A UK Retrospective Comparative Effectiveness Study Assessing Treatment and Rates of Exacerbation in a Chronic Obstructive Pulmonary Disease Population

A study comparing the effects of treatments in patients with chronic obstructive pulmonary disease (COPD) in a real world setting, using the Clinical Practice Research Datalink (CPRD) linked with Hospital Episode Statistics (HES)

Background/Rationale: For people with chronic obstructive pulmonary disease (COPD), standard maintenance inhaler treatments consist of inhaled corticosteroids (ICS) and long acting bronchodilators (principal classes include long-acting beta-2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs)). Clinical trials indicate that adding ICS to treatment combinations including triple therapy (ICS/LABA/LAMA) may provide rapid and sustained improvements (1-3). However, long-term use of ICS may be associated with adverse effects (4-5). There is a need for real-world effectiveness data regarding COPD treatment in order to demonstrate that improvements in lung function translate into reductions in exacerbations, hospitalizations or morbidity.

Objectives: The main objective in this study was to assess the impact of ICS therapy on exacerbation outcomes in a COPD population and identify which patient subgroups may achieve the greatest benefit. We hypothesized that therapy combinations which include ICS, including triple therapy (ICS/LABA/LAMA), may be more effective at preventing acute exacerbations in COPD (AECOPD) than non-ICS including combinations. The comparisons of interest in this study were based on real world medical praxis: 1. ICS/LABA/LAMA vs LABA/LAMA, 2. ICS/LABA/LAMA vs LAMA, 3. ICS/LABA vs LABA/LAMA, and 4. ICS/LABA vs LAMA.

Study design: Cohort study examining comparative effectiveness where the study is conducted in two phases. Phase I described and quantified patients on different ICS containing and non-ICS containing therapy combinations using Global Initiative for Chronic Obstructive Lung Disease (GOLD 2017) assessment tools. Phase II estimated time to exacerbation events per treatment type (ICS or non-ICS containing therapies at a class level) during the follow-up time where risk factor profiles also were updated yearly.

Data source: Clinical Practice Research Datalink (CPRD) GOLD, Hospital Episode Statistics (HES) and Office for National Statistics (ONS) mortality data.

Study population: Patients ≥40 years-old, with a validated diagnosis of COPD registered between the 1st of January 2006 and the 29 February 2016. Eligible patients must have a smoking history, data recorded at least 12 months prior to the study index date and have Up-To-Standard (UTS) data as defined by CPRD.

Exposure(s): New users of ICS containing (ICS/LABA/LAMA and ICS/LABA) regimens and non-ICS containing regimens (LABA/LAMA, LAMA monotherapy).

Outcome(s): Exacerbations of COPD (AECOPD), were defined using a published algorithm, including both GP treated and hospitalised COPD events(6).

Statistical methods: Phase I: Descriptive statistics were used to characterize patients according to baseline demographic, clinical and treatment factors and to study treatment patterns during follow-up. Phase II: Analytical statistics were used to estimate time to exacerbation events per treatment type during the follow-up period. These statistics included extended Cox regression models (HR), marginal structural models (MSM) and inverse probability weighting stabilized (IPW-S). Sensitivity analyses assessed follow-up time in incremental periods in order to examine the impact of drug type and drug changes over time. We analysed associations between demographic and clinical factors and treatment received.

Results: The final analytical model (Phase II) included n=45 958 COPD subjects where 55% were male. The majority were in GOLD grade 2 (52%), and the most prevalent baseline comorbidity was concomitant asthma 38% followed by ischaemic heart disease 18%. ICS containing treatment regimens demonstrated HRs close to 1.00 across all comparisons. Subgroup analyses illustrated a more nuanced effect of ICS on exacerbation: in the comparison between ICS/LAMA/LABA vs LABA/LAMA by GOLD grades 1,2, and 3+ [HR 0.79; 95% CI (0.70-0.88)], [HR 1.04; 95% CI (0.97-1.11)], and [HR 1.15; 95% CI (1.05-1.26)] were the risk estimates for AECOPD over time respectively.

Conclusion: Benefit of ICS treatment in COPD subjects was noted among healthier subjects with less severe airflow obstruction, those over the age of 75 years, and those without concomitant asthma. Whilst the MSM goes some way to improving the standard Cox model, it still does not completely address the main confounding issue of more severe patients receiving more treatment thus suggesting that even using this methodology does not fully elicit the benefit of ICS treatment.

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