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Cystic Fibrosis: Have They Found The Pot Of Gold?

Taryn Bomersback, BScPharm, ACPR
Pharmacist, Pediatric Cystic Fibrosis Clinic, Alberta Children's Hospital

Tara Leong, BScPharm, PharmD
Pharmacist, Adult Cystic Fibrosis Clinic, Foothills Medical Centre

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Presenter Disclosures

Taryn Bomersback B.Sc.Pharm, ACPR
Tara Leong B.Sc.Pharm, PharmD

There are no relationships to disclose related to this presentation

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Objectives

- Review Cystic Fibrosis disease background
- Discuss the newest class of therapy, CFTR Modulators
- Review specifics of the drug elexacaftor-tezacaftor-ivacaftor (ETI,Trikafta®)
- Discuss other general considerations (including issues with drug coverage and distribution)

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Cystic Fibrosis (CF)

- a progressive, genetic disease (autosomal recessive) in which the body makes very thick, sticky mucus.
- 1/25 people (Canada) is a carrier
- 1/3600 babies born in Canada is diagnosed with CF
- ~4300 people in Canada are living with CF (~650 in Alberta)

CF Canada Statistics

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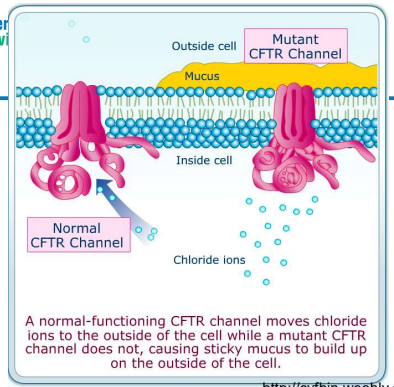

http://cyfbin.weebly.com/cyfb.html

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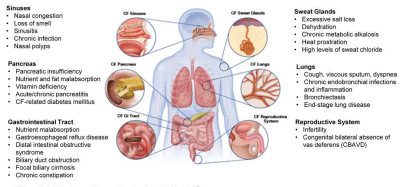
Clinical Manifestations of CF

Loss of CFTR activity causes manifestations of cystic fibrosis

The morbidity of CF[1-3]*



*CF can affect additional organs to the ones shown here (e.g., skeletal system).[1]

References: 1. Ramsey B, Richardson MA. *J Allergy Clin Immunol.* 1992;90(3 Pt 2):547-552. 2. O'Sullivan BP, Freedman SD. *Lancet.* 2009;373(9678):1891-1904. 3. Welsh MJ, Ramsey BW, Accurso F, Cutting GR. In: Valle D, Beaudet A, Vogelstein B, et al, eds. *The Online Metabolic & Molecular Bases of Inherited Disease.* The McGraw-Hill Companies Inc; 2004: part 21, chap 201. www.ommbid.com.

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Cystic Fibrosis (CF) Care in Alberta

- 2 pediatric CF clinics
  - Alberta Children's Hospital (Calgary)
  - Stollery Children's Hospital (Edmonton)
- 2 adult CF clinics
  - Foothills Medical Centre (Calgary)
  - University of Alberta Hospital (Edmonton)
- Patients have clinic visits every 3 months

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Diagnosis

- Sweat chloride > 60 mmol/L
- 2 CF causing genetic mutations
  - CFTR 1 & 2 websites
  - https://cftr2.org/
- Newborn Screening Program
- CFSPID/CRMS – indeterminate diagnosis

Did you know that the CF gene was discovered by Dr. Lap-Chee Tsui - a Canadian researcher, along with Dr. Francis Collins from Michigan?

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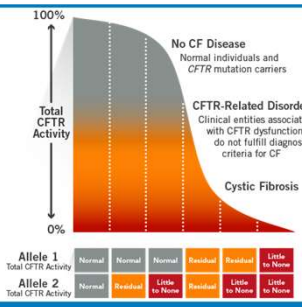
Phenotype associated with CFTR activity of both alleles



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Current Treatments

- Pancreatic enzymes
- Fat soluble vitamins (A,D,E,K)
- Mucolytics (dornase alfa, hypertonic saline)
- GI meds – laxatives, motility drugs, ursodiol
- Chest Physiotherapy
- Antibiotics
- Lung transplant
- And now CFTR modulators!

