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EDITORIAL

Chronic cough and sputum production: a clinical COPD phenotype?

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Chronic obstructive pulmonary disease (COPD) is characterised by incompletely reversible airflow limitation and its severity has been categorised using the level of forced expiratory volume in 1 s (FEV1) [1]. Because marked heterogeneity existed between subjects with comparable FEV1 [2], it has been proposed that identification of subgroups of COPD subjects could represent an alternative to the current FEV1-based classification [3]. A consensus report proposed that COPD phenotypes, as defined by ''a single or combination of disease attributes that describes differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression or death)'', could represent the future of COPD [4].

Chronic cough and sputum production (chronic bronchitis) have long been recognised as a consequence of tobacco smoking. In the 1960s, the British hypothesis proposed that chronic cough and sputum production encouraged bronchial infection, which promoted airway and alveolar damage and led to airflow limitation [5]. In their classical study reported in 1976, FLETCHER and PETO [6] concluded that while chronic cough and sputum production and airflow limitation both occurred in smokers, they were largely unrelated disease processes. Almost 20 yrs later, VESTBO *et al*. [7] reported that chronic cough and sputum production were associated with an excess FEV1 decline and increased risk of hospitalisation because of COPD. Data from the Lung Health Study further indicated that chronic cough and sputum production were associated with increased lower respiratory illnesses (exacerbations) in subjects with mild airflow limitation [8]. These two studies shed new light on the potential importance of chronic cough and sputum production in subjects with COPD. They were followed by studies suggesting that chronic cough and sputum production were associated with increased mortality risk [9–11] and exacerbations [12, 13] in COPD patients.

In the present issue of the *European Respiratory Journal*, MONTES DE OCA *et al*. [14] examined the prevalence of chronic bronchitis in subjects with and without COPD identified in a cross-sectional, population-based study in five Latin American cities (PLATINO study). Although the prevalence of chronic bronchitis was rather low in this population, the authors reported that COPD subjects with chronic bronchitis had worse lung function and general health status, and had more respiratory symptoms, physical activity limitation and exacerbations [14]. The authors proposed that chronic bronchitis in COPD subjects was possibly associated with increased disease severity and represented a COPD phenotype [14]. The study by MONTES DE OCA *et al*. [14] follows several recent cross-sectional studies that compared clinical characteristics of COPD subjects with and without chronic cough and sputum production [2, 15–17]. These studies yielded somewhat variable results regarding the prevalence of chronic cough and sputum production in COPD subjects and their association with other COPD characteristics or outcomes (table 1).

Variations in the prevalence of chronic bronchitis among several studies may be related to differences in its definition and to differences in the study populations. Chronic bronchitis is usually defined by ''cough and phlegm (or sputum production) most days for >3 months in two consecutive years''. The study by MONTES DE OCA *et al*. [14] shows that the use of another definition based on ''phlegm on most days for at least 3 months per year for ⩾2 yrs'' almost doubled the prevalence of chronic bronchitis. Other investigators have defined chronic bronchitis (or chronic mucus hypersecretion) by using a definition based on the ''emission of >30 mL of sputum daily at least 3 months a year, for >1 yr'' [12, 18]. Because all these definitions were based on expert opinion, it is unclear which one should be adopted. Regardless of the definition used, the prevalence of chronic cough and sputum production consistently increased with increasing airflow limitation [2, 15, 17, 19], and this finding may, in part, account for the low prevalence of chronic bronchitis in the PLATINO study, in which COPD subjects had mild airflow limitation.

MONTES DE OCA *et al*. [14] reported that COPD exacerbations were twice as frequent in patients with chronic phlegm production (although this difference was not statistically significant, probably due to lack of power), confirming results obtained in two other studies [15, 16]. However, no association was found between chronic cough and sputum production and exacerbations in the cross-sectional analysis of the ECLIPSE study [2]. During the first year of longitudinal follow-up of the ECLIPSE study, HURST *et al*. [20] reported that chronic cough at study entry was associated (OR 1.20, 95% CI 1.01–1.42) with the occurrence of exacerbations, but this association did not remain significant in the multivariate analysis. In the latter study, chronic bronchitis or chronic phlegm production were

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not associated with exacerbations [20]. Thus, the relationship of chronic cough and/or sputum production to COPD exacerbations, an important clinical outcome, is not consistent among studies. To date, the reasons for these discrepancies remain to be established.

Several studies reported that subjects with chronic cough and sputum production had more severe dyspnoea [14, 16, 17], but these findings were again not reproduced in the ECLIPSE study [2]. Furthermore, it is unclear whether chronic cough and sputum production are independent determinants of dyspnoea in COPD subjects.

