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RESPONSE TO LETTER

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

Mathew Cherian[1,2], Samy Suissa[2,3]

[1]Department of Medicine, Respiratory Division, McGill University, Montreal, Quebec, Canada; [2]Centre for Clinical Epidemiology, Lady Davis Institute-Jewish General Hospital, Montreal, Quebec, Canada; [3]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada

Correspondence: Samy Suissa, Email samy.suissa@mcgill.ca

Dear editor

We thank Prof. Wedzicha and Dr. Kiran for their commentary on our work, in which they question some safety findings reported in our real-world comparative effectiveness and safety study of two single-inhaler triple therapies (SITT), namely fluticasone-umeclidinium-vilanterol (FUV) versus beclomethasone-glycopyrronium-formoterol (BEGF), in patients with COPD from the UK.[1,2]

First, to increase transparency, the overall hazard ratio (HR) of severe pneumonia (requiring hospitalization) comparing FUV to BEGF of 1.06 (95% CI; 0.99–1.13) was explicitly reported in the Abstract, the Results section of the full text, and in Table 4.[2] It clearly does not reach the threshold of "statistical significance" as the confidence interval includes unity. Note that nowhere in the paper did we use the term "statistical significance" or perform "statistical tests", neither for positive nor negative results, as we believe that readers understand the inference from the confidence interval. Additionally, for all outcomes, the overall result was presented before subgroup findings, ensuring that the reader clearly encounters the overall result prior to the subgroup findings. As such, our conclusions and discussion focused on the clinically relevant subgroups that showed an elevated risk.

Second, the authors consider our focus on subgroup analyses as "misleading". However, our subgroup analyses for the effectiveness and safety outcomes were chosen to reflect the very clinical characteristics that GOLD recommends clinicians weigh when initiating pharmacological treatment decisions,[3] including exacerbation history and eosinophil count. Thus, for these key GOLD factors, we reported the HR of severe pneumonia comparing FUV to BEGF of 1.14 (95% CI 1.06–1.24) among those classified as "GOLD Group E" and of 1.10 (95% CI 1.02–1.19) among those with a blood eosinophil count ≤300 cells/μL.

Third, Wedzicha and Kiran raise an important point regarding the technical application of the GOLD "Group E" label, defined until 2026 as two or more moderate or one severe exacerbation in the year prior to treatment initiation and proposed for initial treatment. We acknowledge the technical imprecision of applying the GOLD Group E label to patients already receiving maintenance therapy; however, consistent with its widespread use in the GOLD framework, we used it deliberately as a clinically recognizable shorthand for a high exacerbation burden phenotype that is immediately meaningful to the clinicians for whom this research is intended.

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Fourth, as Wedzicha and Kiran observe, UK coverage criteria require prior maintenance therapy before SITT initiation. Incidentally, our previous study in this population found that 44% of initiators of SITT in the UK had no maintenance therapy in the year prior to initiation, and 60% had no prior exacerbation.[4] Nonetheless, our subgroup analysis of "Group E" patients, who exacerbate despite existing treatment, reflects the normative clinical reality of SITT prescribing in the UK and many other jurisdictions with similar coverage criteria. In this context, this subgroup definition may be more ecologically valid for this specific research question. Regardless of nomenclature, we believe the underlying clinical characteristic of persistent exacerbations prior to SITT initiation remains a meaningful and clinically relevant stratification variable in COPD treatment research.

Fifth, the authors raise regional variation in pneumonia risk as a methodological consideration. We agree this is a reasonable point in the context of some observational studies, though unlikely for studies of head-to-head comparisons of inhalers from the same class. For regional variation in pneumonia risk to introduce confounding in our analysis, it would need to be differentially distributed between FUV and BEGF initiators across regions, so that patients initiating one SITT would need to be systematically concentrated in regions with inherently higher baseline pneumonia risk than patients initiating the other. While possible, we find this rather unlikely. Notably, the fact that a prior study found no difference in the risk of pneumonia between FUV and another SITT, budesonide-glycopyrronium-formoterol (BUGF), does not imply that there should also be no difference in this risk between FUV and BEGF, the beclomethasone-based SITT.[5]

Regarding the impact of the stratified analyses after propensity scores weighing, we note that these concerns would apply equally to the effectiveness findings, which the letter writers acknowledged as valid and consistent with existing literature. The selective application of this methodological concern exclusively to the safety findings, while accepting identical methodology for the effectiveness findings, warrants consideration. Furthermore, the stratified analyses in the study cited by the authors – such as the finding of no difference in the risk of an exacerbation between FUV and BUGF among patients with no prior exacerbations, those with no prior maintenance therapy, or those treated by a pulmonologist[5] – used the same approach and did not seem to attract a similar methodological concern.

In all, the primary goal of our study was not to identify a universally superior single-inhaler triple therapy, but rather to contribute data that may inform the selection of the most appropriate therapy for a given patient, given both FUV and BEGF are effective therapies with an important role in COPD management. When comparing outcomes of equivalent clinical severity – specifically severe COPD exacerbations and severe pneumonia, both requiring hospitalization – the magnitude of effect in our study was broadly similar but in opposite directions, favoring FUV for exacerbation prevention and BEGF for pneumonia safety in specific subgroups. Rather than reflecting a limitation, we believe this trade-off highlights the potential clinical value of both therapies and suggests that the choice between these agents need not be universal but may instead be guided by individual patient characteristics and risk profiles. We acknowledge that these findings require validation and that there is some asymmetry in this trade-off – the exacerbation benefit of FUV was consistent across all subgroup analyses while the severe pneumonia signal was observed only in specific subgroups. We therefore view these data as contributing towards a personalized treatment paradigm and hope they stimulate further research into identifying which patients with COPD are most likely to benefit from different treatment options.

Disclosure

Samy Suissa attended advisory committee meetings for Atara, Novartis and Panalgo, and received speaking fees from Covis Pharma and Novartis. Mathew Cherian attended advisory board meetings for AstraZeneca, GlaxoSmithKline, Sanofi, and Chiesi-Methapharm, and received speaking fees from AstraZeneca and Sanofi. The authors report no other conflicts of interest in this communication.

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