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EDITORIAL

Triple inhaled therapy in COPD: prevention of exacerbations versus the risk of pneumonia. Critical reflections from GOLD and clinical evidence

Triple terapia inhalada en EPOC: prevención de exacerbaciones frente al riesgo de neumonía. Reflexiones críticas desde GOLD y la evidencia clínica

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In this issue of *NCT*, Rivas Ibargüen et al.[1] report Triple vs dual therapy in patients with COPD: a systematic review and meta-analysis, which examines the evidence on triple therapy (TT) with an inhaled long-acting muscarinic antagonist plus long-acting β2-agonist and inhaled corticosteroid (LAMA/LABA/ICS) vs dual therapy (DT) with LAMA/LABA. The major contribution of the authors is to provide an updated assessment of the performance of TT in terms of clinical efficacy and safety, particularly adverse events such as pneumonia, while also evaluating outcomes according to fixed vs open TT regimens and according to low or high exacerbation risk. Alongside lung function and quality of life, exacerbations of chronic obstructive pulmonary disease (COPD) remain a major determinant of morbidity, mortality, and healthcare resource use worldwide. In the most recent reports of the Global Initiative for Chronic Obstructive Lung Disease (GOLD 2026), exacerbations have been consolidated as the main prognostic driver of the disease, regardless of the degree of airflow obstruction.[2] This approach is reflected in the redefinition of group E, in which a single previous moderate exacerbation is sufficient for classification because of its local and systemic impact.

GOLD recommends inhaled TT (LAMA/LABA/ICS) in patients with COPD who continue to experience exacerbations despite dual bronchodilation, particularly when the blood eosinophil count is ≥ 300 cells/μL, or ≥ 150 cells/μL in the presence of recurrent exacerbations.[2] This recommendation reflects the accumulated evidence showing a consistent reduction in moderate and severe exacerbations after the addition of an ICS, although at the cost of an increased risk of pneumonia. This risk-benefit balance is particularly relevant in the context of the new group E.

The impact of moderate exacerbations, defined by the need for antibiotics and/or systemic corticosteroids, is no longer considered benign. Longitudinal studies have shown that a single exacerbation is associated with accelerated decline in forced expiratory volume in 1 second, poorer quality of life, an increased risk of subsequent exacerbations, and higher long-term mortality.[1] This recognition underpins the new GOLD paradigm based on group E: preventing exacerbations

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Table 1. Key characteristics of representative studies of triple therapy in COPD

Study	Previous exacerbations	Eosinophils at baseline	Pneumonia as an adverse event vs DT
TRIBUTE[3]	≥ 2 moderate or ≥ 1 severe (19%)	Not stratified (240 ± 200)	No increase (0%)
IMPACT[4]	≥ 2 moderate or ≥ 1 severe (73%)	57% ≥ 300	3% increase
KRONOS[5]	≥ 2 moderate or ≥ 1 severe (7%)	≥ 150 (52%); ≥ 300 (~27%)	No increase (0%)
ETHOS[6]	≥ 2 moderate or ≥ 1 severe (56.5%)	≥ 150 (60%); ≥ 300 (14.5%)	1.5% increase
Meta-analysis by Mammen et al.[7]	Predominantly high risk	≥ 150 and ≥ 300	HR, 1.41

COPD: chronic obstructive pulmonary disease; DT: dual therapy; HR: hazard ratio.

from the earliest stages, even when the patient has not required hospitalization.

The main randomized clinical trials supporting the use of TT (TRIBUTE, IMPACT, KRONOS, and ETHOS) despite their strengths and comparatively fewer limitations, share methodological characteristics that influence interpretation of their results.[3-7] In general, these studies enrolled highly selected populations with a high exacerbation burden during the previous year and a considerable proportion of patients with elevated blood eosinophil counts.

In IMPACT, for example, more than 70% of participants had experienced either ≥ 2 moderate exacerbations (47%) or ≥ 1 severe exacerbation in the previous year (26%), and 43% had low eosinophil counts (< 150 cells/µL); the benefits of TT were clearly greater in patients with eosinophil counts ≥ 300 cells/µL.[3] Similar findings were observed in TRIBUTE, which included patients who were not frequent exacerbators and were not eosinophilic, as well as in ETHOS, which included noneosinophilic exacerbators, and KRONOS, which included nonexacerbators with a tendency toward eosinophilia.[3,5,6] One consistent finding across studies was an increased risk of pneumonia, particularly with regimens containing fluticasone.[3,4] This adverse effect has been one of the main criticisms of widespread ICS use in COPD.

In contrast, the real-world retrospective study by Suissa et al.[8] provides a complementary and, in some respects, discordant perspective. Based on a United Kingdom population database containing medical records for more than 50 million patients from over 1800 centers, with patients managed in primary care, this analysis included a less selected population with moderate/severe exacerbations during the previous year; 29% of the population had eosinophil counts of 242 ± 210 cells/µL, without systematic eosinophil stratification. In this setting, TT was not associated with a significant reduction in mortality but was associated with a 0.5% increase in the risk of pneumonia and with an increased risk of severe pneumonia (HR, 1.46). The Datalink registry on which this study was based dates back to 2002, and it is likely that many patients received open TT in situations in which it may not have been warranted. This may partly explain the greater harm observed with TT and raises the possibility of inappropriate use of TT.

Putting the concern about pneumonia into perspective, from a clinical and prognostic standpoint, preventing COPD exacerbations should remain a priority, even in the face of a modestly increased risk of pneumonia. Exacerbations have cumulative effects, accelerate disease progression, and are associated with greater long-term mortality. In contrast, ICS-related pneumonia, although clinically relevant, is generally an acute and potentially reversible event. Therefore, in appropriately selected patients, particularly those in group E with marked eosinophilia, the risk-benefit balance clearly favors protection against exacerbations, in line with the strategy proposed by GOLD.

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