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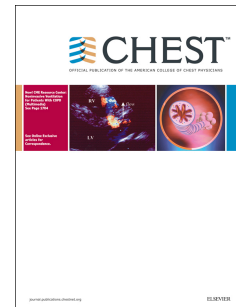
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Counterpoint: Should an attempt be made to withdraw inhaled corticosteroids in all patients with stable GOLD 3 ($30\% \leq \text{FEV1} < 50\%$ predicted) COPD? No

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Inhaled corticosteroids (ICS) have been accepted by successive GOLD documents as being effective agents for the prevention of COPD exacerbations and decline in health status^{1,2}. The combination of an ICS and a long-acting beta-agonist (LABA) is superior to the LABA alone in achieving these positive benefits³. As the major effect of adding ICS is to reduce exacerbations, conventional guidance suggests this treatment in patients with a history of prior exacerbations^{1,2}. However, there has been a reappraisal of the use of ICS mainly driven by two factors: the recognition that treatment is associated with important adverse events, best documented in clinical trials as an approximately doubling of the risk of pneumonia³; and the demonstration in a large and influential clinical trial that combined LABA and long acting antimuscarinic (LAMA) treatment has a larger positive impact on exacerbations, symptoms and lung function and is less likely to be associated with pneumonia than treatment with LABA/ICS⁴. As a result GOLD 2017 recommends LABA/LAMA as a primary exacerbation reduction strategy and a more restricted role for ICS⁵.

One question - posed by the title of this pro-con debate - is should patients with stable COPD and no exacerbations in the previous year should be advised to withdraw ICS treatment? Proponents of this approach will point to the large WISDOM study showing that in patients with COPD established on LABA/LAMA, there are no major deleterious effects of withdrawing ICS⁶. However, this evidence is not relevant to the question as WISDOM only recruited patients with one or more exacerbations in the last year and therefore arguably only proved the safety of ICS withdrawal in patients not responding well to ICS containing treatment. The most important finding of the WISDOM study was evidence that the risk of exacerbations in patients maintained on LABA/LAMA following ICS withdrawal was related to the baseline blood eosinophil count, with patients whose blood eosinophil count was $>2\%$ having an increased risk of exacerbations off ICS⁷. This added to compelling and

consistent evidence that eosinophilic airway inflammation is an identifiable and important treatable trait in a proportion of patients with COPD, associated particularly with the risk of an exacerbations and the likelihood of a positive response to corticosteroid treatment⁸.

It has been known for some time that eosinophils are increased in the airways in a significant proportion of patients with COPD and that the short and longer-term beneficial effects of corticosteroid treatment are greater in patients with this feature⁹⁻¹¹. An important advance has been the identification of the peripheral blood eosinophil count as a reliable and clinically accessible biomarker of eosinophilic airway inflammation¹². A blood eosinophil count of <150 cells/mm³ (equivalent to a differential count of $<2\%$) has been shown to have a high negative predictive value, meaning that the 40-50% of patients with COPD with a blood eosinophil count below this threshold can be reasonably assumed to not have a risk of exacerbation related to eosinophilic airway inflammation¹²⁻¹⁴. Demographic variables such as bronchodilator reversibility, atopy or asthma-COPD overlap are not related to the blood eosinophil count^{13,15}. The reproducibility of blood eosinophils numbers appears to be good and ICS have little suppressive effect¹⁶, meaning that low blood eosinophil counts retain their predictive value in an ICS treated patient.

Two retrospective studies of patients with COPD and a past history of exacerbations have shown that exacerbation numbers increase with increasing blood eosinophil counts^{16,17}. These studies have also shown that the beneficial effect of inhaled corticosteroids on exacerbation frequency increase progressively with increasing blood eosinophil counts. There is no evidence of efficacy against this outcome at counts below 150 cells/mm³ or a differential count of $<2\%$. The effects of inhaled corticosteroids on FEV₁ and QOL are also associated with blood eosinophil count although the findings

are more variable^{16,17}. A reanalysis of the ISOLDE study showed that the rate of decline in FEV1 was more rapid in patients with a blood eosinophil count >2% and that ICS effectively prevented this excess decline¹⁸. The rates of pneumonia are 50-60% higher in patients with a low blood eosinophil count (<2%) irrespective of ICS use¹⁹.

The first prospective study of the utility of this method in stratifying the response to additional ICS therapy in COPD has been published recently. This showed clear benefit of fixed triple therapy vs tiotropium alone in patients with a blood eosinophil count >2% but not <2%²⁰. More prospective data are needed although the existing evidence seems sufficient to make definitive recommendations about the need to routinely measure blood eosinophil count when adding an ICS to other therapy in forthcoming guidelines.

My case is that the only criteria for use of ICS in COPD is possession of the biological process that corticosteroids modify: eosinophilic airway inflammation. It follows that withdrawal of ICS is reasonable only if the clinician can be sure that this process is not present. I argue that blanket, one size fits all management approaches such as that suggested by the title of this debate should be replaced by a new precision medicine, biomarker directed approach. In the blood eosinophil count we have a predicative biomarker offering for the first time the prospect of a new precision medicine, biomarker directed approach to management (figure). The question we could all answer yes to is: should an attempt be made to withdraw inhaled corticosteroids in all patients with stable GOLD 3 ($30\% \leq \text{FEV1} < 50\%$ predicted) COPD and a blood eosinophil count $<150 \text{ cells/mm}^3$? In a patient with a higher blood eosinophil count then it is as ludicrous to withdraw ICS in a stable patient with COPD

as it is to stop anti-hypertensives in a hypertensive patient who has not had a cerebrovascular accident in the last year.

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Figure 1. Proposed management of COPD incorporating two major treatable traits: symptoms due to airflow limitation and risk assessed using the blood eosinophil count. Risk refers to future risk of exacerbation and decline in FEV₁. Treatments with a trait specific effect are included. Rescue short acting bronchodilators (SABA or SAMA) could be used in all situations and patient categories, as required.