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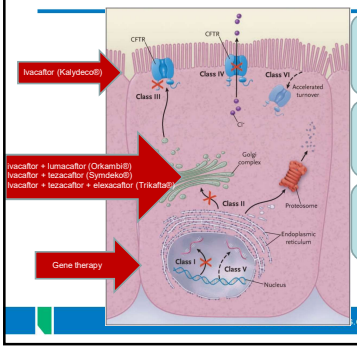
Mutations differ in the CFTR defect they cause



Ivacaftor: Gating mutations
(STRIVE Study)
↑ FEV1 10.6%
↑ weight 2.7 kg
↓ pulm exacerbations by 55%
↓ sweat chloride 48 mmol/L
↑ Q of L 8.6 points

Lumacaftor/ivacaftor (Orkambi®): 2 F508del
(TRAFFIC & TRANSPORT Studies)
↑ FEV1 2.6-4%
BMI ↑0.24-0.28 (significant only in Transport & pooled) ↓ pulm exacerbations 30-39% (only SS in pooled analysis)
↑ Q of L of 1.5-3.9 points (only SS for higher dose)
↓ sweat chloride 9-24.8 mmol/L (phase 2/pediatric trial)

ETI (Trikafta®): 1 F508del
(VX-445-102 Study)
↑ FEV1 14.3%
BMI ↑ 1.04
↓pulm exacerbations 63%
↓ sweat chloride 41.8 mmol/L
↑ Q of L 20.2 points

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Outcomes

	Ivacaftor (Kalydeco®) G551D, R117H, 8 other gating mutations	Ivacaftor + lumacaftor (Orkambi®) F508del x 2	Ivacaftor + tezacaftor (Symdeko®) F508del x 2	Ivacaftor+ tezacaftor+ elexacaftor (Trikafta®) At least one F508del
FEV1	↑ 10.6%	↑ 2.6-4%	↑ 4%	↑14%
Weight	↑ 2.7 kg	BMI ↑0.24-0.28	NS	BMI ↑ 1.04
Risk of Pulm exacerbation	↓ 55%	↓30-39%	↓35%	↓63%
Sweat Cl	↓ 48 mmol/L	↓ 9-24.8 mmol/L	↓ 10 mmol/L	↓42 mmol/L
Quality of life (out of 100)	↑ 8.6 points	↑1.5-3.9 points (SS at 1 dose only, not clinically significant)	↑ 5.1 points	↑20.2 points

Clinically important outcomes?

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CFTR Modulator Regulatory Approvals

	Ivacaftor (Kalydeco®) G551D, R117H, 8 other gating mutations	Ivacaftor + lumacaftor (Orkambi®) F508del x 2	Ivacaftor + tezacaftor (Symdeko®) F508del x 2	Ivacaftor+ tezacaftor+ elexacaftor (Trikafta®) At least one F508del
	Potentiator	Corrector + potentiator		
Approval in Canada	Nov 2012 (G551D) Jun 2014 (other)	January 2016	June 2018	June 2021
Current Age Indication	1 year and up	2 years and up	12 years and up	12 years and up (6-11 data submitted to HC)
Cost	~$300,000/year	~$250,000/year	~$272,000/year	~$308,000/year

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CFTR Modulator Drug Coverage

	Ivacaftor (Kalydeco®) Gating mutations & R117H	Ivacaftor + lumacaftor (Orkambi®) F508del x 2	Ivacaftor + tezacaftor (Symdeko®) F508del x 2	Ivacaftor+ tezacaftor+ elexacaftor (Trikafta®) F508del X 1
CADTH	List with price reduction	Do not list	Not reviewed	See below
Drug Coverage	Private Public over age 6	Private Public with criteria	Private only	Private Public (> age 12)

CADTH Recommendation for Trikafta:
Trikafta should be reimbursed by public drug plans for the treatment of CF in patients aged 12 years and older who have at least one F508del mutation in the CFTR gene

