HOT TOPICS: Pulmonary

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Breakthrough Drug for Cystic Fibrosis: The Best Story in Medicine

• On October 21, 2019, the FDA approved the combination medication elexacaftor-tezacaftor-ivacaftor (trade name Trikafta) for treating CF associated with the F508del mutation

• This drug could treat 85-90% of people with CF (pwCF)

• Demonstrated to be highly effective treatment for F508del, and much superior to previously available CFTR modulators
CFTR Function

- In the resting state, the channel is closed. It opens in response to activation signals.

- In CF, the underlying mutation may result in lack of CFTR at the surface, or in failure of the CFTR to work properly.

- There are over 2,000 known mutations of the CFTR gene.
Approach to Restoring CFTR Function: Mutation Classification

<table>
<thead>
<tr>
<th>CLASS</th>
<th>DESCRIPTION</th>
<th>EXAMPLES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>CFTR is created, reaches cell surface and functions properly, allowing transfer of chloride and water.</td>
<td>G542X, WI128X, R553X</td>
</tr>
<tr>
<td>Class I</td>
<td>No functional CFTR created.</td>
<td>F508del, N1303K, I507del</td>
</tr>
<tr>
<td>Class II</td>
<td>CFTR protein is created, but misfolded, keeping it from reaching the cell surface.</td>
<td>G551D, S549N, V520F</td>
</tr>
<tr>
<td>Class III</td>
<td>CFTR protein is created and reaches cell surface, but does not function properly.</td>
<td>R117H, D1152H, R347P</td>
</tr>
<tr>
<td>Class IV</td>
<td>The opening in the CFTR protein ion channel is faulty.</td>
<td>3849+10kbC-&gt;T, 2789+5G-&gt;A</td>
</tr>
<tr>
<td>Class V</td>
<td>CFTR is created in insufficient quantities.</td>
<td>A455E</td>
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The First Clinical Success in Restoring CFTR Function: Ivacaftor (2012)

“Potentiator”: Increases opening of CFTR channel

Highly effective:
- Dramatic drop in sweat chloride
- Large and rapid increase in FEV1
- Reduced exacerbations
- Improved BMI

But:
Only about 10% of pwCF have an eligible mutation for this drug

“Kalydeco” - now approved down to age 6 months
Effect of Ivacaftor on Ventilation in G551D Positive CF

Baseline

On Ivacaftor 4 weeks

Off Ivacaftor 2 weeks

Altes T et al, J Cyst Fibrosis 2017, 16(2): 267-274.
What about targeting the most common CFTR defect?
CFTR associated with F508del mutation requires both a corrector and a potentiator to restore function.
Dual Combination Modulators:
Lumacaftor/Ivacaftor (“Orkambi”-2015) then Tezacaftor/Ivacaftor (“Symdeko”-2018) for F508del Homozygotes

But.....
-FEV1 increase was modest (3-4% predicted)
-No effect seen if just one copy of F508del, so approved only for homozygous patients

2019-Advancing to TCT (triple combination therapy) for F508del: Two correctors plus one potentiator

• Two phase 3 studies on TCT:
  • F/MF (heterozygous F508del, N=403): Mean absolute improvement of 13.8 points in ppFEV1 from baseline to week 4 compared to placebo (p<0.0001)
    • Triple placebo showed change of -0.2 ppFEV1, vs TCT +13.6 ppFEV1
  • F/F (homozygous F508del, N=107): Mean absolute improvement of 10.0 points in ppFEV1 from baseline to week 4 for TCT compared to placebo-tez-iva (p<0.0001); for pts already on tez-iva dual combination
    • Placebo-tez-iva showed change of +0.4 ppFEV1, vs TCT +10.4 ppFEV1
TCT with Elexacaftor-Tezacaftor-Ivacaftor (“Trikafta”) for **Heterozygous F508del**: Absolute Change from Baseline in ppFEV1 and Rate of Pulmonary Exacerbations

**Figure A**

- Percentage of Predicted FEV$_1$, According to Visit

<table>
<thead>
<tr>
<th>Visit</th>
<th>Placebo</th>
<th>Elexacaftor-Tezacaftor-Ivacaftor</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>100%</td>
<td>95%</td>
</tr>
<tr>
<td>Wk 4</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>Wk 8</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>Wk 12</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>Wk 16</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Wk 24</td>
<td>94%</td>
<td>94%</td>
</tr>
</tbody>
</table>

- Absolute Change from Baseline in Percentage of Predicted FEV$_1$

  +13.6 ppFEV1
  Vs
  -0.2 ppFEV1

**Figure B**

- Individual Responses with Respect to Percentage of Predicted FEV$_1$

- Absolute Change from Baseline in Percentage of Predicted FEV$_1$ through Wk 24

**Figure C**

- Pulmonary Exacerbations

  - Rate ratio, 0.37; 95% CI, 0.23–0.55; P<0.001

Homozygous F508del: Effect of Triple Combination Therapy (ELX-TEZ-IVA) vs. Dual Therapy (TEZ-IVA)

Therapies to Restore CFTR Function: Where We Are

Gating or Residual Function Mutation (but no F508del):
- Age > 6 months: Kalydeco (Ivacaftor) or Symdeko (Tezacaftor-Ivacaftor)

Heterozygous F508del:
- Age > 12y: Trikafta (Elexacaftor-Tezacaftor-Ivacaftor TCT)

Homozygous F508del:
- Age > 12y: Trikafta (Elexacaftor-Tezacaftor-Ivacaftor TCT)
- Age 6-11y: Symdeko (Tezacaftor-Ivacaftor) or Orkambi (Lumacaftor-Ivacaftor)
- Age 2-5y: Orkambi (Lumacaftor-Ivacaftor)

Together this covers ~90% of people with CF
What’s the potential when highly effective modulators can be started very early in life?

- Systemic effects (pill)
- Prospect of dramatic long term impact on pulmonary and non-pulmonary outcomes
- Earlier is better

Children age 2 to 5 years with gating mutation, treated with ivacaftor for 108 weeks:

- Improvement in fecal elastase with time on drug
- 23% of the patients improved to level above cutoff for pancreatic insufficiency