Real-life use of long-acting antimuscarinic agents following their approval for COPD treatment

To the Editor:

Chronic obstructive pulmonary disease (COPD) pharmacological treatment aims to reduce symptoms, represented mostly by dyspnoea and its impact on daily life, and future risk, *i.e.* lung function decline, mortality and exacerbations [1]. Inhaled therapies, including long-acting bronchodilators (LABD) and inhaled corticosteroids (ICS), are the main treatments recommended for COPD patients. LABD have been found not only to improve lung function, decrease dyspnoea, increase exercise tolerance and improve health status, but also to reduce the rate of exacerbations. In that respect, some studies suggested that long-acting antimuscarinic agents (LAMA) could be more effective than long-acting β_2-agonists (LABA) [2]. In most countries, ICS are indicated only as part of fixed-dose combinations (FDC) with LABA and are used mostly to decrease the risk of exacerbations, which is associated with health status improvement [3]. Therefore, it appeared logical to restrict their use to patients at high risk of exacerbations. The long-term benefit of combining LAMA and FDC (triple therapy) is not strongly documented [4].

Many studies in various countries found discrepancies between guidelines and real-life practice regarding long-term maintenance treatment in patients with COPD [5–7]. Although the impact of nonadherence to guidelines on efficacy outcomes is controversial [8], it increases healthcare costs [9] and, therefore, decreases cost-effectiveness. In addition, side-effects might be an issue for some treatments. For instance, ICS may increase the risk of pneumonia and induce clinically detrimental systemic side-effects in the long term [10], suggesting that overuse outside recommended indications might be associated with a decreased benefit–risk ratio.

Many new treatments for COPD have been recently released or are about to be launched [11–14]. They include mostly new LABD, ICS and various combinations of these agents. Therefore, it appears important to understand better how the release of new treatments impacts treatment decisions. The major challenge here is to rationalise physicians' prescription behaviours and improve adherence to guidelines.

The present study was designed to assess how the release of tiotropium on the French COPD market (June 1, 2006) influenced treatment patterns among respiratory physicians. As per June 20, 2012, the multicentre French Initiatives BPCO cohort had recruited 846 COPD outpatients from 17 hospitals, 421 from May 2002 to May 31, 2006 (period 1, before tiotropium release) and 425 from June 1, 2006 to June 20, 2012 (period 2, with tiotropium available). The date of June 20, 2012 was chosen for two reasons: 1) to obtain a comparable number of patients in period 2 and period 1; and 2) to avoid contamination by the appearance of newer products on the market (*e.g.* indacaterol). Table 1 compares selected clinical characteristics and patterns of inhaled therapy between the two periods.

Overall, the period 2 population was slightly younger, comprised of a higher proportion of women, and was characterised by significantly less severe airflow obstruction and numerically less severe quality of life impairment. Dyspnoea and exacerbations during the previous year were similar between the two populations. Tiotropium use increased markedly from 4% (clinical trial patients) in period 1 to 53% in period 2. Tiotropium was prescribed mostly (63%) in association with FDC, with 32.5% of patients receiving triple therapy overall. Furthermore, the proportion of patients receiving triple therapy was far from negligible in patients with mild and moderate airflow obstruction (9.8% and 26.5%, respectively), although these figures remained lower than in patients with severe and very severe airflow obstruction (38.2% and 59.6%, respectively). It was a surprise to observe a low proportion of patients being treated with bronchodilators only, even during period 2 (23.4%). Finally, although the overall proportion of patients on FDC remained perfectly identical throughout the studied periods (56.5%), over half of patients on FDC during period 2 received triple therapy (57.5%).

These data illustrate that the release of a new class of treatment, namely LAMA, resulted in a noticeable increase in overall treatment intensity, with relatively low usage of this treatment outside FDC. This could not be explained by an increased severity of COPD patients in period 2, as patients included during this period actually exhibited less severe COPD than those recruited in period 1.

TABLE 1 Comparison of patient and treatment characteristics between periods preceding and following the release of tiotropium

	Period 1[#]	Period 2[¶]	p-value
Patient characteristics			
Patients n	421	425	
Age years	65 (58–73)	64 (57–72)	0.04
Smoking history pack-years	40 (26–57)	40 (24–57)	0.99
Females %	19	26	0.01
FEV_1 % predicted	48.1 (33.6–65.4)	54.0 (38.0–69.4)	0.001
GOLD grade 3–4 %	53	45	0.02
Exacerbations per patient per year[+]	1.0 (0–3.0)	1.0 (0–2.0)	0.06
mMRC dyspnoea grade	2.0 (1.0–2.0)	2.0 (1.0–2.0)	0.61
SGRQ total score	44 (32–62)	43 (27–58)	0.06
Inhaled treatment %			
LAMA alone	0.7	11.9	<0.0001
LABA alone	9.9	4.5	0.003
ICS alone	9.6	2.1	<0.0001
LABA+LAMA	0.9	7	<0.0001
LABA+ICS alone	54.1	24	<0.0001
LAMA+LABA+ICS	2.4	32.5	<0.0001
All LAMA	4.0[§]	53.0	<0.0001
All LABA	66.4	67.2	0.79
All ICS	66.1	60.1	0.07
All ICS+LABA	56.5	56.5	1

Data are presented as median (interquartile range) unless otherwise stated. FEV_1: forced expiratory volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council; SGRQ: St George's Respiratory Questionnaire; LAMA: long-acting muscarinic agent; LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid. [#]: May 2002 to May 31, 2006 (before LAMA release); [¶]: June 1, 2006 to June 20, 2012 (after LAMA release); [+]: during the year before inclusion; [§]: patients participating in clinical trials.

These findings are a potential cause of concern for two main reasons. Firstly, they suggest that, in the majority of patients, none of the currently available drug classes is able to provide sufficient relief of symptoms when used alone, even in mildly to moderately severe disease. Therefore, physicians tend to combine pharmacological classes in a high proportion of patients, although this might not translate into optimised benefit/risk/cost ratios for each prescribed drug. This underlines the need for new pharmacological approaches. Secondly, there is obviously an important need to clarify the respective roles and performances of drug classes that are currently available in COPD. Independent clinical studies should be performed to help identifying categories of patients more prone to respond to one treatment than to another (*e.g.* by comparing maximal bronchodilation to anti-inflammatory approaches, in well-defined patient groups).

In conclusion, the arrival of new pharmacological agents for COPD treatment appears to increase the proportion of patients of all severity stages receiving double or triple therapy, suggesting large unmet needs in terms of treatment effectiveness and strategy assessment.

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New agents for COPD treatment appear to increase overall treatment intensity in all severity categories http://ow.ly/BS6Wq

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Volumetric and scintigraphic changes following endoscopic lung volume reduction

To the Editor:

Bronchoscopic treatment of emphysema represents an emerging therapeutic modality for advanced emphysematous lung destruction in chronic obstructive pulmonary disease (COPD). Within the proposed techniques for endoscopic lung volume reduction (ELVR), a significant amount of experience exists for the placement of endobronchial valves (EBV) (Zephyr® valves; Pulmonx, Inc., Redwood City, CA, USA) targeting atelectasis of the treated, emphysematous lobe [1, 2]. However, post-procedural clinical