Remarkable survival with chronic respiratory failure with Trikafta- a case for not giving up in the setting of advanced cystic fibrosis lung disease

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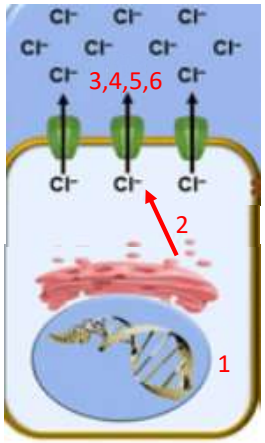
Learning Objectives

1) Trikafta has a documented median increase in precent predicted FEV1 of 13.8%, and decrease in cystic fibrosis (CF) related exacerbations by 63%.
2) Even without a documented lung function improvement, Trikafta can help stabilize patients with advanced lung disease due to its extrapulmonary effects.
3) Trikafta is currently used as a bridge to lung transplant in patients with CF.

Background

- CF is an autosomal recessive disease that results from a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) and effects 1 in 3200 people.
- Multiple mutations have been identified, but the most common is ΔF508 which results in misfolding of the CFTR protein and inability to reach the surface of the cell.
- Trikafta is a combination drug that increases the amount of mature CFTR protein delivered to the cell surface and potentiates the channel gating to facilitate ion transport.



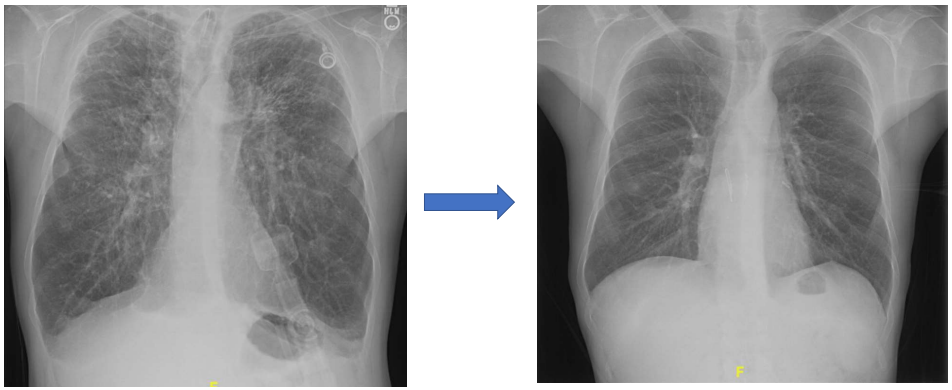
Mutation	Defect Result
Class 1	No protein made at all
Class 2	No protein trafficking to surface/misfolding
Class 3	Non functional protein at cell surface
Class 4	Less functional protein at cell surface
Class 5	Reduced quantity of normally functioning protein
Class 6	Less stable protein resulting in increased cell turnover

Clinical Case

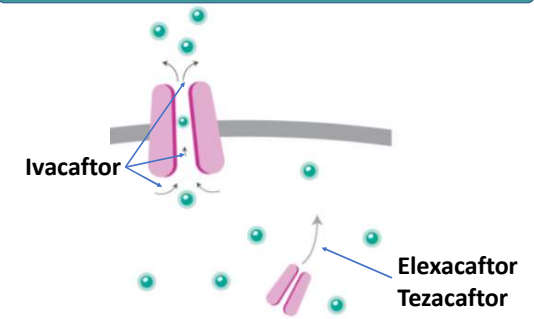
Timeline of Events

A 42 year-old man with CF (homozygous ΔF508) presented to the University of Washington (UW) CF clinic after disengaging from the CF community 7 years prior.

- 2013: During the next 6 years he received oral antibiotics from his PCP 3-4 times a year
- Sept 2018: Prescribed oral antibiotics, but failed to improve and was admitted to a rural hospital following spontaneous pneumothorax resulting in out of hospital cardiac arrest. He was started on standard of care CF medications.
- Dec 2018: Had chronic respiratory failure requiring tracheostomy and long-term acute care facility for 1 month till he was discharged home with his wife managing his ventilator.
- Jan-July 2019: He had >5 more admissions for CF related exacerbations requiring nearly continuous IV antibiotics. He was referred to UW CF clinic for lung transplant workup.
- Aug 2019: Was seen in UW CF clinic. Below characteristics were identified.
  - Ventilator dependent requiring 6-10 L O2 at a baseline, and pressure support dependent at night. This was managed by his wife.
  - Colonialized with MSSA & Pseudomonas.
  - Severely malnourished (nadir BMI of 14.6 kg/m2) despite eating >2500 calories/day.
  - FEV1 of 0.47L (11% predicted) and FCV 1.05 (20% predicted).
- He was restarted on tube feeds and asked to follow up 3 months later
- Sept-Nov 2019: Had repeated hospitalizations for CF related exacerbations requiring IV antibiotics.
- Dec 2019:Trikafta was approved by his insurance and he was initiated on therapy. In the weeks following he had dramatic improvement in pulmonary and sinus symptoms, oxygen requirements, tidal volumes, sleep, cough, 20% reduction in sputum production, and significant improvement in his weight. At this point he was placed on lung transplant list.
- Jan 2020: Was called in for lung transplant and successfully underwent bilateral orthotopic lung transplantation. (**Pre and post transplant chest x-ray below).**
- July 2020: FEV_1 76% and FVC 67%.



Mechanism of Action



Discussion

- Currently is indicated in patients with one or two copies of ΔF508 and native lungs.
- Trikafta is a life changing medication for patients with CF due to its mechanism of action resulting in improved CFTR function.
- It works both on the pulmonary system and extrapulmonary organs that have CFTR expression (gut, pancreas, mucosa, skin). This results in improved quality of life.
- Even among patients with end-stage lung disease, Trikafta can provide substantial benefit and help bridge to transplant.
- Trikafta has the potential to delay and lung transplantation and extend life pre-transplant.

References

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