recombinant human deoxyribonuclease I (rhDNase)
  - Hydrolyzes the DNA in sputum of CF patients & reduces sputum viscoelasticity
- Dose: 2.5 mg single-use ampule inhaled once daily using a jet nebulizer/compressor system
- Ampules should be stored in their protective foil pouch under refrigeration & protected from light
- ADRs: Voice alteration, pharyngitis, rash, laryngitis, chest pain, conjunctivitis, rhinitis, dyspepsia & dyspnea

Hypertonic Saline

- Sterile, preservative-free sodium chloride inhaled solution available in 3.5% & 7% strengths
- Indicated for ≥ 6 years old & those with an FEV$_1$ ≥ 40%
- MOA: Mucolytic agent
  - Restores moisture to pulmonary system
  - ↑ hydration of airway surface liquid via osmotic flow
- Dose: 4 mL/vial via inhalation BID
- ADRs: Increased cough, sore throat & chest tightness
PHARMACOTHERAPY: RESTORATION OF CFTR FUNCTION

Ivacaftor (Kalydeco®)
Lumacaftor + Ivacaftor (Orkambi®)
Tezacaftor + Ivacaftor (Symdeko®)
Ivacaftor (Kalydeco®)

- **MOA:** Potentiator of the CFTR protein
  - Facilitates increased chloride transport

- Baseline & follow-up ophthalmological exams are recommended in pediatrics initiating Ivacaftor

- Assess ALT & AST prior to initiation, every 3 months during the 1st year of treatment & annually thereafter

- ADRs: HA, oropharyngeal pain, URI, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea & dizziness

Headache: HA
Upper Respiratory Infection: URI
Ivacaftor (Kalydeco®)

Available as oral tablets for patients ≥ 6 years old & oral granules for patients 1-5 years of age

Once mixed, oral granules should be consumed within the hour

Should be taken with fat containing foods

Co-administration with:
- Strong CYP3A inducers: not recommended
- Strong CYP3A inhibitors: dose should be reduced to one tablet or one packet of oral granules twice a week

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 6 years</td>
</tr>
<tr>
<td>150 mg tablet PO every 12 hours</td>
</tr>
<tr>
<td>Age 1-5 years and weighing 7 kg to &lt; 14 kg</td>
</tr>
<tr>
<td>One 50 mg packet PO every 12 hours</td>
</tr>
<tr>
<td>Age 1-5 years and weighing ≥ 14 kg</td>
</tr>
<tr>
<td>One 75 mg packet PO every 12 hours</td>
</tr>
</tbody>
</table>

Kalydeco (ivacaftor) [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; August 2018.
<table>
<thead>
<tr>
<th>Gene Mutations</th>
<th>Response to Ivacaftor (Kalydeco®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E56K</td>
<td>G178R</td>
</tr>
<tr>
<td>P67L</td>
<td>E193K</td>
</tr>
<tr>
<td>R74W</td>
<td>L206W</td>
</tr>
<tr>
<td>D110E</td>
<td>R347H</td>
</tr>
<tr>
<td>D110H</td>
<td>R352Q</td>
</tr>
<tr>
<td>R117C</td>
<td>A455E</td>
</tr>
<tr>
<td>R117H</td>
<td>S549N</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>S549R</th>
<th>S977F</th>
<th>F1074L</th>
<th>2789+5G→A</th>
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</thead>
<tbody>
<tr>
<td>G551D</td>
<td>F1052V</td>
<td>D1152H</td>
<td>3272-26A→G</td>
<td></td>
</tr>
<tr>
<td>G551S</td>
<td>K10607</td>
<td>G1244E</td>
<td>3849+10kbC→T</td>
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</tr>
<tr>
<td>D579G</td>
<td>A1067T</td>
<td>S125IN</td>
<td></td>
<td></td>
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<tr>
<td>711+3A→G</td>
<td>G1069R</td>
<td>D1270N</td>
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<tr>
<td>E831X</td>
<td>R1070Q</td>
<td>G1349D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R1070W</td>
<td>S1255P</td>
<td></td>
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</tr>
</tbody>
</table>
Lumacaftor + Ivacaftor (Orkambi®)

- Indicated for pts ≥ 2 years who are homozygous for the F508del mutation in the CFTR gene
- MOA:
  - Lumacaftor improves the conformational stability of F508del-CFTR
  - Ivacaftor is a CFTR potentiator that facilitates increased Cl⁻ transport
**Lumacaftor + Ivacaftor (Orkambi®)**

<table>
<thead>
<tr>
<th>Dosing Regimen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>2-5 years of age and weighing &gt; 14 kg</td>
<td>One lumacaftor 100 mg/ ivacaftor 125 mg packet of granules every 12 hours</td>
</tr>
<tr>
<td>2-5 years of age and weighing ≥ 14 kg</td>
<td>One lumacaftor 150 mg/ ivacaftor 188 mg packet of granules every 12 hours</td>
</tr>
<tr>
<td>6-11 years of age</td>
<td>Two lumacaftor 100 mg/ ivacaftor 125 mg tablets every 12 hours</td>
</tr>
<tr>
<td>12 years and older</td>
<td>Two lumacaftor 200 mg/ ivacaftor 125 mg tablets every 12 hours</td>
</tr>
</tbody>
</table>

- Should be taken with fat containing foods
- ADRs: dyspnea, nasopharyngitis, nausea, diarrhea, URI, fatigue, ↑ blood CPK, rash, flatulence, rhinorrhea & influenza
Tezacaftor + Ivacaftor (Symdeko®)

- Indicated for pts ≥ 12 years of age who are homozygous for the F508del mutation or who have ≥ 1 mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor.

