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ORIGINAL RESEARCH

Lack of Clinical Control in COPD Patients Depending on the Target and the Therapeutic Option

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Introduction: According to the Global Initiative for chronic obstructive lung disease (GOLD), when a treatment is not achieving an appropriate response it should be switched taking into account the predominant treatable trait to target (dyspnea or exacerbations). The objective of the present study was to investigate the lack of clinical control according to the target and medication groups.

Materials and Methods: This was a post-hoc analysis of the CLAVE study, an observational, cross-sectional, multicenter study which evaluated the clinical control, and related-factors, in a cohort of 4801 patients with severe chronic obstructive pulmonary disease (COPD). The primary endpoint was the percentage of uncontrolled patients defined as COPD Assessment Test (CAT) >16 or presence of exacerbations in the last 3 months despite receiving long-acting beta$_2$-agonist (LABA) and/or long-acting antimuscarinic antagonist (LAMA) with or without inhaled corticosteroids (ICS). Secondary objectives included the description of sociodemographic and clinical characteristics of patients by therapeutic group and the identification of characteristics potentially associated with the lack of control of COPD including low adherence measured by the test to adherence to inhalers (TAI).

Results: In the dyspnea pathway, lack of clinical control was of 25.0% of patients receiving LABA or LAMA in monotherapy, 29.5% by those with LABA + LAMA, 38.3% with LABA + ICS and 37.0% with triple therapy (LABA + LAMA + ICS). In the exacerbation pathway, percentages were 87.1%, 76.7%, 83.3%, and 84.1%, respectively. Low physical activity and high Charlson comorbidity index were independent factor of non-control in all therapeutic groups. Additional factors were lower post-bronchodilator FEV1 and poor adherence to inhalers.

Conclusion: There are still room for improvement in COPD control. From the pharmacological perspective, every step in treatment have a pool of uncontrolled patients in which a step-up could be considered according to a trait to target strategy.

Keywords: COPD, control, target, dyspnea, comorbidities, treatment

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex and very heterogeneous disorder that presents with differential characteristics and severity.[1,2] Primary goals for the management of COPD are to reduce the symptoms and prevent the exacerbations.[3] Despite the efficacy of pharmacological and non-pharmacological strategies,[4] a number of COPD patients experience them frequently.[5] According to the Global Initiative for chronic obstructive lung disease (GOLD), an initial treatment should be maintained when achieving an appropriate response.[3] Nevertheless, when not, GOLD suggests considering the predominant treatable trait to target (dyspnea or exacerbations), where the exacerbation pathway actually corresponds to the target of both dyspnea and exacerbations. Their pharmacological algorithm involves mainly 4 therapeutic options: long-acting beta$_2$-agonist (LABA) or long-acting antimuscarinic antagonist (LAMA) in monotherapy; the combination of LABA and LAMA (LABA + LAMA); the combination of LABA and inhaled corticosteroid (ICS, LABA + ICS); and triple therapy (LABA + LAMA + ICS). Escalation or de-escalation of medications

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should be based on their efficacy and safety; however, the decision finally yields on healthcare provider's perception.[6] The concept of clinical control has been introduced in COPD for determining the current clinical status of the patients, and thus to improve the management of their disease.[7,8] In Spain, the observational, cross-sectional, multicenter CLAVE study (`Estudio observacional transversal para Caracterizar La EPOC grAVe en España´; Severe COPD categorization in Spain) evaluated the clinical control, and related-factors, in a cohort of 4801 patients with severe COPD.[9] Authors demonstrated that less than one-third of the patients receiving maintenance therapy could be considered as having the disease controlled. Available studies on the clinical control in severe COPD patients are indeed limited.[6,10–12] The primary objective of the present study was to investigate the lack of clinical control according to the predominant treatable trait to target and medication groups.

Materials and Methods

Study Design

This is a post-hoc analysis of data obtained in the CLAVE study.[9] Briefly, patients were males and females aged ≥40 years, active smokers or ex-smokers with a smoking history of ≥10 pack-year, who had diagnosis of COPD; post-bronchodilator forced expiratory volume in 1 second (FEV_1) <50% of predicted; and were receiving a maintenance treatment. Exacerbated patients, who received oral corticosteroids or antibiotics, due to a COPD exacerbation, were not included in the study. Procedures were approved by the Research Ethics Committee of the Hospital Clinic of Barcelona (Spain) and were in accordance with the Declaration of Helsinki.

