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EDITORIAL

Inhaled Corticosteroids for Chronic Cough: Yes or FeNO?

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If you're reading this, chances are you've sat in a consultation room with a chronic cough patient wondering whether to prescribe a course of inhaled corticosteroids (ICS) or not. As you ponder, you'll no doubt recall those that improved, offset somewhat by memories of patients reporting no such benefit. The truth is, despite wide recognition that cough can be the sole clinical manifestation of asthma [1] and associated with conditions such as eosinophilic bronchitis [2, 3], both of which respond well to ICS, guidance is somewhat vague. From the inception of the anatomic diagnostic protocol by Irwin and colleagues [4] to the most recent consensus on cough management [5, 6], empirical trials of ICS have been advocated but with little agreement on treatment dose and duration and how those most likely to respond might be selected. This latter issue is perhaps where most uncertainty lies. Over the last few years there has been a fashion for identifying treatable traits when managing chronic respiratory disease [7]. Chronic cough is no different and Type-2 high airway inflammation represents one such trait. In the past, sputum eosinophil counts offered some guide to initiating a trial of ICS but the technique was cumbersome and technically challenging. As an alternative, fractional exhaled nitric oxide (FeNO) has become more widely used despite variance as to what constitutes an 'elevated' FeNO level or what cut-off value is likely to predict a favorable response to corticosteroids. The recently published British Thoracic Society Clinical Statement on Chronic Cough in Adults [6] proposed that patients with a FeNO level > 25 ppb should be considered for a 4-week trial of ICS. This suggested cut-point was based on a meta-analysis and is somewhat lower than values proposed by others as being predictive of an ICS response [8]. Clearly more evidence is required.

In this edition of *Lung*, Lee and colleagues undertook a prospective open-label study of 50 adult patients with chronic cough and an elevated FeNO level (≥ 25 ppb) [9]. All participants had normal spirometry with the common causes associated with cough excluded in line with current guidelines [5, 10]. With a mean age of 58 years and almost 60% female, participant demographics were similar to those typically presenting with chronic cough although the median cough duration of 6 months was considerably shorter than those referred to specialist cough services where cough duration can be many years. Participants received 200 µg fluticasone furoate daily (2000 µg BDP equivalent) for 3–4 weeks, the dose and duration chosen to align with guidelines and systematic reviews [5, 11]. The key objectives were to evaluate the response of cough to the ICS trial and identify any factors predictive of a positive treatment effect. So, what did they find? Well, just over two-thirds had a treatment response, defined as achieving the minimal clinically important difference of > 1.3 on the Leicester Cough Questionnaire [12], a widely used measure of cough-related health status. Responders were more likely to be female and have more severe cough at baseline than non-responders. What was especially interesting was that while median FeNO levels and cough severity scores decreased with ICS treatment, there was no significant correlation between FeNO levels and cough scores, either at baseline or after treatment. This finding suggests that while reduction in FeNO level is a surrogate for the effect of ICS on T2 airway inflammation, it is not mechanistically linked to the improvement in cough. The authors proposed that ICS exert their effect on eosinophils which they speculate are associated with cough reflex sensitization. There is certainly solid evidence for how eosinophils might alter airway nerve density and function and contribute to irritant responses including cough [13].

So, how does this study help us? It clearly has limitations not least the open-label design, small size and the suspicion that some of the treatment effect simply reflected a placebo response or regression to the mean. The authors recognize these flaws but have offered us something that is pragmatic and aligns with current practice and therefore relevant to all clinicians who see patients with chronic cough. To me, it suggests that patients with chronic cough and a FeNO

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above 25 ppb should be offered a 4-week trial of high-dose ICS therapy. If it helps, great; if not, then consideration may be given to a longer trial of treatment or the addition of an anti-leukotriene. Finally, it should be emphasized that any trial of therapy should be discontinued when it is clearly ineffective. A negative treatment trial should not be seen as a failure. Rather, it may represent a step along the way to making an alternative diagnosis such as refractory chronic cough and we should not be afraid to reach this point because new treatments are surely coming [14].

Declarations

Conflict of interest LMG is Founding Chair and Chief Investigator of the ERS NEuroCOUGH Clinical Research Consortium. He reports honoraria from Chiesi, Bellus Health, GSK, Merck, NeRRe Therapeutics, Nocion, Trevi, Shionogi Inc and Reckitt Benckiser; grant support from Merck and Bellus Health.

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