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To accompany manuscript CHEST: Cough-Specific Quality of Life Predicts Disease Progression among Patients with Interstitial Lung Disease: Data from the Pulmonary Fibrosis Foundation Patient Registry

Editorial

The Curious Case of Cough in Interstitial Lung diseases

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Interstitial Lung Diseases (ILD) comprise a heterogeneous group of diffuse parenchymal lung disorders characterized by variable amounts of inflammation and fibrosis.[1] Cough is one of the most common symptoms in ILD, affecting up to 80%, and has shown to be significantly associated with reduced quality of life (QoL).[1,2] There are several ways to measure cough; objectively with cough monitors or cough challenge tests, or subjectively with visual analogue scales and cough-specific QoL questionnaires, such as the Leicester cough questionnaire (LCQ).[2] Cough is not only a life-impacting symptom in ILD, but several studies have reported that cough may also independently predict disease progression, mortality and transplant-free survival in Idiopathic Pulmonary Fibrosis (IPF).[3-5]

In contrast to previous studies focusing exclusively on cough in patients with IPF, in this issue of CHEST Lee et al[6] report findings of a large heterogeneous group of 1447 patients with data in the pulmonary fibrosis foundation patient registry (PFFRR). The authors aimed to analyse associations between characteristics of patients with ILD and LCQ scores, and if LCQ scores could predict disease severity and other clinical outcomes. They report that at baseline, younger age, less common ILD diagnosis, reflux, and lower forced vital capacity correlate with worse cough-specific QoL. Interestingly, worse LCQ scores were associated independently with higher risk of respiratory hospitalization, lung transplantation and death in a one-year follow-up period. Strengths of the study include a large study population with a range of ILD diagnoses from multiple centers across the United States, and the use of a cough-specific patient reported outcome measure. Instead of the often used 'yes/no' question to assess cough, the more extensive 19-item LCQ was used which represents broader aspects of cough-specific QoL in a patient-friendly measurement tool.

Arguably, the advantage of registry data is a realistic reflection of the heterogeneous group of ILD in 'real life'. However, registries are subject to selection-bias. Patients with sarcoidosis were not included in the PFFRR data, whilst sarcoidosis is one of the most common ILD with a known high occurrence of cough symptoms and reduced cough-related QoL. Furthermore, the majority of patients studied had severe disease with more than 60% using home oxygen, yet three-quarters of patients reported only mildly reduced cough-related QoL. In previous studies, cough seemed to be more frequent in severe ILD,[3,7] but lung function parameters and cough measures showed surprisingly limited association.[2,7]

Also, more than 20 percent of patients used an ACE-inhibitor, a well-known cause of chronic cough. Other treatable traits of cough such as reflux, sleep apnoea, asthma and COPD were also common. These co-morbidities, if not treated optimally, may have influenced LCQ scores. Interestingly, reflux was the only trait that remained significantly associated with worse cough-specific QoL in the multivariate analyses. Moreover, the authors could not distinguish between acute and chronic cough (lasting more than eight weeks). Acute cough could confound the results through association with respiratory infection or acute exacerbation and deterioration of ILD that might therefore influence prognosis. If, as Lee et al. show, the patients' experience of cough is indeed an independent predictor of prognosis in ILD, the question arises what is the underlying mechanism of cough in ILD and how could it influence disease progression?

Currently, hypersensitivity of the cough reflex is the unifying mechanism to explain chronic cough that is idiopathic or refractory to treatment of underlying disease. Cough hypersensitivity is characterised by increased afferent neuronal sensitivity and/or central perception in response to cough stimuli. The heightened cough reflex sensitivity in ILD could be driven through one or more of the common comorbidities linked to chronic cough. For instance, eosinophilic bronchitis may be present in IPF.[1]

Furthermore, heightened sensitivity of upper airway cough nerves may be driven by reflux secondary to esophageal dysmotility or lower esophageal sphincter relaxation, which are common in ILD[8] and provide a potential link between cough and disease progression. Reflux, which may be silent (without heartburn), has been strongly linked with ILD progression, although data on the effects of anti-reflux interventions are inconclusive. This may be because non-acid reflux is more important than acid, explaining why treatment with proton pump inhibitors has proven ineffective,[1,9] and esophageal dysmotility will not be helped by traditional gastroesophageal reflux disease treatments such as surgical fundoplication.

