[Point and Counterpoint]

CHEST

POINT:
Should an Attempt Be Made to Withdraw Inhaled Corticosteroids in All Patients With Stable GOLD 3 ($30\% \leq FEV_1 < 50\%$ Predicted) COPD? Yes

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ABBREVIATIONS: GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist

> "One of the first duties of the physician is to educate the masses not to take medicine."
> (Sir William Osler, *Aphorisms*, 1961)

Inhaled corticosteroids (ICSs) are overused to an unjustified degree in patients with COPD. Over the past two decades they have been the dominant treatment option for COPD.[1] A recent analysis of a large primary care database in the United Kingdom examined the first maintenance therapy prescription for 29,815 patients with GOLD (Global Initiative for Chronic Obstructive Lung Disease) A/B COPD (based on the GOLD 2016 classification) and excluding patients with recorded asthma. Contrary to guidelines, an average 63% received an inhaled corticosteroid-based regimen as their initial therapy.[2]

ICS treatment for the majority of patients with COPD makes little biological sense. ICS is effective against eosinophilic airway inflammation, but neutrophilic inflammation is the dominant "endotype" in patients with severe COPD.[3-5] Neutrophils are not only resistant to the antiinflammatory effects of ICS, but there is increasing evidence that the combination of neutrophils, bacteria, and ICS results in harm.[4-6] ICS disables some neutrophil antimicrobial responses, leading to increased airway bacterial load with potential implications for increased pneumonia or exacerbation risk.[4-6] The converse is that for the minority of patients with COPD who have eosinophilic inflammation, which is not associated with bacterial airway infection, ICS can be highly beneficial.[4-7] This argues for a personalized medicine approach whereby ICS is withdrawn in the majority with neutrophilic disease, where there will be minimal benefit, and continued in those who have eosinophilic disease and a proportion who experience objective benefit after stepping up from long-acting β_2-agonist/long-acting muscarinic antagonist (LABA/LAMA).[3] Such personalized approaches should be the future of COPD treatment.[3]

The recent GOLD strategy has therefore rightly relegated the role of ICS to that of an add-on therapy to combined bronchodilators in patients with frequent exacerbations (GOLD D).[8] The complete absence of ICS as an option for patients with GOLD B COPD (those with symptoms but without frequent exacerbations) is recognition that ICS have only limited effects on lung function and are not an effective therapy for breathlessness.[8,9] Studies comparing ICS/LABA with LABA/LAMA in breathless patients have consistently shown that combined bronchodilators should be the preferred option.[8,9]

If these recommendations are adhered to, this should mean a greatly reduced role for ICS, but what to do with the large numbers of patients with COPD who are currently treated with ICS/LABA or "triple therapy"? It must be right, in view of the long-term safety issues associated with ICS, and the limited evidence of efficacy compared with combined bronchodilators, that all patients are at least considered for withdrawal. This is certainly the view of GOLD that incorporates the option of ICS withdrawal into the 2017 GOLD D algorithm (Fig 1).[8]

I recognize this is an area of controversy. The counterargument to the above position is that ICS are effective drugs in reducing exacerbations and that