Endpoints and Variables

In the present post-hoc study, patients from CLAVE study receiving a specified inhaled therapy were included in the analysis. The primary endpoint included the percentage of uncontrolled patients receiving the main therapeutic options, and considering the target. For such aim, patients were initially classified according to the predominant treatable trait to target (dyspnea or exacerbation), following the GOLD's pharmacological treatment algorithm. Only patients showing no exacerbations in the last 12 months were included in the dyspnea pathway; whereas the exacerbation group included patients with exacerbations in the last 12 months. An uncontrolled patient had to show a value for the Spanish version of the COPD assessment test (CAT^{TM}) >16, for the dyspnea pathway; whereas a CAT^{TM} >16 together with exacerbations in the last 3 months, for the exacerbation pathway.[9] The CAT^{TM} is an 8-item questionnaire that evaluates the impact of COPD on health status; where items are scored between 0 (no limitation) and 5 (very limited).[13] Secondary objectives included the description of sociodemographic and clinical characteristics in patients depending on the therapeutic group, ie LABA or LAMA in monotherapy, LABA + LAMA, LABA + ICS, and triple therapy. A last secondary objective was to identify the characteristics in patients potentially associated with the lack of control of COPD for each therapeutic group. Factors initially evaluated in the univariate analysis were: post-bronchodilator FEV_1 (as percentage of predicted; mean value and categorized as <30% and ≥30%), age group (<70 and ≥70 years), place of residence (rural, semi-urban, and urban), smoking status (active smoker and ex-smoker; pack-year of smoking), physical activity (determined with the International Physical Activity Questionnaire; categorized as high, moderate, and low/inactive),[14] hospital level of care (primary care and specialist), adherence to inhalers (using the adherence to inhalers questionnaire; categorized as good, intermediate, and poor),[15] and Charlson comorbidity index (mean value and categorized as ≥2 and 1).[16]

Statistical Analyses

Qualitative variables were expressed as absolute and relative frequencies (%), whereas quantitative ones as the mean and standard deviation (SD). A backward binary logistic regression was carried out to identify patient's features potentially associated with lack of control (Odds ratio, OR; 95% confidence interval, 95% CI). In the univariate analysis, factors showing a significance <0.1 were included in the multivariate analysis. Statistical significance was set when $P < 0.05$. Statistical analyses were performed with SAS version 9.4.

Results

A total of 4778 patients received a specified inhaled therapy in CLAVE study. Of them, 957 patients (dyspnea pathway) showed no exacerbations in the last 12 months [636 (66.5%) being considered as controlled patients, and 321 (33.5%) as uncontrolled ones]. By contrast, 3821 patients (exacerbation pathway) did show exacerbations in the last 12 months. Of these patients, 684 (17.9%) and 3137 (82.1%) are considered as controlled and uncontrolled patients, respectively.

Clinical Control of COPD According to Different Treatment Groups

The distribution of controlled and uncontrolled patients considering the target and the treatment option is shown in Figure 1. Approximately 1% and 2% of patients were not classified in the respective dyspnea and exacerbation pathways, because having a different medication pattern. These percentages represent patients either with other monotherapies other than LABA/LAMA, with other double combinations other than LABA/LAMA or LABA/ICS or with only rescue medication, which were not included in the large groups that were studied. In the dyspnea pathway, non-clinical control was reported in 25.0% of patients receiving monotherapy, 29.5% by those with LABA + LAMA, 38.3% with LABA + ICS, and 37.0% with triple therapy. In the exacerbation pathway, percentages were 87.1%, 76.7%, 83.3%, and 84.1%, respectively.

Characteristics of Controlled and Uncontrolled Patients

Sociodemographic and clinical characteristics of controlled and uncontrolled patients considering their therapeutic option are shown in Table 1. The mean age of all patients was 69 years (SD, 9 years). The mean age was slightly higher in uncontrolled patients than controlled ones, in all medication groups. The mean post-bronchodilator FEV_1 was 39.1% of predicted (SD, 8.3%), slightly higher in controlled patients, compared with uncontrolled ones. The mean mMRC grade of dyspnea was 2.1 (SD, 1.0). The mean Charlson comorbidity index was 2.2 (SD, 1.5). Uncontrolled patients showed a higher dyspnea mean value and Charlson comorbidity index than controlled ones in all therapeutic options.

Factors Associated with Lack of Clinical Control

Factors independently associated with non-control of COPD and considering the therapeutic option is shown in Table 2. Physical activity (low/inactive versus high and moderate versus high) and Charlson comorbidity index (≥2 versus 1) were independent factors of lack of control in all medication groups. Low or inactive physical activity showed higher risk of uncontrolled [OR: 8.1

