

Comparative Effectiveness and Safety of Fluticasone-Umeclidinium-Vilanterol and Beclomethasone-Glycopyrronium-Formoterol Single-Inhaler Triple Therapies for COPD: Real-World Observational Study [Letter]

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Dear Editor

We read with interest the manuscript by Cherian et al¹ that reports on a comparison of real-world effectiveness and safety of two single-inhaler triple therapies (SITT) in patients with COPD in the UK. This large observational study builds upon the increasing volume of real-world differentiation data amongst SITTs,^{2–6} in the absence of any head-to-head randomised controlled trials between the SITTs.

The authors conclude that

initiating triple therapy with FUV was associated with a lower incidence of moderate and severe exacerbations than with BEGF.

On the other hand, the incidence of a severe pneumonia requiring hospitalisation was higher with FUV among GOLD Group E subjects or those whose blood eosinophil count is not elevated.

We would like to highlight important areas that may aid the interpretation of the comparative effectiveness results, specifically concerning 1) the interpretation of the safety outcomes and 2) limitations of using real-world retrospective datasets for safety outcomes.

In regard to the interpretation of safety outcomes, the authors observed that patients initiated on fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI, or FUV) had a 9% lower risk of moderate and severe exacerbations than patients initiated on beclomethasone/glycopyrronium/formoterol fumarate (BDP/GLY/FORM, or BEGF) (adjusted hazard ratio [HR] 0.91, 95% CI 0.89–0.93). This primary effectiveness outcome is clearly stated, unambiguous and in line with other database studies comparing FUV with BEGF or other similar SITTs (eg, budesonide/glycopyrronium/formoterol [BUGF])^{2–6} By contrast, the reporting of the primary safety outcome (the risk of severe pneumonia requiring hospitalisation) might be difficult for busy practitioners to assess from reading the paper. While the adjusted HR comparing FUV with BEGF was reported as 1.06 (95% CI 0.99–1.13), the authors did not mention that the result was statistically non-significant between FUV and BEGF in the overall population of over 74,000 patients. The authors go on to highlight the subgroup analysis for the subpopulation of GOLD Group E and those with a blood eosinophil count ≤ 300 cells/ μ L.

In addition to making clear that there was no statistically significant difference between SITTs for the co-primary safety outcome of severe pneumonia requiring hospitalisation (based on adjusted HR and 95% CI), there are other aspects that we feel are important to clarify.

Firstly, we would like to remind readers that GOLD Group E classification only applies to patients initially assessed who are naïve to treatment based on symptoms and exacerbation history, designed to guide initial pharmacological choices.⁷ According to the baseline characteristics in the study by Cherian and colleagues,¹ all patients had prior

maintenance treatment. Hence, the classification of patients by GOLD Group E in this study appears to be erroneous. Moreover, in the UK, all SITTs are licenced only for patients who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β_2 -agonist or a combination of a long-acting β_2 -agonist and a long-acting muscarinic antagonist. The GOLD Group E classification (from 2025) has been incorrectly attributed to patients already receiving maintenance therapy who continue to experience exacerbations (≥ 2 moderate exacerbations or 1 severe exacerbation) within the previous 12 months.

A spirometric assessment of the degree of airflow obstruction (% predicted FEV₁) remains the standard assessment of COPD severity, useful at a population level to predict outcomes and drive treatment decisions (GOLD Grade 1, 2, 3, 4). The availability of such data for 89% of subjects in this large study is a unique strength.

While the primary effectiveness outcomes across these subgroups in the study by Cherian et al were consistent with results for the overall population, the risk of severe pneumonia requiring hospitalisation differed.¹ In those patients with more frequent baseline exacerbations (erroneously described as GOLD Group E), the risk of pneumonia associated with FUV was higher than BEGF (adjusted HR 1.14, 95% CI 1.06–1.24), whereas, in those patients with more severe airflow obstruction at baseline ($<50\%$ predicted FEV₁), there was no statistically significant difference in the risk of severe pneumonia between FUV and BEGF (adjusted HR 1.04, 95% CI 0.94–1.15).

Similarly, the findings for the subgroups by baseline blood eosinophils are not in line with previous comparative effectiveness data with SITTs.⁵

We consider the focus on these subpopulations to be misleading, as the reliability of the safety results within the populations is limited due to key study design issues.

Additionally, we note inconsistencies in the reporting of several statistics. Unlike the effectiveness data (where the authors have reported the 1-year cumulative incidence rate of exacerbation between FUV and BEGF [60.54% on FUV and 64.12% on BEGF]), the 1-year cumulative incidence of severe pneumonia is not stated in the paper but left to the reader to discern from the cumulative incidence graph. Whilst the groups in each graph are comparative, no statistical tests have been applied.

While the observation of pneumonia is recognised as a class effect in patients with COPD on inhaled corticosteroid regimens, we would nonetheless kindly request clarification for readers on the safety results. Given that the busy healthcare professional may just read the abstract, and that AI-generated medical summaries are based on text rather than raw data, we ask the authors to consider clarifying the above-mentioned issues.

Regarding methodological limitations for assessing safety outcomes, propensity score matching was applied to the overall cohorts, but it is not specified within subgroups. This means that even with the stratification weights from the probability of treatment propensity scores, comparisons are susceptible to significant confounding, since patients within a subgroup may be spread across propensity score-defined strata. Furthermore, there is an omission in the propensity score matching of significant risk factors for pneumonia, such as matching on clinical site/region to mitigate regional variability in pneumonia risk (as demonstrated by NHS England data).⁸ This contrasts with the design of the comparative effectiveness study by Feldman et al,⁵ which accounted for such factors and found identical hazard of first admission to hospital with pneumonia when comparing FUV with BUGF in the overall population (HR 1.00, 95% CI 0.91 to 1.10) and across all subgroups analysed.

In summary, we welcome the observations provided from this new real-world SITT comparison and its contribution to the growing body of evidence differentiating effectiveness within the class. Careful consideration of the methodological limitations is essential when interpreting the data. We read the results cognisant of these limitations. However, given the importance of continually aiming for optimal treatment options for patients with COPD, we ask the authors to comment on the safety findings in the overall population and the reliability of safety data within the subpopulations.

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