CFTR modulators and the impact on nutritional status

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Great Ormond Street Hospital for Children
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Overview

• Background to cystic fibrosis (CF) and nutritional management

• What are CFTR modulators?

• Impact of CFTR modulators on nutritional status

• Implications for clinical practice and future considerations

CFTR, cystic fibrosis transmembrane conductance regulator
Background

CF caused by variants in the gene for CFTR protein, responsible for chloride transport across cell surface.

Source: Southern et al, JCF. 2022

CFTR, cystic fibrosis transmembrane conductance regulator
Non-pulmonary symptoms of CF

• First described as ‘cystic fibrosis of the pancreas’ in 1938 (Andersen)

- Early onset
  - Exocrine pancreatic insufficiency
    - Maldigestion & malabsorption
    - Malnutrition & growth failure
  - Endocrine pancreatic dysfunction
    - Glucose dysregulation
    - CF diabetes

- Later onset
Nutritional management

Treatments have targeted symptoms of CFTR dysfunction

• Pancreatic enzyme replacement therapy
• High calorie, high fat “CF legacy diet”
• Oral/enteral nutritional support
• Fat-soluble vitamin & mineral supplementation

→ Improved growth, pulmonary function and survival (Corey et al)

Corey et al, Ped Pulm. 1988
What are CFTR modulators?

- Small molecule agents which target the underlying **CFTR defect** by improving **function** and increasing **quantity** of CFTR protein

- These agents are either a **potentiator** or a combination of both potentiator and **corrector/s**

- Oral medications taken 12 hourly with fat-containing food and enzymes
<table>
<thead>
<tr>
<th>Modulator</th>
<th>Agent</th>
<th>Variants and class</th>
<th>Date licenced in UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivacaftor* (Kalydeco®)</td>
<td>Potentiator</td>
<td>Gating (e.g. G551D) Class III-V</td>
<td>Infants ≥4m since 2020 Children ≥12y &amp; adults since 2013</td>
</tr>
<tr>
<td>Lumacaftor/Ivacaftor (Orkambi®)</td>
<td>Potentiator &amp; corrector</td>
<td>df508 homozygous Class II</td>
<td>Children ≥2y since 2020 Children ≥12y &amp; adults since 2015</td>
</tr>
<tr>
<td>Tezacaftor/Ivacaftor (Symkevi®)</td>
<td>Potentiator &amp; corrector</td>
<td>df508 heterozygous Class II-V</td>
<td>Children 6-11y since 2021 Children ≥12y &amp; adults since 2019</td>
</tr>
<tr>
<td>Elexacaftor/Tezacaftor/ Ivacaftor* (Kaftrio®)</td>
<td>Potentiator &amp; correctors</td>
<td>df508 homozygous df508 heterozygous Class II-V</td>
<td>Trials in children 1-2y due to start Trials in 2-5y awaiting approval Children 6-11y since 2022 Children ≥12y &amp; adults since 2020</td>
</tr>
</tbody>
</table>

* IVA and ELX/TEZ/IVA are described as highly effective modulator therapies
European registry data: modulator use
UK registry data: modulator use

**UK CF Patient Registry 2021 Annual Report, CFTrust 2022**
European registry data: nutritional status

<table>
<thead>
<tr>
<th></th>
<th>Median BMI</th>
<th>% underweight</th>
<th>% overweight</th>
<th>% obese</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children 2-17y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>38.6</td>
<td>18.74</td>
<td>5.75</td>
<td>1.96</td>
</tr>
<tr>
<td>2018</td>
<td>40.9</td>
<td>18.33</td>
<td>7.32</td>
<td>2.96</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Median BMI</th>
<th>% underweight</th>
<th>% overweight</th>
<th>% obese</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adults ≥18y</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>20.9</td>
<td>20.5</td>
<td>9.11</td>
<td>1.89</td>
</tr>
<tr>
<td>2018</td>
<td>21.6</td>
<td>14.67</td>
<td>14.11</td>
<td>3.35</td>
</tr>
</tbody>
</table>

*Zolin et al, ECFSPR 2020. Reproduced with permission*
UK registry data: nutritional status

