Eur Respir Rev 2010; 19: 116, 94–96
DOI: 10.1183/09059180.00004410

EDITORIAL

Mucus hypersecretion in COPD: should we only rely on symptoms?

P-R. Burgel and C. Martin

In the present issue of the *European Respiratory Review*, CERVERI and BRUSASCO [1] propose that ''the view that chronic mucus hypersecretion plays a secondary role in the pathogenesis of COPD should be abandoned and instead, mucolytic agents should be considered as a treatment option'' [1]. In the same series, BALSAMO *et al.* [2] provide an overview of currently available mucoactive drugs, and DECRAMER and JANSSENS [3] examine the evidence for proposing long-term treatment with so-called ''mucolytics'' (*e.g. N*-acetylcysteine and carbocysteine) in patients with chronic obstructive pulmonary disease (COPD).

Mucus hypersecretion has long been limited to chronic cough and sputum production. Thus, epidemiological studies that have focused on the potential impact of chronic cough and sputum production in COPD called it chronic mucus hypersecretion [4, 5]. In this editorial, we examine the evidence suggesting that mucus hypersecretion is a major feature in all COPD patients, including those without cough and sputum production. We suggest that mucus hypersecretion should be a therapeutic target in all COPD subjects (*i.e.* subjects with and without chronic cough and sputum production) and discuss some aspects of the development of drugs targeting mucus hypersecretion in COPD.

Chronic cough and sputum production and COPD are associated with smoking exposure, but chronic cough and sputum production are present only in a subset of subjects with COPD [6, 7]. Although these symptoms were initially believed to be irrelevant to the natural history of COPD [4], VESTBO *et al.* [5] reported that chronic cough and sputum production were associated with disease progression (*i.e.* forced expiratory volume in 1 s (FEV_1) decline) in subjects with COPD. Investigators further reported that chronic cough and sputum production were associated with premature death in subjects with COPD [7–9] and were closely associated with the occurrence of COPD exacerbations, including those requiring hospitalisations [10]. These studies revealed that chronic cough and sputum production, which are probably related to airway mucus hypersecretion, are not innocent bystanders in patients with COPD, but should be regarded as important clinical manifestations associated with major outcomes [11].

An important question needs to be addressed: should mucus hypersecretion in COPD airways be identified only based on symptoms of chronic cough and sputum production? Pathological studies have suggested that these symptoms were mostly associated with changes in large (proximal) airways [12, 13], where mucus-producing cells (epithelial goblet cells and mucus glands) are increased [14, 15]. Mucus accumulation was also identified in the epithelium and lumen of small conducting airways, and the extent of mucous exudates within airway lumens was closely associated with the severity of airflow limitation in a large group of subjects with COPD [16]. Furthermore, severity of luminal obstruction by mucous exudates was independently associated with mortality at 3 yrs in 101 COPD subjects undergoing lung volume reduction surgery [17]. In the latter study chronic cough and sputum production failed to associate with occlusion of the small airways by mucous exudates [17]. Another study also suggested that mucus hypersecretion in peripheral airways was independent of the presence of cough and sputum production [18]. These findings are perhaps not surprising because cough receptors are absent in peripheral airways, leading to the suggestion that mucus accumulation in small airways may occur in the absence of chronic cough and sputum production [19]. We conclude that mucus hypersecretion occurs in all COPD subjects, increases with airflow limitation and is not always associated with chronic cough and sputum production.

Currently available drugs have limited or no impact on hypersecretion in COPD. So-called mucoactives (*e.g. N*-acetylcysteine and carbocysteine) have shown some efficacy in reducing exacerbations in long-term randomised controlled trials, especially in COPD patients not receiving inhaled corticosteroids [3]. As discussed in this issue of the *European Respiratory Review* by DECRAMER and JANSSENS [3], there is no evidence that the effects of these drugs are mediated through effect on mucus hypersecretion. Inhaled and oral steroids may also have no or limited effect on mucus production in airways [17, 20], and mucus obstruction in small airways was present in patients treated with long-acting bronchodilators [16, 17]. The development of new drugs for targeting mucus hypersecretion in COPD patients will probably require: 1) a precise understanding of the pathophysiology of mucus accumulation

Service de Pneumologie, Hôpital Cochin, AP-HP, and Paris-Descartes University, Paris, France.

