Real-life use of inhaled corticosteroids in COPD patients *versus* the GOLD proposals: a paradigm shift in GOLD 2011?

To the Editor:

Clinical trials in chronic obstructive pulmonary disease (COPD) patients have shown that the long-term use of inhaled corticosteroids (ICS) in COPD patients reduced the number of exacerbations per patient per year and improved health status [1]. Early studies have suggested increased ICS efficacy in patients with low lung function and frequent exacerbations [2]. The efficacy was reinforced when ICS was used in conjunction with long-acting β_2-agonists (LABA) [3]. In most countries, health authorities approved ICS/LABA combinations in COPD patients with severe airflow impairment and frequent exacerbations, as also recommended in the Global Initiative for Obstructive Lung Disease (GOLD) 2007 document [4]. However, several surveys found poor adherence to this proposal among primary care physicians and pulmonologists in "real life", ICS being often prescribed at a milder stage of the disease.

The GOLD 2011 document proposed a new multidimensional system for the assessment and management of patients with COPD [5]. This system classifies COPD patients into four categories (A, B, C and D) based on the level of symptoms (dyspnoea or global clinical impact) and the risk of future exacerbations, as assessed using the severity of airflow limitation and the past history of exacerbations [5]. The GOLD 2011 proposal, largely based on expert opinions, was challenged by studies investigating the association of COPD categories with future risk of exacerbation, hospitalisation and mortality [6, 7]. Notably, some authors found that subgroups of categories C and D (named C1, C2, C3, D1, D2 and D3) had different risks of exacerbation depending on whether a patient enters these categories because of low forced expiratory volume in 1 s (FEV_1) only, past exacerbations only or both criteria combined [6]. Importantly, GOLD 2011 also proposed substantial changes in therapeutic options, ICS/LABA combinations being proposed as the first-line treatment option in GOLD categories C and D [5]. Thus, some patients with FEV_1 >50% predicted or without repeated exacerbations could now be eligible for ICS/LABA therapy [5]. Consequences of this change in the indication of ICS/LABA combinations between GOLD 2007 and GOLD 2011 have not been specifically addressed in any clinical study to date.

Here, we investigated ICS use in real-life COPD patients and compared it to GOLD 2007 and GOLD 2011 proposals. Data were issued from the French COPD longitudinal cohort INITIATIVES BPCO, enrolling COPD subjects in 17 university hospitals [8]. For this analysis, data were extracted between June 2006 (when the long-acting muscarinic antagonist (LAMA) tiotropium was released in France) and June 2012 (before dissemination of the GOLD 2011 document). Classification of these patients (n=421) according to GOLD 2011 is presented in table 1. 253 (60%) patients were using ICS as single therapy (n=9, 2%), double therapy (n=107, 25%; including eight patients using ICS/LAMA and 99 using ICS/LABA) or triple therapy (ICS/LABA/LAMA; n=137, 33%). Based on the GOLD 2007 proposal [4], ICS/LABA was inappropriately prescribed in patients with FEV_1 ⩾50% pred (n=116, 46%) and in those with FEV_1 <50% pred but with fewer than two exacerbations in the previous year (n=62, 25%); ICS monotherapy (n=4) or ICS/LAMA combination (n=1) were also considered inappropriate. Thus, according to GOLD 2007, 183 (72%) out of 253 patients were inappropriately receiving ICS therapy. Because the ICS/LABA combination salmeterol/fluticasone is approved in France in patients with FEV_1 <60% pred and frequent exacerbations, we further examined ICS prescription in patients with FEV_1 ⩾50% to <60% pred: only 13% (n=34) of ICS patients had FEV_1 in this range, of whom only half (n=17) had more than two exacerbations per year. Next, we compared ICS prescription to the GOLD 2011 proposal: ICS were inappropriately prescribed in GOLD A patients (n=44, 17%) and GOLD B patients (n=28, 11%); ICS prescription was also considered inappropriate in GOLD C and D patients receiving ICS alone (n=5, 2%) or ICS/LAMA (n=4, 2%). Thus, according to GOLD 2011, only 81 (32%) out of 253 patients were inappropriately receiving ICS therapy.

