ERJ Express. Published on October 31, 2013 as doi: 10.1183/09031936.00162313

Letter to the Editor

Title: Real-life use of inhaled corticosteroids in COPD patients vs. GOLD proposals: a paradigm shift in GOLD 2011?

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Word count: 930

References: 13 references

Figure and Table: one table.

Short Title: Real-life use of ICS in COPD

Keywords: ICS, LABA, COPD exacerbations, Global Initiative for Obstructive Lung Disease (GOLD)

Short sentence summarizing our work: "Real-life use of inhaled corticosteroid in French COPD patients were closer to GOLD 2011 than to GOLD 2007 proposals"

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Main manuscript

Clinical trials in chronic obstructive pulmonary disease (COPD) patients have shown that the long-term use of ICS in COPD patients reduced the number of exacerbations/patient/year and improved health status [1]. Early studies have suggested increased ICS efficacy in patients with a low lung function and frequent exacerbations [2]. The efficacy was reinforced when ICS were used in conjunction with long-acting beta2agonists (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 the 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 (dyspnea 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 risks of exacerbations, hospitalizations, and mortality [6, 7]. Notably, some authors found that subgroups of C and D categories (named C1, C2, C3 and D1, D2, D3) had different risks of exacerbations depending on whether a patient enters these categories because of low 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 first line treatment option in GOLD C and D categories [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 yet.

Here, we investigated ICS use in real-life COPD patients and compared it to GOLD 2007 and GOLD 2011 proposals. Data are 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 antimuscarinic agent – 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**. Two hundred and fifty three (60%) patients were using ICS, as single therapy (n=9, 2%), double therapy (n=107, 25% -including 8 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% predicted (n=116; 46%) and in those with FEV_1<50% predicted but with less than 2 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, 183/253 (72%) patients were inappropriately receiving ICS therapy. Because the ICS/LABA combination salmeterol/fluticasone is approved in France in patients with FEV_1<60% predicted and frequent exacerbations, we further examined ICS prescription in patients with 50%≥FEV1<60% predicted: only 13% (n=34) of ICS patients had 50%≥FEV1<60% predicted of whom only half (n=17) had more than 2 exacerbations/patient/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 the GOLD 2011 only 81/253 (32%) 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 evidences based on new findings and randomized 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% predicted. In this group of patients, evidences supporting the prescription of ICS/LABA are limited, except for salmeterol/fluticasone in patients with FEV_1 between 50% and 60% predicted and frequent exacerbations [3]. Further, 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 attitude is highly acknowledged and used, but most of the 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 as 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 if the benefit-risk ratio of ICS/LABA remains favorable under these circumstances.

Funding: The Initiatives BPCO cohort is supported by unrestricted grants from Boehringer Ingelheim France and Pfizer France.

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Table 1. Inhaled and oral respiratory therapy in 421 COPD patients according to GOLD 2011 classification

	Total n=421	GOLD A n=105 (25%)	GOLD B n=56 (13%)	GOLD C n=116 (28 %)				GOLD D n=144 (43%)			
				Total GOLD C	C1 n=48	C2 n=41	C3 n=27	Total GOLD D	D1 n=53	D2 n=28	D3 n=63
ICS (any)	253 (60%)	44 (42%)*,**	28 (50%)*,**	69 (59%)	26 (54%)*	25 (61%)*	18 (67 %)	112 (78%)	36 (68%)*	19 (68%)*	57 (90%)
LABA (any)	283 (67%)	47 (45%)	37 (66%)	80 (69%)	27 (56%)	31 (76%)	22 (81%)	119 (83%)	39 (74%)	21 (75%)	59 (94%)
LAMA (any)	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%)

*** inappropriate prescription according to GOLD 2007; ** inappropriate prescription according to GOLD 2011**

GOLD A = mMRC < 2, FEV_1 ≥50 % predicted and exacerbations/patient/yr < 2
GOLD B = mMRC ≥ 2, FEV_1 ≥50 % predicted and exacerbations/patient/yr < 2
GOLD C = mMRC < 2, FEV_1 <50 % predicted or exacerbations/patient/yr ≥ 2
C1 = FEV_1 <50 % predicted
C2 = exacerbations/patient/yr ≥ 2
C3 = both FEV_1 <50 % predicted and exacerbations/patient/yr ≥ 2
GOLD D = mMRC ≥ 2, FEV_1 <50 % predicted or exacerbations/patient/yr ≥ 2

D1 = FEV_1 <50 % predicted
D2 = exacerbations/patient/yr ≥ 2
D3 = both FEV_1 <50 % predicted and exacerbations/patient/yr ≥ 2