CORRESPONDENCE: P-R Burgel, Service de Pneumologie, Hôpital Cochin, Assistance Publique Hôpitaux de Paris, 27 rue du Faubourg St Jacques, 75679 Paris Cedex 14, France. E-mail: pierre-regis.burgel@cch.aphp.fr

Received: April 18 2010; Accepted: April 19 2010

PROVENANCE: Submitted article, peer reviewed.

in the airways of COPD patients; and 2) the definition of appropriate outcomes for testing these drugs in clinical trials. These issues are discussed in the following paragraphs.

Airway mucus is a complex mixture of watery secretions (water, ions and soluble mediators), inflammatory cells and secreted mucins. Mucus accumulation in the airway lumens can be the result of increased mucin production and secretion [19], decreased mucociliary clearance [21] and/or reduced mucin degradation within the airways [22]. Dissecting these mechanisms has been the focus of many studies within the past 15 yrs [23]. These studies have already identified potential molecular targets. For example, epidermal growth factor receptor (EGFR) is a convergent pathway of many stimuli (including cigarette smoke) leading to mucus overproduction in human airways [19], and therapies targeting complex cascades of events leading to EGFR activation and mucin production have been proposed in the treatment of COPD [19, 24]. Identification of important steps necessary for mucin secretion (*e.g.* myristoylated alanine-rich C kinase substrate, MARCKS) suggests the possibility of inhibiting mucin release within the airways [25]. As our understanding of the mechanisms of mucus accumulation in the airways increases, there is little doubt that many more targets will be identified.

The overall concept that excessive mucus accumulation in airways is detrimental and that reduction in mucus hypersecretion is beneficial in COPD patients will need to be tested in clinical trials. Before testing new drugs targeting mucus hypersecretion in large phase III trials assessing their safety and efficacy on usual outcomes (*e.g.* FEV1, exacerbations, health-related quality of life, mortality), these drugs will first have to be tested for their ability to reduce mucus hypersecretion in human airways *in vivo*. Assessing mucus production and secretion in human airways is not an easy task. Technical aspects of measuring mucin concentrations in airway secretions (induced sputum or bronchoalveolar fluid) have not yet been standardised. A recent study used quantitative morphometric analysis of bronchial biopsies to evaluate mucin content in epithelium and mucin gene expression using qPCR in bronchial brushings [24]. Importantly, these pathological studies are limited to large airways, whereas small airways are not easily assessed. In the future, progress in imaging techniques may allow noninvasive assessment of mucous exudates obstructing small airways, but this is not achieveable using current computed tomography scans. Thus, improvement in our ability to measure mucus hypersecretion in human airways *in vivo* will be an important step for designing future clinical studies.

In conclusion, current COPD therapies have limited effects in modifying the natural history of the disease. Mucus hypersecretion occurs in all COPD subjects and increases with airflow limitation. Pathological and physiological studies suggest that chronic cough and sputum production is a manifestation of mucus hypersecretion in proximal airways, but that mucus hypersecretion in small airways is not necessarily associated with symptoms. These major findings suggest that therapies targeting mucus hypersecretion in COPD could be beneficial regardless of the presence of chronic cough and sputum production. Proof of this concept will require carefully designed clinical trials evaluating the impact of novel therapies on mucus hypersecretion and COPD-relevant outcomes.

STATEMENT OF INTEREST

None declared.