Conditions:
- Baseline FEV1 ≤ 90%
- After 6 months must demonstrate improvement in FEV1 by 5% OR no decline in BMI OR decrease in days of antibiotic use OR decrease in number of hospitalizations OR improvement of ≥ 4 points on CFQR quality of life survey
- Reduction in price (90% reduction required to be cost effective based on $50,000/QALY willingness to pay threshold)

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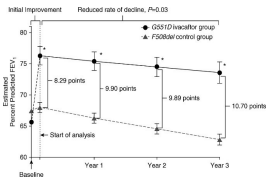
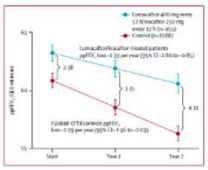
? Impact of modulators on lung function decline

Rate of FEV1 decline seen with open label extension study participants vs matched registry controls:

- **47% lower with ivacaftor**
- **42% lower with lumacaftor/ivacaftor (Orkambi®)**



Sawicki G S., McKone E.F., Pasta D.J., Millar S.J., Wagener J.S., Johnson C.A. Sustained Benefit from ivacaftor demonstrated by combining clinical trial and cystic fibrosis patient registry data. Am J Respir Crit Care Med. 2015;192:836–842.



Konstan MW, McKone EF, Moss RB, Marigowda G, Tian S, Waltz D, Huang X, Lubarsky B, Rubin J, Millar SJ, Pasta DJ, Mayer-Hamblett N, Goss CH, Morgan W, Sawicki GS. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. Lancet Respir Med. 2017 Feb;5(2):107-118.

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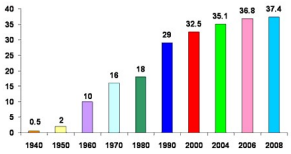
? Impact on Survival

- Estimated Median Age of Survival in Canada is 55.4 yrs

Average Life Expectancy in Cystic Fibrosis
Better Treatment = Improved Survival



Source: Cystic Fibrosis Foundation

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? Impact on Survival

US modeling study of ivacaftor
- model assumed age 25+, assumed efficacy halved after 2 yrs
- ivacaftor associated with 18 additional years, 18% absolute ↓ in likelihood of lung tx

Dilokthornsakul P, Hansen RN, Campbell JD. Forecasting US ivacaftor outcomes and cost in cystic fibrosis patients with the G551D mutation. Eur Respir J 2016;47:1697–705.

US modeling study 1 lumacaftor/ivacaftor (Orkambi®)
- 8 additional years overall
- 23 additional yrs if started age 6, 18 additional yrs if started age 12

Rubin JL, O'Callaghan L, Pelligra C, Konstan MW, Ward A, Ishak JK, et al. Modeling long-term health outcomes of patients with cystic fibrosis homozygous for F508del-CFTR treated with lumacaftor/ivacaftor. Ther Adv Respir Dis 2019;13.

US modeling study 2 lumacaftor/ivacaftor (Orkambi®)
- Additional 3 yrs assuming adherence is halved after 2 yrs
- Additional 8 yrs without assumption

Dilokthornsakul P, Patidar M, Campbell JD. Forecasting the long-term clinical and economic outcomes of lumacaftor/ivacaftor in cystic fibrosis patients with homozygous phe508del mutation. Value Health 2017;20:1329–35.

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Other Benefits

- Improvement in pancreatic function
- Improvement to sinus symptoms
- Improved fertility in female CF patients
- Potential impact on CFRD & insulin requirements
- Decrease in lung transplants

Elexacaftor/tezacaftor/ivacaftor (ETI) (Trikafta®) - Dosing

- 2 tablets (elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg - orange) in the morning + ivacaftor 150 mg (blue) in the evening, approximately 12 hours apart
- Take with fat containing food

ETI – Adverse effects

- Headache (~17%)
- Elevated LFTs (10%)
- Isolated high indirect bilirubin (11%)
- Abdo pain, diarrhea (13%), distension, flatulence, DIOS
- URTI (16%), infection, sinusitis, rhinitis, nasal congestion, rhinorrhea, pharyngitis, UTI
- Cataracts (pediatric), conjunctivitis (2-5%)
- Increased blood pressure (4%)
- Dizziness (2-5%)
- Skin rash (women 16%, men 5%), acne, eczema, pruritis
- Hypoglycemia (2-5%)
- Dysmenorrhea (2-5%)
- Increased CRP (2-5%), increased CK (9%)