Median BMI percentiles in children & young people

BMI in adults 2018-2021

↑ overweight / ↓ underweight
Impact on nutritional status

Table 1. Summary of the effects of highly effective CFTR modulators on markers of growth, nutritional status and gastrointestinal health.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ivacaftor</th>
<th>ELEX-TEZ-IVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-Z</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Height-Z</td>
<td>Increased in youth</td>
<td>To be determined</td>
</tr>
<tr>
<td>BMI-Z</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Fat Mass</td>
<td>Increased</td>
<td>To be determined</td>
</tr>
<tr>
<td>Fat-Free Mass</td>
<td>Unchanged to increased</td>
<td>To be determined</td>
</tr>
<tr>
<td>Bile Acid Metabolism</td>
<td>Increased FGF-19 and decreased C4</td>
<td>To be determined</td>
</tr>
<tr>
<td>CF Liver Disease</td>
<td>To be determined, case reports of improved steatosis</td>
<td>To be determined</td>
</tr>
<tr>
<td>Exocrine Pancreatic Insufficiency</td>
<td>Increased fecal elastase at younger ages</td>
<td>To be determined</td>
</tr>
<tr>
<td>Bicarbonate Secretion</td>
<td>Decreased time to reach pH 5.5</td>
<td>To be determined</td>
</tr>
<tr>
<td>Energy Expenditure</td>
<td>Decreased</td>
<td>To be determined</td>
</tr>
<tr>
<td>GI Microbiome</td>
<td>Changes in intestinal flora and decreased calprotectin</td>
<td>To be determined</td>
</tr>
</tbody>
</table>

Bass, Brownell and Stallings, Nutr. 2021
# Impact on anthropometry

<table>
<thead>
<tr>
<th>Modulator</th>
<th>Parameters</th>
<th>Follow up</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVA</td>
<td>WFA and BMI z-scores</td>
<td>8 to 48 wk</td>
<td>Mean baseline WFA -0.292 and BMI -0.199. ↑ WFA and BMI z-scores by 0.35 and 0.39 respectively compared to placebo</td>
</tr>
<tr>
<td>IVA Adults ≥1 G551D</td>
<td>Wt and BMI</td>
<td>4 to 48 wk</td>
<td>Optimal or low mean BMI at baseline, ↑ wt and BMI by 2.9kg and 0.58-1.2 respectively</td>
</tr>
<tr>
<td>ELX/TEZ/IVA ≥12y</td>
<td>BMI</td>
<td>24 wk</td>
<td>Baseline nutritional status not reported. Mean change in BMI 1.04</td>
</tr>
<tr>
<td>dF508 homozygous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELX/TEZ/IVA ≥12y</td>
<td>Wt and BMI</td>
<td>4 wk</td>
<td>Baseline nutritional status not reported. Mean change in BMI 0.6. Mean change in wt 1.6kg</td>
</tr>
<tr>
<td>dF508 heterozygous</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
57 studies 2012-2019 (children & adults)

Highly consistent & sustained clinical benefit in both pulmonary & non-pulmonary outcomes, including nutritional markers after 5y
Impact on anthropometry: ELX/TEZ/IVA

‘PROMISE’ n=487, US adolescents & adults ≥12y

At 6m ↑ BMI percentile to 65th in adolescents, 24.5kgm² in adults (even after FEV1 plateaued)

Nichols et al, Am J Resp Crit Care Med. 2021
Impact on growth: ELX/TEZ/IVA

n=66 children 6-11y
↑ wt & BMI z-scores at 24wks,
ht z-score maintained

Zemanick et al, Am J Resp Crit Care Med. 2021
Impact on body composition: IVA

Body composition and weight changes after ivacaftor treatment in adults with cystic fibrosis carrying the G551 D cystic fibrosis transmembrane conductance regulator mutation: A double-blind, placebo-controlled, randomized, crossover study with open-label extension