These results indicate that the real-life prescription of ICS in COPD patients in France was closer to GOLD 2011 than to GOLD 2007. Changes in proposals on ICS use between GOLD 2011 and GOLD 2007 are not based on new findings or randomised controlled studies (RCTs) [9], but result mostly from differences in interpretation of previously available data by experts. In our cohort, approximately half of the patients receiving ICS had FEV_1 >50% pred. In this group of patients, evidence supporting the prescription of ICS/LABA

TABLE 1 Inhaled respiratory therapy in 421 chronic obstructive pulmonary disease patients according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 classification

	GOLD category										
	Total[#]	A[¶]	B[+]	C[§]				D[ƒ]			
				Total	C1[##]	C2[¶¶]	C3[++]	Total	D1[§§]	D2[ƒƒ]	D3[###]
Any ICS	253 (60)	44 (42)[¶¶¶,+++]	28 (50)[¶¶¶,+++]	69 (59)	26 (54)[¶¶¶]	25 (61)[¶¶¶,+++]	18 (67)	112 (78)	36 (68)[¶¶¶]	19 (68)[¶¶¶]	57 (90)
Any LABA	283 (67)	47 (45)	37 (66)	80 (69)	27 (56)	31 (76)	22 (81)	119 (83)	39 (74)	21 (75)	59 (94)
Any LAMA	223 (53)	50 (48)	34 (61)	50 (43)	27 (56)	10 (24)	13 (48)	89 (62)	28 (53)	17 (61)	44 (70)
ICS alone	9 (2)[¶¶¶,+++]	2 (2)[¶¶¶,+++]	2 (4)[¶¶¶,+++]	0	0	0	0	5 (3)[¶¶¶,+++]	1 (2)[¶¶¶,+++]	1 (4)[¶¶¶,+++]	3 (4)[¶¶¶,+++]
ICS/LABA	99 (24)	17 (16)[¶¶¶,+++]	8 (14)[¶¶¶,+++]	39 (34)	9 (19)	22 (54)[¶¶¶]	8 (30)	35 (24)	14 (26)[¶¶¶]	5 (18)[¶¶¶]	16 (25)
ICS/LAMA	8 (2) [¶¶¶,+++]	4 (4)[¶¶¶,+++]	0	1 (1)[¶¶¶,+++]	1 (2)[¶¶¶,+++]	0	0	3 (3)[¶¶¶,+++]	2 (4)[¶¶¶,+++]	1 (4)[¶¶¶,+++]	0
ICS/LABA/LAMA	137 (33)	21 (20)	18 (32)[¶¶¶,+++]	29 (25)	16 (33)[¶¶¶]	3 (7)[¶¶¶]	10 (37)	69 (48)	19 (36)	12 (43)	38 (60)
LABA/LAMA	28 (7)	4 (4)	8 (14)	6 (5)	1 (2)	3 (7)	2 (7)	10 (7)	3 (6)	2 (7)	5 (8)

Data are presented as n (%). ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonist. [#]: n=421; [¶]: modified Medical Research Council (mMRC) dyspnoea score <2, forced expiratory volume in 1 s (FEV_1) ⩾50% predicted and fewer than two exacerbations per year, n=105 (25%); [+]: mMRC dyspnoea score ⩾2, FEV_1 ⩾50% pred and fewer than two exacerbations per year, n=56 (13%); [§]: mMRC dyspnoea score <2, FEV_1 <50% pred or two or more exacerbations per year, n=116 (28%); [ƒ]: mMRC dyspnoea score ⩾2, FEV_1 <50% pred or two or more exacerbations per year, n=144 (43%); [##]: FEV_1 <50% pred, n=48; [¶¶]: two or more exacerbations per year, n=41; [++]: both FEV_1 <50% pred and two or more exacerbations per year, n=27; [§§]: FEV_1 <50% pred, n=53; [ƒƒ]: more than two exacerbations per year, n=28; [###]: both FEV_1 <50% pred and two or more exacerbations per year, n=63; [¶¶¶]: inappropriate prescription according to GOLD 2007; [+++]: inappropriate prescription according to GOLD 2011.

is limited, except for salmeterol/fluticasone in patients with FEV1 between ⩾50% and <60% pred and frequent exacerbations [3]. Furthermore, the efficacy of ICS/LABA in patients with severe airflow limitation but without frequent exacerbations remains unclear.

