STUDENTS' CORNER
LETTER TO THE EDITOR

Ensifentrine, a novel dual phosphodiesterase 3 and 4 inhibitor in the treatment of chronic obstructive pulmonary disease

Hassan Farooq, Uzair Naeem, Riva Khan

Dear Editor, Chronic obstructive pulmonary disease (COPD) is a disease related to the respiratory system which causes bronchoconstriction and excess release of mucous leading to airway remodelling and obstruction. This condition is also involved with airway inflammation and oedema. Statistically, according to WHO, chronic obstructive pulmonary disease is the third leading cause of death worldwide.[1]

Over the past four decades, standard-of-care COPD treatment has been based on inhaled short- and long-acting bronchodilators [including long-acting β2 agonists (LABAs) and long-acting muscarinic receptor antagonists (LAMAs)] and inhaled corticosteroids.[1] Still, patients may remain largely symptomatic due to the wide range of spectrum of COPD complications, often requiring concomitant use of both bronchodilators and anti-inflammatory drugs. Furthermore, their use is limited due to several reasons. They are unable to reverse airway wall damage and they cannot stimulate lung regeneration. Also, there is very limited sensitivity of the inflamed airways to the available medical options. Lastly, there are side effects associated with their use hence these reasons limit their use.[2]

Ensifentrine (RPL554) is the latest FDA-approved advancement available for COPD. It is a novel drug that works by dual inhibition of phosphodiesterase (PDE) 3 and 4 enzymes (PDE3, PDE4) and is delivered via inhalation. Inhibitors of PDE3 and PDE4 target multiple respiratory functions at the cellular and tissue level. PDE3 regulates cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) levels in the airway smooth muscles, which mediates bronchial tone. PDE4 regulates cAMP levels in the airway cells associated with inflammation and is involved in activation of these cells. PDE4 inhibitors also stimulate the cystic fibrosis transmembrane conductance regulator (CFTR) and improve bronchial epithelial cell ciliary movements.[3] This dual inhibition of PDE3 and PDE4 enzymes results in a synergistic effect, making Ensifentrine the first ever drug to treat both COPD associated inflammation as well as bronchoconstriction.[4]

Ensifentrine not only delivers significant improvement in lung function as sole therapy at doses of 3 mg and 6 mg[4] but also its pivotal role as an adjuvant to existing treatment regimens comprising long-acting muscarinic antagonists (LAMA) or long-acting beta-agonists with inhaled corticosteroids (LABA+ICS), as well as enhancing their combined efficacy over longer periods[5] has now been clearly demonstrated and documented. Moreover, it may well be therapy that reduces exposure to bronchodilators or inhaled steroids in such patients on maximal therapy.

On this basis, we call for more research and clinical trials to ensure maximum benefit from this breakthrough.

Disclaimer: None.

Conflict of interest: None.

Funding disclosure: None.

DOI: https://doi.org/10.47391/JPMA.31152

References

1. Keam SJ. Ensifentrine: First Approval. Drugs 2024;84:1157-63. doi: 10.1007/s40265-024-02081-w.
2. Jiang Z, Zhu L. Update on molecular mechanisms of corticosteroid resistance in chronic obstructive pulmonary disease. Pulm Pharmacol Ther 2016;37:1-8. doi: 10.1016/j.pupt.2016.01.002.
3. Faruqi MA, Khan MMKS, Mannino DM. Perspectives on Ensifentrine and Its Therapeutic Potential in the Treatment of COPD: Evidence to Date. Int J Chron Obstruct Pulmon Dis 2024;19:11-6. doi: 10.2147/COPD.S385811.
4. Yappalparvi A, Balaraman AK, Padmapriya G, Gaidhane S, Kaur I, Lal M, et al. Safety and efficacy of ensifentrine in COPD: A systemic review and meta-analysis. Respir Med 2025;236:107863. doi: 10.1016/j.rmed.2024.107863.
5. Dransfield M, Marchetti N, Kalhan R, Reyner D, Dixon AL, Rheault T, et al. Ensifentrine in COPD patients taking long-acting bronchodilators: A pooled post-hoc analysis of the ENHANCE-1/2 studies. Chron Respir Dis 2025;22:14799731251314874. doi: 10.1177/14799731251314874.

4th Year MBBS Student, Ameer-ud-Din Medical College, Lahore, Pakistan.
Correspondence: Hassan Farooq. e-mail: hassanfarooqijaz@gmail.com
ORCID ID: 0009-0004-9784-0088

Submission completed: 10-05-2025 **1st Revision received:** 17-05-2025
Acceptance: 30-07-2025 **2nd Revision received:** 29-07-2025

Author Contribution:
HF: Topic selection and literature review.
UN: Writing.
RK: Literature review and editing.