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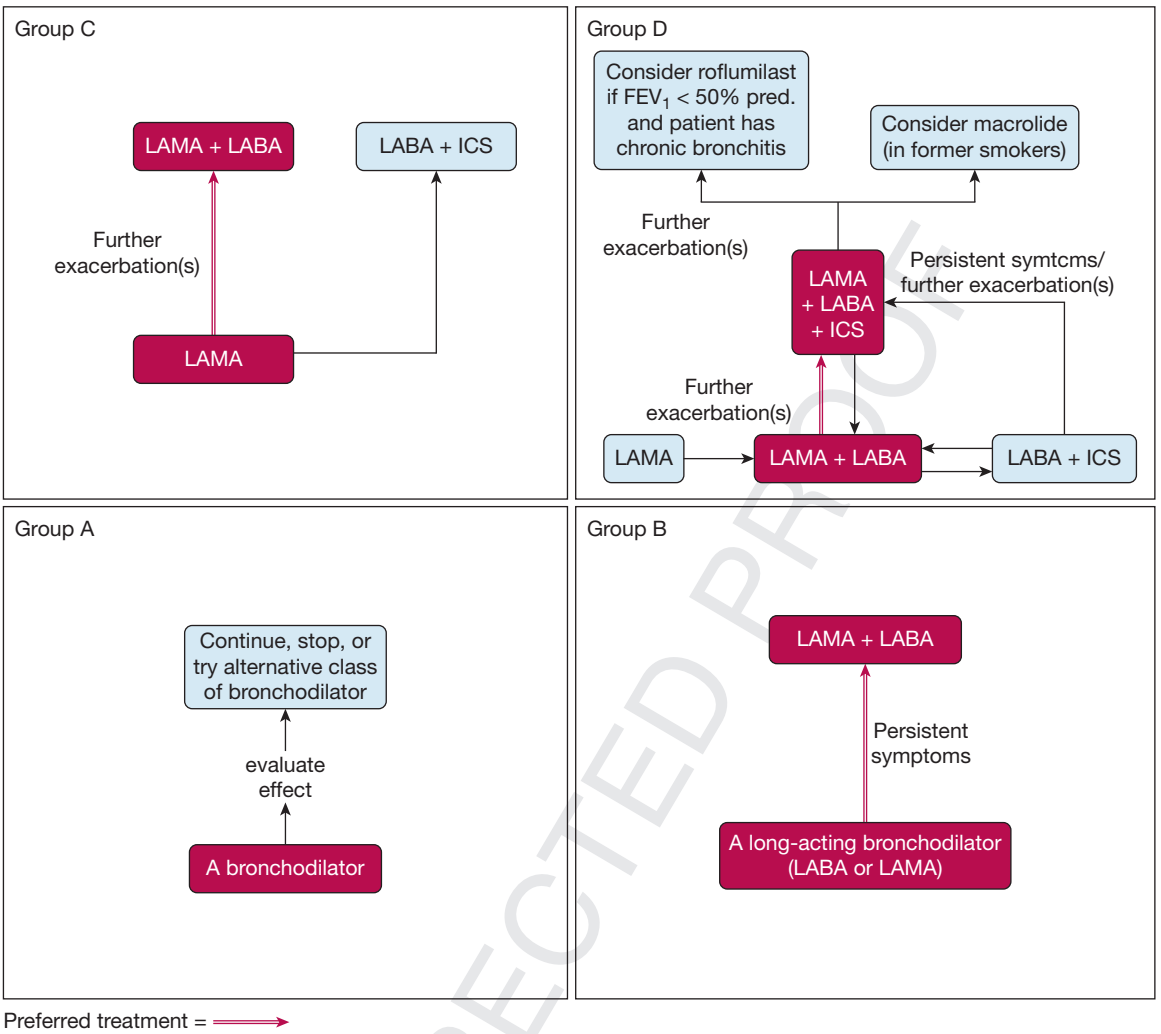

Figure 1 – *Current GOLD treatment recommendations. (Reproduced with permission from Vogelmeier et al.[8]) GOLD = Global Initiative for Chronic Obstructive Lung Disease; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LAMA = long-acting muscarinic antagonist.*

withdrawal of ICS will result in an unacceptable increase in the frequency of exacerbations in some patients. Others have argued that while ICS may be limited in their effectiveness, once established ICS suppress the adrenocortical axis and therefore withdrawal exposes patients to the dangers of adrenal insufficiency.[10] Below, I will address these issues of efficacy and safety of ICS withdrawal.

First, the efficacy of ICS in COPD is widely overestimated. The Cochrane review of combined ICS/LABA vs LABA, which represents the majority of the evidence supporting the use of ICS in COPD, shows a pooled effect (rate ratio) of 0.76 (95% CI, 0.68-0.84), indicating a 24% reduction in the frequency of exacerbations.[11] It is important to note this is compared with LABA monotherapy, a treatment that is not recommended for patients with a history of exacerbations. The largest study contributing to this meta-analysis is TORCH (Towards a Revolution in COPD Health), which contributes a rate ratio of 0.88 (95% CI, 0.81-0.96), or a 12% reduction in exacerbations.[11] Thus the exacerbation reduction benefit of ICS, even compared with an inappropriately weak comparator, is very modest (Fig 2).[11]

A comparison against a single agent, tiotropium, failed to show a benefit in terms of exacerbations,[12] and it has not been clearly demonstrated that ICS/LABA is less effective than LABA/LAMA for the prevention of exacerbations, with no patient subgroup in the FLAME (Effect of Indacaterol Glycopyronium vs Fluticasone Salmeterol on COPD Exacerbations) study apparently having benefit from ICS/LABA compared with bronchodilators.[13] Rates of pneumonia were also higher in ICS/LABA users compared with LABA/LAMA users,

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