- Other postmarketing reports: mental health changes, memory issues, dry eyes, gallstones, kidney stones, testicular pain

ETI – Drug Interactions

- CYP 3A4 inhibitors/inducers (rifampin, rifabutin, St. John's Wort, antiepileptics (phenytoin, carbamazepine, phenobarbital) clofazimine, antifungals, clarithromycin, erythromycin, grapefruit juice, aprepitant)
- P-glycoprotein inhibitors (rifaximin, tacrolimus, sirolimus, morphine, cyclosporine, colchicine)
- Hormonal contraceptives – may increase adverse effects of Trikafta - especially rash

ETI: Other Considerations

- Managing expectations & other therapies
- Emotional aspects – survivor's guilt, "what if I'd gotten sooner?", changing thoughts about and relationship with CF, thoughts of the future
- Use in pregnancy and breastfeeding
- Limited experience in patients with advanced lung disease
- Use in transplant patients (interactions, coverage)
- Weight gain and associated issues
- Less ability to provide good sputum samples – impact on diagnosing bacterial colonization & infection

Monitoring & Initiation Protocol

Monitoring Schedule

CFTR modulator Name: _____

Start Date of Drug: _____ Patient ID Label

Routine Clinic Visits (Clinical Care monitoring)	Baseline	1 month visit	3 month visit	6 month visit	9 month visit	1 year visit
Date						
Clinical assessment, review of CFTR genotype & past medical Hx						
# outpatient exacerbations in previous year / # days on abx						
# inpatient exacerbations in previous year/ # days on abx						
# DIOS episodes in previous year						
Sweat Chloride Test						
Height						
Weight and Weight Percentile						
BMI and BMI Percentile						
Blood pressure						
BW – CBC/ ALT/AST/ALP/bilirubin (direct +indirect)/CK/INR/lipase						
Spirometry (FEV1)						
Sputum microbiology						
Ophthamology exam						
PHQ-9 & GAD-7 questionnaires (if age >6 yrs)						
Safety review						
Review of prescribed therapy						
CFQ-R/RD questionnaire						
CT imaging of chest (if age > 6 yrs)						
Fecal elastase						

Key monitoring:

- LFTs, bili at least every 3 months
- Baseline and yearly eye exam
- BP at clinic visits
- Outcome measures for coverage

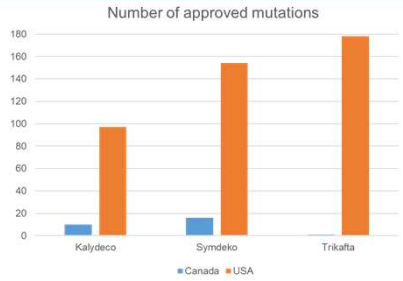
CFTR Modulators – other considerations

- Lack of long term efficacy & safety data
- Identification of patients (age, mutation & coverage dependent)
- $$$$ / Funding / Coverage issues
- Dispensing Issues
- US – Canadian variation in indication

Canada vs. USA age indications

	Canada	USA
Ivacaftor (Kalydeco®)	≥ 1 year of age	≥ 4 months of age
Tezacaftor / ivacaftor (Symdeko®)	≥ 12 years of age	≥ 6 years of age
Elexacaftor / tezacaftor / ivacaftor (Trikafta®)	≥ 12 years of age	≥ 6 years of age

Canada vs. USA eligible mutations



What's Next

- Post-marketing data
- Increasing accessibility
- Expanding eligible population
- CFTR modulator pipeline
  - New standard of care
- Gene therapy

Summary

- Survival in CF has been steadily increasing and the proportion of adults with CF is increasing
- Highly effective CFTR modulators represent an exciting new therapy that has been shown to improve lung function, growth/weight, and quality of life; and to decrease antibiotic use and hospitalizations
- The true benefits on progression of lung disease and survival will hopefully be determined in the near future
- ~ 5% of CF patients do not qualify for these therapies
- Research for the true pot of gold "a cure" still continues!

Questions??