Placebo Control is Vital in Assessing Therapy in Chronic Cough

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We read with interest the work by Ji-Ho Lee and his colleagues (*Lung. 2024 Jun;202(3):275-280*), which purports to provide evidence of short-term efficacy of high-dose inhaled corticosteroid (ICS) in chronic cough in adults. They studied patients with a fractional exhaled nitric oxide (FeNO) greater than 25 ppb. In this study, all patient-reported outcomes (PROs) significantly improved. There was a notable decline in FeNO levels after three weeks of high-dose ICS therapy. The authors claim these findings support the guideline recommendations for a short-term ICS trial for such patients.

This study was a prospective observational study without a placebo control. Such studies are prone to a high degree of bias representing a placebo response. There are several factors contributing to this (i.e., social learning, human communications, and the Hawthorne effect), which we have previously enunciated[1]. Among these factors are patients' expectation, particularly prevalent in patients naïve to cough clinics, such as the authors' population.

The primary endpoint of this study was defined as the proportion of patients achieving a minimal clinically important difference of Leicester Cough Questionnaire (LCQ) (≥ 1.3 points increase). This was the same as that in the two largest randomised controlled trials with over 2000 rigorously defined chronic cough patients[2]. The later review by the U.S. Food and Drug Administration determined the placebo response rates as 68% in the COUGH-2 and 63% in the COUGH-1[3]. This is similar to the effect size reported in the current study (68%). Thus, placebo response may be the overriding factor in the efficacy reported in the study by Ji-Ho Lee et al. The cough improvement did not significantly correlate with changes in FeNO levels despite studying a population specifically targeted with a phenotype likely to respond to ICS. Surely, this is evidence that another factor rather than a pharmacological mechanism is responsible for the improvement.

We fail to agree the current study supports the guideline recommendation of a short-term ICS trial for chronic cough. Indeed, it suggests the opposite. In the accompanying editorial[4], Lorcan McGarvey also suggests the four-week ICS use as a diagnostic trial, however, perhaps a short course of oral prednisone may be a simpler and more pragmatic approach since, in steroids responsive patients, a dramatic improvement is seen within a few days. The apparent response to ICS is likely to be an artefact which may condemn the patient to long-term steroid therapy with all its familiar consequences.

Declarations

Author contributions

Mengru Zhang and Prof. Alyn H. Morice drafted the manuscript. Prof. Alyn H. Morice had the idea for the work. All authors critically revised the work and approved it for publication.

Conflict of interest

Alyn H. Morice declares that he has received consulting fees from Bayer (2019 – 2021), Shionogi (2019 – 2021), Bellus (2019 – present), Merck (2019 – present), NeRRi (2019 – present), and Trevi. (2019 – present), and lecture fees from Chiesi (2019 – 2021), Boehringer Ingelheim (2019 – 2022), and Merck (2019 – present), as well as grant support from Bayer (2019 – 2021), Shionogi (2019 – 2021), Bellus (2019 – present), Merck (2019 – present), Nocion (2019 – present), Philips (2019 – present), NeRRi (2019 – present), and Trevi (2019 – present). Alyn H. Morice is also the founder and CEO of Tussogenics Ltd (2019 – present).

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Not applicable.

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