REFERENCES

1 Cerveri I, Brusasco V. Revisited role for mucus hypersecretion in the pathogenesis of COPD. *Eur Respir Rev* 2010; 19: 109–112.
2 Balsamo R, Lanata L, Egan CG. Mucoactive drugs. *Eur Respir Rev* 2010; 19: 127–133.
3 Decramer M, Janssens W. Mucoactive therapy in COPD. *Eur Respir Rev* 2010; 19: 134–140.
4 Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ* 1977; 1: 1645–1648.
5 Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. *Am J Respir Crit Care Med* 1996; 153: 1530–1535.
6 Kanner RE, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV1 decline in current smokers but not ex-smokers with mild chronic obstructive pulmonary disease: results from the lung health study. *Am J Respir Crit Care Med* 2001; 164: 358–364.
7 Pelkonen M, Notkola IL, Nissinen A, *et al.* Thirty-year cumulative incidence of chronic bronchitis and COPD in relation to 30-year pulmonary function and 40-year mortality: a follow-up in middle-aged rural men. *Chest* 2006; 130: 1129–1137.
8 Lange P, Nyboe J, Appleyard M, *et al.* Relation of ventilatory impairment and of chronic mucus hypersecretion to mortality from obstructive lung disease and from all causes. *Thorax* 1990; 45: 579–585.
9 Ekberg-Aronsson M, Pehrsson K, Nilsson JA, *et al.* Mortality in GOLD stages of COPD and its dependence on symptoms of chronic bronchitis. *Respir Res* 2005; 6: 98–107.
10 Burgel PR, Nesme-Meyer P, Chanez P, *et al.* Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. *Chest* 2009; 135: 975–982.
11 Melton L. Does mucus hypersecretion matter in airway disease? *Lancet* 2002; 359: 1924.
12 Mullen JBM, Wright JL, Wiggs B, *et al.* Reassessment of inflammation in the airways in chronic bronchitis. *BMJ* 1985; 291: 1235–1239.
13 Saetta M, Turato G, Facchini FM, *et al.* Inflammatory cells in the bronchial glands of smokers with chronic bronchitis. *Am J Respir Crit Care Med* 1997; 156: 1633–1639.
14 Innes AL, Woodruff PG, Ferrando RE, *et al.* Epithelial mucin stores are increased in the large airways of smokers with airflow obstruction. *Chest* 2006; 130: 1102–1108.
15 O'Donnell RA, Richter A, Ward J, *et al.* Expression of ErbB receptors and mucins in the airways of long term current smokers. *Thorax* 2004; 59: 1032–1040.
16 Hogg JC, Chu F, Utokaparch S, *et al.* The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med* 2004; 350: 2645–2653.
17 Hogg JC, Chu FS, Tan WC, *et al.* Survival after lung volume reduction in chronic obstructive pulmonary disease: insights from small airway pathology. *Am J Respir Crit Care Med* 2007; 176: 454–459.
18 Caramori G, Di Gregorio C, Carlstedt I, *et al.* Mucin expression in peripheral airways of patients with chronic obstructive pulmonary disease. *Histopathology* 2004; 45: 477–484.
19 Burgel PR, Nadel JA. Epidermal growth factor receptor-mediated innate immune responses and their roles in airway diseases. *Eur Respir J* 2008; 32: 1068–1081.

20 Burgel PR, Cardell LO, Ueki IF, *et al.* Intranasal steroids decrease eosinophils but not mucin expression in nasal polyps. *Eur Respir J* 2004; 24: 594–600.

21 Randell SH, Boucher RC. Effective mucus clearance is essential for respiratory health. *Am J Respir Cell Mol Biol* 2006; 35: 20–28.

22 Innes AL, Carrington SD, Thornton DJ, *et al. Ex vivo* sputum analysis reveals impairment of protease-dependent mucus degradation by plasma proteins in acute asthma. *Am J Respir Crit Care Med* 2009; 180: 203–210.

23 Curran DR, Cohn L. Advances in mucous cell metaplasia: a plug for mucus as a therapeutic focus in chronic airway disease. *Am J Respir Cell Mol Biol* 2010; 42: 268–275.

24 Woodruff PG, Wolff M, Hohlfeld JM, *et al.* Safety and efficacy of an inhaled epidermal growth factor receptor inhibitor (BIBW 2948 BS) in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010; 181: 438–445.

25 Singer M, Martin LD, Vargaftig BB, *et al.* A MARCKS-related peptide blocks mucus hypersecretion in a mouse model of asthma. *Nat Med* 2004; 10: 193–196.