Susannah J. King Ph.D. a,b,c,1, Audrey C. Tieney Ph.D. a,b,c,d,1, Deirdre Edgeworth B.M.B.B., B.A.O. Dominic Keating M.D. a,b,c,1, Elyssa Williams B.Sc., R.N. b, Tom Kotsimbos M.D. a,b,c,1, Brenda M. Button John W. Wilson M.B.B.S., Ph.D. a,b,c

n=20 adults
After 28d: ↑ wt, BMI & FFM
After 6m: ↑ fat mass, plateaued at 2.5y

At baseline: 20% overweight / 5% obese
After 6m: ↑ to 25% overweight / 10% obese

King et al, Nutr. 2021

n=23 children & adults (5-61y)
At 3 m: ↑ wt, BMI, fat mass & FFM

Stallings et al, J Ped. 2018

FFM, Fat-free mass
Impact on pancreatic function: IVA

‘KIWI’ study, n=34 young children 2-5y
- Improvement pancreatic function (n=27): ↑elastase, ↓IRT
- Wt & BMI z-scores ↑ by wk 2, sustained to wk 24, ht z-score similar from baseline to wk 24

Similar results shown in ‘ARRIVAL’ study children aged 1-2y with ≥1 gating variant
Rosenfeld et al, Lancet Resp Med. 2018

IRT, immunoreactive trypsin

Impact on fat-soluble vitamin status

**CFTR Modulator Therapy with Lumacaftor/Ivacaftor Alters Plasma Concentrations of Lipid-Soluble Vitamins A and E in Patients with Cystic Fibrosis**

Olaf Sommerburg 1,2, Susanne Hammerling 1,2, S. Philipp Schneider 3, Jürgen Okun 3, Claus-Dieter Langhans 3, Patricia Leutz-Schmidt 2,4, Mark O. Wielpütz 2,4, Werner Siems 5, Simon Y. Gräber 6,7,8,9, Marcus A. Mall 6,7,8,9, and Mirjam Stahl 5,9,10

*n=41 (2-21y), ↑ in plasma vitamin A, ↓ in vitamin E, within normal ranges*  
*Sommerburg et al, Antioxid. 2021*

**Real-Life Safety and Effectiveness of Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis**

Pierre-Régis Burgel 1,2,3, Anne Münck 4, Isabelle Durieu 2,5,6, Raphaël Chiron 7, Laurent Mely 8, Anne Prevotat 9, Marlene Muris-Espin 10, Michele Porzio 11, Michel Abeley 12, Philippe Rex 13,14, Christophe Marguet 15, Julie Macey 16, Isabelle Sernet-Gaudelus 17,18, Harriet Corvill 19, Stéphanie Bulf 20, Lydie Lemonnier 21, Clémence Dehollot 22, Jennifer Da Silva 13,17, Jean-Louis Paillasou 23, and Dominique Hubert 1,2; for the French Cystic Fibrosis Reference Network Study Group

*n=845 adolescents & adults, no ↑ in serum vitamin A, E or D after 1y*  
*Burgel et al, Am J Resp Crit Care. 2020*

**Case reports of raised ICP & mild hypervitaminosis A in children after starting ELX/TEZ/IVA**

*Miller & Foroozan, Can J Ophthal. 2022; Wisniewski et al, JCF. 2022*

n=41 (2-21y), ↑ in plasma vitamin A, ↓ in vitamin E, within normal ranges  
*Sommerburg et al, Antioxid. 2021*

ICP, intracranial pressure
Re-thinking nutritional management

• Nutritional assessment to include body composition markers in addition to anthropometry

• Dietary management to focus on quality, rather than quantity

• May be able to reduce/discontinue enzymes in younger children?

• Review frequency of fat-soluble vitamin monitoring, with adjustment of supplementation
“(15) Regular monitoring of nutritional status & dietary intake, according to changing energy requirements”

“(16) Frequency of support of nutritional assessment should be individualised, depending on age, clinical status & modulator therapy”

Southern et al, JCF. 2022
• CFTR modulators have transformed CF care, moving from treating the symptoms of CFTR dysfunction → targeting the underlying defective CFTR protein

• CFTR modulators have a significant impact on nutritional status, the extent to which is variant-specific & depends on the type of modulator used

• Nutritional assessment & dietary management are evolving, becoming more individualised & focusing on optimising long term health
Thank you for listening

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