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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:[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.

1. Lipson D, et al. *N Engl J Med* 2018;3;378:1671–80; 2. Lipson DA et al. *Am J Resp Crit Care Med* 2020;201:1508–16.

Background: The IMPACT trial

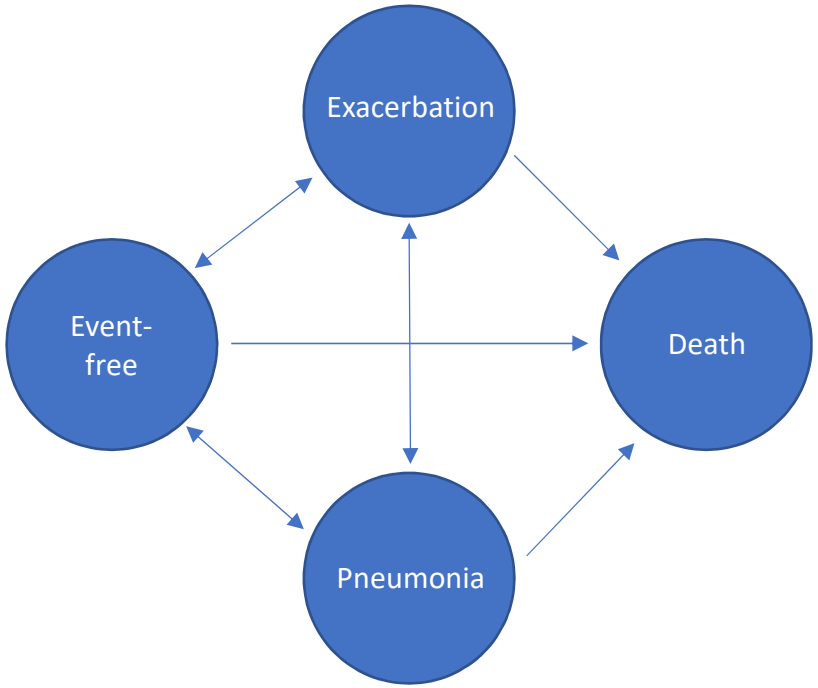
- IMPACT was a Phase 3, randomized, double-blind, 52-week trial comparing once-daily FF/UMEC/VI with FF/VI and UMEC/VI in patients (N=10,355) at least 40 years of age with:
  - Symptomatic COPD (CAT score ≥10)
  - FEV_1 <50% predicted and ≥1 moderate or severe exacerbation in the prior year, or FEV_1 50–<80% predicted and ≥2 moderate or ≥1 severe exacerbations in the prior year

CAT, COPD Assessment Test; FEV_1, forced expiratory volume in 1 second.

Lipson D, et al. *N Engl J Med*. 2018;3;378:1671–1680.

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

	FF/UMEC/VI		FF/VI		UMEC/VI	
	Male	Female	Male	Female	Male	Female
Mean number of exacerbations per year	1.03	1.27	1.15	1.42	1.35	1.65
Mean length of a single exacerbation event	14.1 days	14.7 days	14.1 days	14.7 days	13.9 days	14.5 days
Mean number of pneumonia events per year	0.07	0.06	0.06	0.06	0.05	0.05
Mean length of a single pneumonia event	18.3 days	18.7 days	18.2 days	18.5 days	17.6 days	17.8 days
Probability of death during 1 year	0.98%	0.50%	1.26%	0.57%	1.89%	0.87%

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 FEV_1; no history of pneumonia; former smoker; eosinophils 222 cells/µL; baseline neutrophils 5.2 $10e^9$/L.

Results: Effect of FF/UMEC/VI vs UMEC/VI on each transition

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

- 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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