Benefit–risk profiles of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus UMEC/VI in patients with chronic obstructive pulmonary disease: a Markov model

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Introduction

- Evaluating benefit–risk profiles for COPD therapies is complex
  - Clinical outcomes are affected in multiple ways by both patient characteristics and treatments and it is important to assess these together rather than individually
- In the IMPACT trial, patients who received FF/UMEC/VI demonstrated:\textsuperscript{1,2}
  - Significantly greater reductions in the annual rate of moderate/severe exacerbations vs FF/VI and UMEC/VI
  - Significantly reduced risk of all-cause mortality vs UMEC/VI
  - An increased risk of pneumonia was seen in both FF-containing arms vs UMEC/VI
- This post hoc analysis applied Markov modeling to understand the benefit–risk of FF/UMEC/VI, FF/VI and UMEC/VI by assessing the overall time a patient may be expected to be in disease state (eg, exacerbation, pneumonia, death) for different patient characteristics

COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; UMEC, umeclidinium; VI, vilanterol.
Background: The IMPACT trial

- IMPACT was a Phase 3, randomized, double-blind, 52-week trial comparing once-daily FF/UMEC/VI with FF/VI and UMEC/VI in patients (N=10,355) at least 40 years of age with:
  - Symptomatic COPD (CAT score ≥10)
  - FEV₁ <50% predicted and ≥1 moderate or severe exacerbation in the prior year, or FEV₁ 50–<80% predicted and ≥2 moderate or ≥1 severe exacerbations in the prior year

CAT, COPD Assessment Test; FEV₁, forced expiratory volume in 1 second.
Methods: A Markov model

- Generalize competing risk models by describing risk of different on-treatment intermediate events.
- Patients with COPD are modeled as being in one of four mutually exclusive disease “states” at any given time:
  - Death
  - Exacerbation alone
  - Pneumonia (with/without exacerbation)
  - Event-free (none of the above)
- There are 9 different “transitions” possible each shown by an arrow.
Methods: Time-to-event

- Each “transition”, can be modeled using a time-to-event model
  - The resolution of an exacerbation or pneumonia event was assessed by investigators

- Potentially important covariates were included in the model for each transition:
  - Study treatment, sex, age, BMI, FEV$_1$, region, exacerbation history, pneumonia history, baseline eosinophil and neutrophil levels

- This allowed us to construct individual benefit–risk profiles based on the covariates in the model
  - We present profiles for an average male and female patient in IMPACT

BMI, body mass index.
Results: Predicted outcomes for a reference male/female patient

<table>
<thead>
<tr>
<th></th>
<th>FF/UMEC/VI</th>
<th>FF/VI</th>
<th>UMEC/VI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Mean number of exacerbations per year</td>
<td>1.03</td>
<td>1.27</td>
<td>1.15</td>
</tr>
<tr>
<td>Mean length of a single exacerbation event</td>
<td>14.1 days</td>
<td>14.7 days</td>
<td>14.1 days</td>
</tr>
<tr>
<td>Mean number of pneumonia events per year</td>
<td>0.07</td>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean length of a single pneumonia event</td>
<td>18.3 days</td>
<td>18.7 days</td>
<td>18.2 days</td>
</tr>
<tr>
<td>Probability of death during 1 year</td>
<td>0.98%</td>
<td>0.50%</td>
<td>1.26%</td>
</tr>
</tbody>
</table>

Covariates for reference patient were: 65 years of age; BMI: 27; non-Asian region; ≥2 moderate or ≥1 severe exacerbation in the prior year; <50% predicted FEV₁; no history of pneumonia; former smoker; eosinophils 222 cells/µL; baseline neutrophils 5.2 10e⁹/L.
Results: Effect of FF/UMEC/Vi vs UMEC/Vi on each transition

<table>
<thead>
<tr>
<th>Event State Transition</th>
<th>HR</th>
<th>95% CI</th>
<th>Effect of FF/UMEC/Vi vs UMEC/Vi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event-free/pneumonia to exacerbation state</td>
<td>0.77</td>
<td>(0.71, 0.84)</td>
<td>Risk of exacerbations reduced</td>
</tr>
<tr>
<td>Event-free/exacerbation to pneumonia state</td>
<td>1.46</td>
<td>(1.13, 1.91)</td>
<td>Risk of pneumonias increased</td>
</tr>
<tr>
<td>Event-free to death state</td>
<td>0.49</td>
<td>(0.28, 0.86)</td>
<td>Risk of death during event-free state reduced</td>
</tr>
<tr>
<td>Exacerbation/pneumonia to death state</td>
<td>1.03</td>
<td>(0.35, 3.07)</td>
<td>Similar risk of death during respiratory event</td>
</tr>
<tr>
<td>Exacerbation/pneumonia to event-free state</td>
<td>0.98</td>
<td>(0.93, 1.04)</td>
<td>Similar time to resolution of respiratory event</td>
</tr>
</tbody>
</table>

- HRs are for a male/female patient with a baseline blood eosinophil level of 200 cells/µL from the non-Asian region.
- HRs were the same for a male or female patient.

CI, confidence interval; HR, hazard ratio.
Conclusions

- Exacerbation events occur more frequently than pneumonia events. While pneumonia events are slightly longer, on average patients with COPD in all three arms of the IMPACT study still spent a longer time in the exacerbation state vs pneumonia state over 1 year.

- Treatment with FF/UMEC/VI vs UMEC/VI
  - Reduced the risk of exacerbations, and the risk of death from event-free state
  - Increased the risk of pneumonia
  - Did not statistically change the time to resolution of exacerbation/pneumonia events or the risk of death during an exacerbation/pneumonia event
  - Overall, provided a favorable benefit:risk profile

- Markov modeling enables a greater understanding of the benefit–risk profile of treatment and may help model costs at a patient level.

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