A direct effect of mechanical distortion due to lung fibrosis has been hypothesised to increase activation of cough fibres or lead to loss of inhibitory nerves. Altered mechanotransduction in fibrotic lung may promote activation of the pro-fibrotic mediator TGF-β1[10], providing a potential direct mechanistic link between cough and ILD progression.

Positive results of the P2X3 antagonist gefapixant on cough counts and LCQ scores in unexplained chronic cough[11] provide optimism that modulation of tussive neural pathways will also be effective for treating cough in patients with ILD. A small trial of gefapixant for IPF cough was hampered by methodological issues but secondary endpoints suggested a potential therapeutic effect.[12] Several agents are being studied in clinical trials, including drugs targeting receptors for excitatory neurotransmitters (e.g. NK-1, NMDA) and opioids.[13] These trials give hope of ameliorating cough in ILD and improving QoL. An intriguing possibility remains that suppressing cough could also slow progression of ILD.

References

1. Birring SS, Kavanagh JE, Irwin RS, et al. Treatment of Interstitial Lung Disease Associated Cough: CHEST Guideline and Expert Panel Report. *Chest.* 2018;154(4):904-917.
2. van Manen MJG, Wijsenbeek MS. Cough, an unresolved problem in interstitial lung diseases. *Curr Opin Support Palliat Care.* 2019;13(3):143-151.
3. Ryerson CJ, Abbritti M, Ley B, Elicker BM, Jones KD, Collard HR. Cough predicts prognosis in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2011;183(1).
4. Jo HE, Glaspole I, Grainge C, et al. Baseline characteristics of idiopathic pulmonary fibrosis: analysis from the Australian Idiopathic Pulmonary Fibrosis Registry. *Eur Respir J.* 2017;49(2).
5. Zaman T, Moua T, Vittinghoff E, Ryu JH, Collard HR, Lee JS. Differences in Clinical Characteristics and Outcomes Between Men and Women With Idiopathic Pulmonary Fibrosis: A Multicenter Retrospective Cohort Study. *Chest.* 2020;158(1):245-251.
6. Lee J, White E, Freiheit E, et al. Cough-specific Quality of Life Predicts Disease Progression Among Patients with Interstitial Lung Disease: Data from the Pulmonary Fibrosis Foundation Patient Registry. *Chest.* 2022.
7. Key AL, Holt K, Hamilton A, Smith JA, Earis JE. Objective cough frequency in Idiopathic Pulmonary Fibrosis. *Cough.* 2010;6:4.
8. Jones R, Krishnan A, Zeybel GL, et al. Reflux in idiopathic pulmonary fibrosis: treatment informed by an integrated approach. *ERJ Open Res.* 2018;4(4).
9. Dutta P, Funston W, Mossop H, et al. Randomised, double-blind, placebo-controlled pilot trial of omeprazole in idiopathic pulmonary fibrosis. *Thorax.* 2019;74(4):346-353.
10. Froese AR, Shimbori C, Bellaye PS, et al. Stretch-induced Activation of Transforming Growth Factor-beta1 in Pulmonary Fibrosis. *Am J Respir Crit Care Med.* 2016;194(1):84-96.
11. McGarvey LP, Birring SS, Morice AH, et al. Efficacy and safety of gefapixant, a P2X3 receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet.* 2022;399(10328):909-923.
12. Martinez FJ, Afzal AS, Smith JA, et al. Treatment of Persistent Cough in Subjects with Idiopathic Pulmonary Fibrosis (IPF) with Gefapixant, a P2X3 Antagonist, in a Randomized, Placebo-Controlled Clinical Trial. *Pulm Ther.* 2021;7(2):471-486.
13. Morice A, Dicpinigaitis P, McGarvey L, Birring SS. Chronic cough: new insights and future prospects. *Eur Respir Rev.* 2021;30(162).