<table>
<thead>
<tr>
<th>Gene mutations responsive to Tezacaftor + Ivacaftor (Symdeko®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F508del</td>
</tr>
<tr>
<td>E56K</td>
</tr>
<tr>
<td>P67L</td>
</tr>
<tr>
<td>R74W</td>
</tr>
<tr>
<td>D110E</td>
</tr>
<tr>
<td>D110H</td>
</tr>
</tbody>
</table>
Tezacaftor + Ivacaftor (Symdeko®)

MOA:
- Tezacaftor: Facilitates cellular processing & trafficking of CFTR to ↑ amount of mature CFTR protein delivered to the cell surface
- Ivacaftor: CFTR potentiator that facilitates increased Cl⁻ transport

Symdeko [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; February 2018
Tezacaftor + Ivacaftor (Symdeko®)

- Packaged as tezacaftor 100 mg/ivacaftor 150 mg fixed dose combination tab & ivacaftor 150 mg tab

- Dose: One tab (tezacaftor 100 mg + ivacaftor 150 mg) in AM and one tab (ivacaftor 150 mg) in PM

- Should be taken with fat containing foods

- Requires dose reduction in pts with hepatic impairment & those taking concomitant CYP inducers or inhibitors

- ADRs: HA, nausea, sinus congestion & dizziness
PHARMACOTHERAPY: ANTI-INFECTIVES

Amikacin Liposome Inhalation Suspension (Arikayce®)
Azithromycin (Zithromax®)
Aztreonam (Cayston®)
Tobramycin (TOBI Podhaler®, Bethkis®)
Gram negative rod widely distributed in nature & commonly present in moist environments

Most frequently encountered lung pathogen in CF

~80% of patients are chronically colonized by *Pseudomonas aeruginosa* by the age of 20

Colonization & infection with *Pseudomonas aeruginosa* remains the most important contributor to CF morbidity & mortality
Amikacin Liposome Inhalation Suspension (Arikayce®)

- Approved in Sep. 2018 under the Accelerated Approval Pathway

- Criteria for indication:
  - Adults with *Mycobacterium avium* complex (MAC)
  - Limited/no alternative treatment options
  - Failed to achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy

- MOA: Disruption & inhibition of protein synthesis in the target bacteria by binding to the 30S ribosomal subunit

Amikacin Liposome Inhalation Suspension (Arikayce®)

- Dose: Once daily oral inhalation of the contents of one 590 mg/8.4 mL Arikayce® vial
  - To be used only with the Lamira™ Nebulizer System

- ADRs: Dysphonia, cough, bronchospasm, hemoptysis, musculoskeletal pain, fatigue/asthenia & exacerbation of underlying pulmonary disease
Azithromycin (Zithromax®)

- **MOA:** Inhibits RNA-dependent protein synthesis at the chain elongation step by binding to the 50S ribosomal subunit
  - Contains anti-inflammatory properties that may benefit CF patients
  - Exact mechanism in CF is still unknown

- **Dose:**
  - < 40 kg: 250 mg three times weekly
  - ≥ 40 kg: 500 mg three times weekly

- **ADRs:** Nausea, diarrhea, & wheezing
Azithromycin (Zithromax®)

- Treatment of pts with CF chronically infected with *P. aeruginosa* with azithromycin led to ↓ morbidity & mortality
  - Pulmonary function & nutritional status improved
  - Pulmonary exacerbation rates decreased

- Emergence of macrolide-resistant nontuberculous mycobacteria is of concern when considering chronic azithromycin therapy
  - MDs considering azithromycin therapy should assess patients with CF for nontuberculous mycobacteria before & every 6 months after initiating azithromycin

Aztreonam (Cayston®)

- An aerosolized formulation of the monobactam antibiotic aztreonam & lysine
- Indicated to improve respiratory symptoms in CF pts ≥ 7 years old with *Pseudomonas aeruginosa*
- MOA: Binds to penicillin-binding proteins of susceptible bacteria, which leads to inhibition of bacterial cell wall synthesis & death of the cell


Aztreonam (Cayston®)

- **Dose:** Inhale one single use vial (75 mg aztreonam) reconstituted with 1 mL of sterile diluent TID for a 28 day course, followed by 28 days off drug
  - To be used only with the Altera® Nebulizer System

