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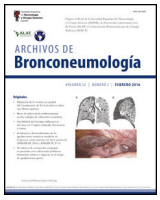

Editorial

Optimal Treatment of the Symptomatic Smoker: Make a Diagnosis Not Empiric Treatment

A general paradigm of treatment in chronic diseases is that early diagnosis and treatment will improve long-term outcomes. In chronic obstructive pulmonary disease (COPD) this improvement in outcomes has been very difficult to demonstrate with current therapies such that pharmacologic treatments are currently prescribed with the principal aims of improving symptoms and preventing exacerbations.[1] In part, this reflects the challenge of diagnosing 'early COPD', and the variable definitions that have been applied. Nevertheless, following this argument, if the objectives of COPD treatment are to mitigate symptoms and exacerbations, why not treat smokers or former smokers with these manifestations irrespective of pulmonary function impairment or diagnostic label?

Current evidence supporting the efficacy and safety of inhaled medications in COPD derives from clinical trials in patients with a robust diagnosis of COPD; i.e. adult smokers or former smokers with poorly reversible airflow limitation. To date, there has been no evidence for treating symptomatic patients without airflow limitation.[2,3]

The prevalence of respiratory symptoms is very frequent in the adult general population, the EPI SCAN 2 study on 9092 individuals older than 40 years in Spain reported at least one chronic respiratory symptom in 47.5% of participants and in 55% of those who reported being smokers.[4] Similarly, in the SPIROMICS cohort,[5] 50% of smokers with preserved pulmonary function had respiratory symptoms, and they experienced a mean of 0.27 respiratory infections ('exacerbations') per year. Woodruff et al.[5] also reported that among symptomatic current and former smokers, 42% and 23% used off label bronchodilators and inhaled glucocorticoids respectively, without any evidence of efficacy and safety in this population.

In order to investigate the efficacy of dual bronchodilation (long-acting anticholinergic agents – LAMA – and long-acting beta-2 agonists – LABA) in symptomatic smokers or ex-smokers with preserved lung function, Han et al.[6] conducted an important double-blind, randomised, placebo-controlled trial of indacaterol/glycopyrrolate. The study was conducted in persons who had a tobacco-smoking history of at least 10 pack-years, respiratory symptoms as defined by a COPD assessment test (CAT) score of at least 10 and preserved lung function on spirometry (ratio of forced expiratory volume in 1 second [FEV1] to forced vital capacity [FVC] $\geq$0.70 and FVC $\geq$70% of the predicted value after bronchodilator use). The results showed that after 12 weeks of treatment there was not a significant effect of dual bronchodilation on the primary outcome, the St George's Respiratory Questionnaire (SGRQ); in fact, the proportion of participants with a clinically significant improvement of 4 units or greater in the SGRQ was 56.4% in the treatment group and 59% in the placebo group (adjusted odds ratio, 0.91; 95% confidence interval 0.60–1.37; $p = 0.65$). The dual bronchodilator did have a physiological effect as demonstrated by an improvement in FEV1 (% predicted) of 2.48% in the treatment arm versus −0.09% in the placebo arm, and the mean change in inspiratory capacity was 0.12 l in the treatment arm versus 0.02 l on placebo. However, these changes were not perceived clinically in terms of improvements in symptoms by the participants.[6]

There are several aspects of this trial that merit discussion. Firstly, the population included is unusual, they had a high level of respiratory symptoms despite preserved spirometry. Their mean SGRQ score was 38.2 units, while the mean SGRQ in an adult population of smokers of more than 20 pack-years is 10.7 and the 95th percentile at ages 50–60 years is only 29.9.[7] Regarding dyspnoea, they had a mean BDI score of 7.6 units, whereas patients in the TONADO trial with a mean FEV1 (%) of only 50% had a BDI of 6.54.[8] Similarly, the mean CAT score was 17.6 units, similar to the 17 units observed in the POPE study in 3452 COPD patients with a mean FEV1 (%) of 50%[9] and much worse that the 11 units in the study by Casanova et al.[10] on 768 COPD patients with a mean FEV1 (%) of 60%. Since dyspnoea, SGRQ and CAT scores can be influenced by several factors beyond COPD, co-morbidities such as cardiovascular disease or anxiety and depression, for example,[11] these data suggest that the notable impairment in symptoms in this population with preserved lung function may be due, at least in part, to factors beyond the lungs, which may not be influenced using bronchodilators.

Another important aspect of the study is that patients already on inhaled medication and who were unable to undergo a 30-day medication washout were excluded. It has been argued that this strategy excluded possible responders to bronchodilators, which may be true. Nevertheless, the remaining subjects (those who were included) constitute the real target population: subjects with significant symptoms who are treatment naïve, and results in these patients were clearly negative.

Finally, the selection of SGRQ as the main outcome is controversial; SGRQ scores may be influenced by several factors, including psychological aspects. This can be illustrated by the mean improvement of almost 9 units in the placebo arm (more than twice the minimal clinically important difference of 4 units), and higher than the 7.7 unit improvement observed in the active treatment arm.[6] However, the TDI breathlessness score, which may be more "respiratory specific" did not show any difference either (0.92 units improvement with placebo and 0.93 with treatment).[6]

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We cannot rule out that the improvements in lung function parameters observed in the trial may translate to improved longer-term outcomes such as a reduction in the rate of lung function decline or prevention of exacerbations. Secondary analysis of the UPLIFT trial suggested that tiotropium significantly reduced the rate of decline in FEV1 in milder patients (GOLD 2).[12] Confirmation of this hypothesis in patients with preserved lung function would require larger and prolonged clinical trials. However, it may be challenging for patients to adhere to inhaled therapy for years without the perception of any symptomatic improvement.

The recent epidemiological study EPI SCAN 2 has shown a prevalence of COPD among the general population older than 40 years in Spain of 11.8%, with underdiagnosis still concerningly high at 74.7%.[13] A recent survey showed that only 59% of adults with chronic respiratory symptoms consulted a physician and, of these, only two thirds underwent diagnostic spirometry.[14] With this extremely high rate of underdiagnosis and the established, demonstrated efficacy of treatments in COPD patients, we believe that efforts should be directed to early diagnosis and treatment of airflow limitation, i.e. early COPD, whereas individuals with symptoms and preserved lung function should be encouraged to quit smoking, and possible causes of respiratory symptoms beyond the lungs should be explored. We now know that bronchodilator therapy is, in general, not indicated in these patients.

Competing Interests

Marc Miravitlles has received speaker or consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, CSL Behring, Kamada, GlaxoSmithKline, Grifols, Menarini, Mereo Biopharma, Novartis, Palobiofarma SL, TEVA, Spin Therapeutics, and Zambon, and research grants from Grifols.

John Hurst has received support to attend meetings, and personal payment and payment to his employer (UCL), for educational and advisory work from pharmaceutical companies that make medicines to treat COPD.

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