In summary, real-life treatment of COPD patients in France anticipated the new GOLD 2011 proposal. This observation questions the development and dissemination of recommendations for chronic diseases, including COPD. Most of the guidelines try to grade recommendations based on evidence, relying on the results of RCTs. This approach is highly acknowledged and well used, but most COPD patients are not eligible for RCTs for many reasons [10]. Clinical trials cannot answer all real-life questions, which may in part explain the marked discrepancies between GOLD 2007 proposals, based on RCT results, and daily practice. By contrast, GOLD 2011 appeared to be a paradigm shift by providing a more flexible expert interpretation of published evidence, leading to proposals reflecting more closely the attitude of clinicians. The GOLD 2011 document presents itself as a research-stimulating set of proposals that should be prospectively validated [5, 6]. We suggest that the proposal to use ICS/LABA outside indications validated by registration RCTs and, in many countries, outside indications approved by regulatory agencies should prompt new academic-based clinical trials to investigate whether the benefit–risk ratio of ICS/LABA remains favourable under these circumstances.

@ERSpublications
Real-life use of inhaled corticosteroid in French COPD patients were closer to GOLD 2011 than to GOLD 2007 proposals http://ow.ly/qyAOo

Pierre-Régis Burgel[1,2], Gaetan Deslée[3], Gilles Jebrak[4], Graziella Brinchault[5], Denis Caillaud[6], Pascal Chanez[7], Isabelle Court-Fortune[8], Roger Escamilla[9], Pascale Nesme-Meyer[10], Jean-Louis Paillasseur[11], Thierry Perez[12] and Nicolas Roche[1,2] on behalf of the Initiatives BPCO scientific committee
[1]Service de Pneumologie, Hôpital Cochin, Assistance Publique Hôpitaux de Paris (AP-HP), Paris, [2]Université Paris Descartes, Sorbonne Paris Cité, Paris, [3]Service de Pneumologie, Hôpital Maison Blanche, Centre Hospitalier Universitaire (CHU) de Reims, Reims, [4]Service de Pneumologie, Hôpital Bichat, AP-HP, Paris, [5]Service de Pneumologie, Hôpital Pontchaillou, Rennes, [6]Service de Pneumologie, Hôpital Gabriel Montpied, CHU Clermont-Ferrand, Clermont-Ferrand, [7]Département des Maladies Respiratoires, Assistance Publique Hopitaux de Marseille, Aix Marseille Université, Marseille, [8]Service de Pneumologie, CHU Saint Etienne, Saint Etienne, [9]Clinique des Voies Respiratoires, Hôpital Larrey, Toulouse, [10]Service de Pneumologie, Hôpital de la Croix Rousse, Lyon, [11]EFFI-STAT, Paris, and [12]Service de Pneumologie, Hôpital Calmette, Lille, France.

Correspondence: P-R. Burgel, Service de Pneumologie, Hôpital Cochin, AP-HP, 27 rue du Faubourg St Jacques, 75014 Paris, France. E-mail: pierre-regis.burgel@cch.aphp.fr

Received: Sept 16 2013 | Accepted after revision: Oct 14 2013

Support statement: The INITIATIVES BPCO cohort is supported by unrestricted grants from Boehringer Ingelheim France and Pfizer France.

Conflict of interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

References

1 Yang IA, Clarke MS, Sim EH, *et al.* Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012; 7: CD002991.
2 Jones PW, Willits LR, Burge PS, *et al.* Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. *Eur Respir J* 2003; 21: 68–73.
3 Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
4 Rabe KF, Hurd S, Anzueto A, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007; 176: 532–555.
5 Vestbo J, Hurd SS, Agusti AG, *et al.* Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; 187: 347–365.
6 Agusti A, Hurd S, Jones P, *et al.* FAQs about the GOLD 2011 assessment proposal of COPD: a comparative analysis of four different cohorts. *Eur Respir J* 2013; 42: 1391–1401.
7 Agusti A, Edwards LD, Celli B, *et al.* Characteristics, stability and outcomes of the 2011 GOLD COPD groups in the ECLIPSE cohort. *Eur Respir J* 2013; 42: 636–646.
8 Burgel PR, Paillasseur JL, Caillaud D, *et al.* Clinical COPD phenotypes: a novel approach using principal component and cluster analyses. *Eur Respir J* 2010; 36: 531–539.
9 Rabe KF, Cooper CB. Global Initiative on Obstructive Lung Disease revised: what constitutes a guideline? *Am J Respir Crit Care Med* 2013; 187: 1035–1036.
10 Herland K, Akselsen JP, Skjønsberg OH, *et al.* How representative are clinical study patients with asthma or COPD for a larger ''real life'' population of patients with obstructive lung disease? *Respir Med* 2005; 99: 11–19.