- **ADRs:** cough, nasal congestion, wheezing, pharyngolaryngeal pain, pyrexia, chest discomfort, abdominal pain & vomiting
Tobramycin (TOBI Podhaler®)

- **MOA:** Aminoglycoside antimicrobial that acts primarily by disrupting protein synthesis in the bacterial cell which eventually leads to cell death

- **Dose:** Inhalation of the contents of four TOBI Podhaler® capsules twice daily for 28 days, followed by 28 days off drug
  - One capsule contains 28 mg tobramycin
  - Capsules should be used with the Podhaler device only

- **ADRs:** cough, dyspnea, pyrexia, oropharyngeal pain, dysphonia, hemoptysis, & HA
Tobramycin (Bethkis®)

- **MOA:** Aminoglycoside antimicrobial that acts primarily by disrupting protein synthesis in the bacterial cell which eventually leads to cell death

- **Dose:** One ampule BID by oral inhalation in repeated cycles of 28 days on drug, followed by 28 days off drug
  - One 4 mL ampule contains 300 mg tobramycin
  - Administered using a hand-held PARI LC PLUS Reusable Nebulizer with a PARI Vios Air compressor

- **ADRs:** ↓ FEV, rales, ↑ red blood cell sedimentation rate, & dysphonia

- **Light sensitive**

- **Store in refrigerator**

THE ROLE OF A PHARMACIST
The Role of a Pharmacist

- Identify potential drug interactions
  - Kalydeco, Symdeko, and Orkambi
    - Substrates of CYP3A4

- Patient Counseling
  - Encourage adherence to medication regimen
  - Verify appropriate inhaler/nebulizer technique
  - Kalydeco, Symdeko, and Orkambi should be taken with high fat meals

- Ensure correct antibiotic selection in the setting of an acute exacerbation
  - Broad spectrum coverage
  - Two antipseudomonal agents
Acute Exacerbations

- Diagnosis of an acute exacerbation is based on changes from an individual pt’s recent baseline health status.

- Most exacerbations are not associated with the appearance of bacterial species or strains that are *new* to the pt.

- Treatment:
  - Continuation of chronic treatment regimen
  - Glucocorticoids
  - Respiratory support
  - Systemic antibiotics
Pharmacokinetics in CF Population

- Large volumes of distribution
- Enhanced metabolic clearance
- Increased risk for antimicrobial resistance
- Difficulty with lung tissue penetration

Great difficulty in attaining & maintaining therapeutic drug concentrations!
Chronic CF Therapies: Recommended Order

1. Bronchodilator
2. Hypertonic Saline
3. Dornase alfa
4. Airway clearance
5. Aerosolized antibiotics
WHAT’S NEXT?
The Future of CF
New Therapies

- CF care has largely focused on the downstream effects of CFTR dysfunction
- New therapies aim to treat the underlying abnormality
- CF has among the highest number of gene-therapy trials
- CFTR pharmacotherapy:
  - CFTR gene mutations have different functional consequences
  - Must target the distinct classes of mutation
- Treating the early & root causes of CF will improve outcomes & reduce the burdens of treatment
New Therapies

- Introduction of CFTR modulators has revolutionized CF care
- Drug screening campaigns have identified agents capable of suppressing CFTR nonsense alleles, augmenting potentiator activity & further promoting F508del correction
- Advancement of new drugs that address specific CFTR defects has been bolstered by clinical studies of F508del rescue in combination with ivacaftor
## Drug Development Pipeline

### Phase 1
- Eluforsen (QR-010)
- MRT5005
- AZD5634
- ALX-009
- SNSP113
- SPI-1005
- POL6014

### Phase 2
- QBW251
- FDL169
- GLPG2222
- PTI-428
- PTI-801
- VX-561
- OligoG
- SPX-101
- Inhaled Nitric Oxide
- Intravenous Gallium
- Acebilustat (CTX-4430)
- lenabasum (JBT-101)
- LAU-7b

### Phase 3
- VX-445 + tezacaftor + ivacaftor
- VX-659 + tezacaftor + ivacaftor
- Inhaled Mannitol (Bronchitol®)
- Inhaled Levofloxacin (Quinsair®)
- Vancomycin Inhalation Powder (AeroVanc®)
Summary

- CF is a disease state resulting from a dysfunction in the CFTR
- Multiple organ systems are affected in CF individuals
- Mortality is most commonly due to chronic organ damage or resistant pulmonary infections
- Breakthrough in CF treatment focuses on treating the basic defect of the disease: CFTR dysfunction
Test Your Knowledge
True or False?

- The most common cause of pneumonia in patients with cystic fibrosis is *Burkholderia cepacia*. **FALSE**

- Inhaled antibiotics, such as Aztreonam (Cayston®) and Tobramycin (TOBI®), should be administered last in a patient’s inhaled medication regimen after bronchodilators and other inhaled therapies. **TRUE**

- The most common CFTR gene mutation is delta F508. **TRUE**
Additional References

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