Assessment of chronic cough and sputum production relies on patient perception and recollection of symptoms, which is subject to bias. It may be affected by several factors including social behaviour (*e.g.* females often had lower prevalence of chronic cough and sputum production [2, 17], suggesting that they may be less prone to report such symptoms) and cultural factors in various geographic areas. It is also conceivable that the recent occurrence of a COPD exacerbation, in which cough and sputum production increase, result in increased reporting of chronic cough and sputum production. Furthermore, investigators have consistently reported that chronic cough and sputum production were more prevalent in current *versus* ex-smokers with COPD [2, 14–17]. These considerations may explain why chronic cough and sputum production were persistent over time in some, but not all, COPD subjects [7, 11], further complicating the understanding of their potential impact.

In the end, can we really consider that chronic cough and sputum production is a clinical COPD phenotype? It is suggested that chronic cough and sputum production cannot in itself be considered as a clinical COPD phenotype because: 1) conflicting data exist regarding its association with important clinical manifestations (*e.g.* dyspnoea) and outcomes (*e.g.* exacerbations); and 2) the two studies suggesting that chronic bronchitis was associated with increased mortality in COPD subjects will require confirmation before any definitive conclusion can be made [9, 11]. However, it is likely that chronic cough and sputum production are not innocent symptoms and may help in identifying specific COPD phenotypes. Interesting data supporting this view come from the results of recent clinical trials. *Post hoc* analysis of studies assessing the efficacy of roflumilast (a phosphodiesterase-4 inhibitor) [21, 22] or pulsed moxifloxacin [23] for the prevention of COPD exacerbations suggested that these interventions were efficacious in the subset of COPD subjects with chronic cough and/or sputum production at study entry. Such *post hoc* analyses have been used to define characteristics of patients included in a prospective clinical trial that demonstrated the reduction of exacerbations by roflumilast in a specific subset of COPD subjects [22, 24]. These subjects with severe airflow limitation (FEV_1 <50% predicted), repeated exacerbations and chronic cough and sputum production experienced improvement with roflumilast [24], whereas no effect was found when selecting subjects only on the basis of severe airflow limitation [21].

Finally, COPD is a very heterogeneous disease and it seems unlikely that a single disease attribute would be sufficient to identify a specific patient phenotype. A working hypothesis is that the combination of multiple characteristics (including

TABLE 1 Summary of cross-sectional studies that compared clinical characteristics in chronic obstructive pulmonary disease subjects with and without chronic cough and sputum production

First author [ref.]	Population	Subjects n	Chronic cough and/or sputum	Current smokers		Exacerbations per patient per year		Dyspnoea MMRC scale		HRQoL	
				Cough + sputum	No cough + sputum	Cough + sputum	No cough + sputum	Cough + sputum	No cough + sputum	Cough + sputum	No cough + sputum
Agusti [2]	Clinic based (multinational)	2161	34.6	GOLD 2: 52%* GOLD 3: 46%* GOLD 4: 37%*	GOLD 2: 31 GOLD 3: 3 GOLD 4:21	GOLD 2: 0.6±1.1 GOLD 3: 1.0±1.2 GOLD 4: 1.2±1.6	GOLD 2: 0.7±1.0 GOLD 3: 1.0±1.4 GOLD 4: 1.2±1.3	GOLD 2: 1.5±1.0* GOLD 3: 1.8±1.0 GOLD 4: 2.4±1.0	GOLD 2: 1.3±1.0 GOLD 3: 1.8±1.1 GOLD 4: 2.3±1.0	SGRQ-C GOLD 2:50.3±18.8* GOLD 3: 58.8±17.6* GOLD 4:65.0±16.5*	SGRQ-C GOLD 2:38.9± 20.5 GOLD 3:51.2±18.2 GOLD 4:59.4±15.2
Burgel [15]	Clinic based (France)	433	74.1	28*	18	2.2±2.2*	1.0±1.2	N/A	N/A	N/A	N/A
Kim [16]	Clinic-based (USA)	1061	27.3	48*	27	1.2±1.6*	0.63±1.1	3 (2–4)*	2 (1–3)	SGRQ 62.5±19.0*	SGRQ 38.0±22.4
Montes de Oca [14]	Population based (Latin America)	759	14.4#	47*	32	5.42	2.66	Present: 76*	Present: 47	SF-12 physical score 44.6±1.01*	SF-12 physical score 49.5±0.36
Lu [17]	Population based (China)	1668	30.0	48*	37	N/A	N/A	MMRC >2: 64*	MMRC >2: 29	N/A	N/A

Data are presented as %, mean±SD or median (interquartile range), unless otherwise specified. MMRC: modified Medical Research Council; HRQoL: heath-related quality of life; GOLD: Global initiative for chronic Obstructive Lung Disease; SGRQ: St. George's Respiratory Questionnaire; SGRQ-C: chronic obstructive pulmonary disease version of the SGRQ; N/A: not applicable; SF-12: Short Form-12 questionnaire. #: phlegm most days, at least 3 months a year for ⩾2 yrs. *: $p<0.05$.

gene–environment data, age, comorbidities, imaging, biomarkers, *etc*.) and their analysis using mathematical techniques may be more suitable for the identification of clinically meaningful COPD phenotypes [25–27].

STATEMENT OF INTEREST

A statement of interest for P-R. Burgel can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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