"ONCE-DAILY SINGLE-INHALER TRIPLE VERSUS DUAL THERAPY IN PATIENTS WITH COPD"

David A. Lipson et al, May 3, 2018
The New Medical Journal of England

By Caitlin Foulds

Introduction

- Primary Objective
  - *Evaluate effects of 3 drug combinations, once a day for 52 weeks on the rate of moderate or severe Chronic Obstructive Pulmonary Disease (COPD) exacerbations*
    - Triple therapy (ICS, LAMA, LABA) and 2 dual therapies (ICS+LABA or LABA+LAMA)
      - *ICS – Fluticasone furoate (F)*
      - *LAMA – Umeclidinium (U)*
      - *LABA – Vilanterol (V)*

- Basis behind study: Triple therapy is recommended
  - *Currently inhalers taken multiple times a day compared to a single triple therapy inhaler*

Patient Selection

- Symptomatic COPD
- 40 or more years old
- COPD assessment test (CAT) score >/=10
- FEV1 of <50% normal + history of one exacerbation in past year (moderate/severe)

OR

- FEV1 of 50-80% normal + history of least 2 mod exacerbations or 1 severe in past year

Method

- Phase 3 randomised, double blind, parallel study and multicentre trial
  - *37 different countries from June 2014 to July 2017*
- 10,355 patients were recruited
- Compared
  - *Triple therapy:*
    - Fluticasone furoate (100ug) + Umeclidinium (62.5ug) + Vilanterol (25ug)
  - *Dual therapy:*
    - Fluticasone furoate + Vilanterol
    - Umeclidinium + Vilanterol
- Single dry powdered Inhaler
  - *Own brand of GlaxoSmithKline (Ellipta)*

- Primary Efficacy Outcome
  - *Recorded symptoms in electronic diary each morning*
- Secondary Efficacy Outcome
  - *Measured FEV1 (lung function)*
  - *St George's Respiratory Questionnaire score at start and end*
  - *Time from start till 1st exacerbation in patients with a blood eosinophil level of at least 150ml baseline*
  - *Dyspnoea (using Transition Dyspnoea Index)*
  - *Time from start till any cause death*

- Pre-trial
  - *Patients continued own medication for 2 weeks during the 2 week run in period before randomisation.*
- Baseline CXR
  - *Radiologists were blinded*

Results

- The rate of moderate/severe exacerbations was significantly lower with triple therapy compared to both dual therapies
- Significant differences of SGRQ score from base measure to the end between triple therapy and the two dual therapies.
  - *Larger percentage (42%) of triple therapy patients had a decrease of SGRQ score of 4 points compared to the other two (34%)*
- Mortality of all causes were significantly lower in therapy with fluticasone furoate than dual therapy umeclidinium-vilanterol
  - *Low hazard ratios of 0.58 and 0.61 between triple and U+V and F+V and U+V*
- Higher incidence of pneumonia in the ICS groups than in U+V group

ANALYSIS

Patient Analysis using PICO framework

- Patient:
  - *Demographics*
    - 40 years old or more (mainly 65)
    - Symptomatic COPD
    - Smokers
    - BMI>25
  - *Condition*
    - COPD
- Intervention:
  - *Triple therapy*
- Comparison:
  - *Dual therapies in a single inhaler*
- Outcome:
  - *Reducing moderate/severe exacerbations*
  - *Lung function*
  - *Quality of life (STRQ)*
  - *Dyspnoea*

Method Analysis

- Randomised trial
  - *Method did not specify how*
- Concealment methods
  - *Radiologists and external adjudicator committee*
  - *Unable to identify treatment allocation*
- Measuring Outcomes
  - *Primary outcome*
    - Symptomatic diary –valid
    - Clear criteria for differentiating exacerbations into moderate and severe

- Withdrawals
  - *Starting patient population 10,355*
  - *7991 (77%) completed, receiving investigational medication*

  Deaths
  - *Triple (1%), F+V (1%), V+U (2%)*
  - *Didn't affect outcome due to number*

- Comparable results between sites
  - *No mention of differences between 37 countries*
- Inclusion and exclusion criteria
  - *Minimal inclusion criteria included, not clear on exclusion criteria*

Results Analysis

- Clinical significance and relevance
  - *95% confidence intervals in primary outcome results*
  - *P<0.001, statistically significant*
  - *Conclusions of study are accurate and relevant to results and objective*
- Application to patient group and clinical use
  - *Patients have COPD but varies with drug type and clinical use*

Conflict of Interest & Sponsors

- Funded and sponsored by GlaxoSmithKline
- Along with academic partners, helped design the study

- Lead author and others
  - *Employee of GlaxoSmithKline*
  - *Shareholders*

DISCUSSION

Questions

- The aim
  - *Clarity and included in methodology*
- Lack of control group to make it a RCT
- Specification of format of electronic diary
  - *formulating notes or prompted questions*
- Questionable time lines for ECG measurements, vital signs, chemical and haematologic assessments
  - *4, 28, 52 weeks and 16, 28, 52 weeks*
- Deaths possibly linked to the treatment
  - *They only mention cardiovascular, respiratory and COPD deaths.*
- “Robust approach" was used to aid in understanding adverse events of pneumonia
- The lead author has referenced some of his own papers
  - *one of them favours the use of triple therapy over dual therapy*

Proposals

- Control group
  - *Potential control with no medication –unethical*
  - *Continuation of their original treatment; comparison to trialled treatment*
- Electronic diary
  - *Clarify form of electronic diary*
  - *Prompted option could mean missing some symptoms*
    - Possible other section at bottom for additional notes
  - *Free text it is harder to compare patients symptoms for their exacerbations if they can't remember or bring to mind what symptoms they had*

Conclusion

Overall a good paper

- Their primary objective was answered from results and the results could be easily interpreted.
- Adequate double blinding people involved
  - *Radiologists and an independent adjudicator committee*
- Identifying opposing studies and thinking of the difference between them
  - *What could have influenced the conflicting results.*
- Good some academics volunteered their involvement with the sponsor

However

- Wasn't clearly written and writing style difficult to understand
- Could involve more detail in method
  - *About the randomisation of patients and how treatment was and how the data was recorded on the electronic diary*

THANKS FOR LISTENING

Any Questions?