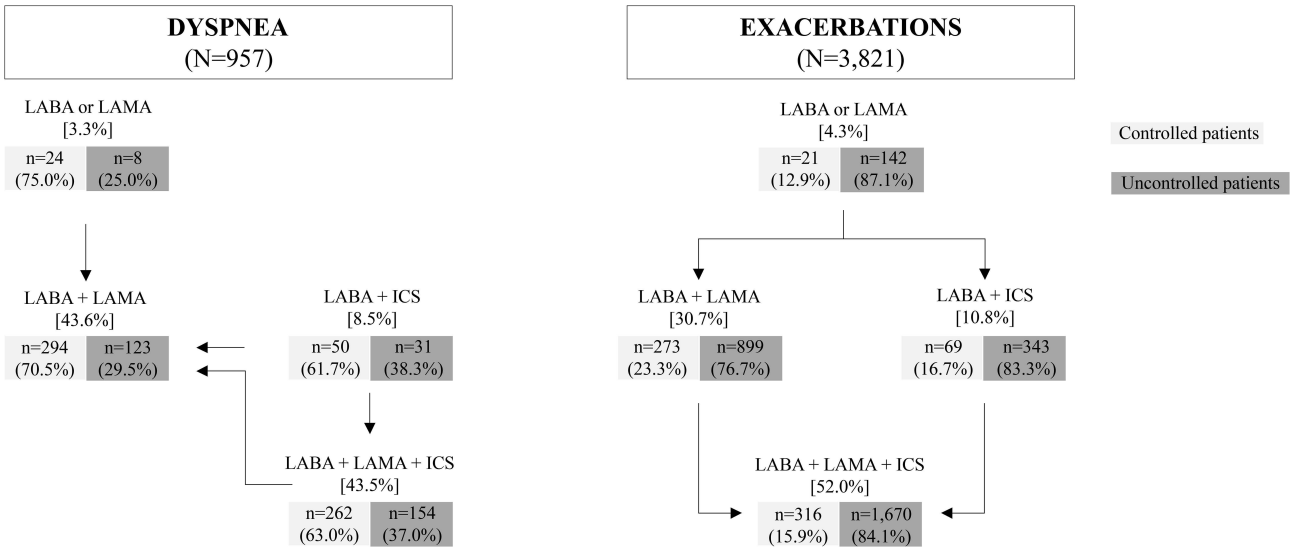

Figure 1 Distribution of controlled and uncontrolled patients considering the predominant treatable target and the therapeutic option (GOLD's follow-up pharmacological treatment algorithm). Percentages in brackets represent the frequency of each treatment option in each respective pathway, whereas those in parentheses are the frequency of control and non-control for each treatment option. Approximately 1% and 2% of patients were not classified in the respective dyspnea and exacerbation pathways because having a different medication pattern.

Table 1 Sociodemographic and Clinical Characteristics of Controlled and Uncontrolled Patients Considering Their Therapeutic Option

	Total (N=4679)	LABA or LAMA		LABA + LAMA		LABA + ICS		LABA + LAMA+ ICS	
		Controlled (N=45)	Uncontrolled (N=150)	Controlled (N=567)	Uncontrolled (N=1022)	Controlled (N=119)	Uncontrolled (N=374)	Controlled (N=578)	Uncontrolled (N=1824)
Age, mean years (SD)	69.5 (9.3)	67.6 (7.8)	71.0 (9.8)	68.8 (8.6)	69.3 (9.2)	67.5 (10.5)	69.7 (10.3)	68.7 (8.7)	70.2 (9.2)
Age groups, n (%)									
< 70 years	2269 (48.5)	30 (66.7)	64 (42.7)	297 (52.4)	508 (49.7)	66 (55.5)	183 (48.9)	301 (52.1)	820 (45.0)
≥ 70 years	2410 (51.5)	15 (33.3)	86 (57.3)	270 (47.6)	514 (50.3)	53 (44.5)	191 (51.1)	277 (47.9)	1004 (55.0)
Post-bronchodilator FEV_1 (% of pred.), mean (SD)	39.1 (8.3)	43.2 (7.1)	38.6 (8.2)	41.7 (6.9)	40.1 (8.0)	43.8 (6.0)	41.5 (7.1)	38.8 (8.3)	37.0 (8.6)
Dyspnea scale, n (%)									
Grade 0	121 (2.6)	6 (13.3)	4 (2.7)	41 (7.2)	15 (1.5)	4 (3.4)	3 (0.8)	30 (5.2)	18 (1.0)
Grade 1	1175 (25.1)	24 (53.3)	39 (26.0)	243 (42.9)	225 (22.0)	56 (47.1)	79 (21.1)	216 (37.4)	293 (16.1)
Grade 2	1771 (37.8)	15 (33.3)	60 (40.0)	225 (39.7)	433 (42.4)	50 (42.0)	147 (39.3)	240 (41.5)	601 (32.9)
Grade 3	1218 (26.0)	0 (0.0)	33 (22.0)	56 (9.9)	284 (27.8)	8 (6.7)	117 (31.3)	82 (14.2)	638 (35.0)
Grade 4	394 (8.4)	0 (0.0)	14 (9.3)	2 (0.4)	65 (6.4)	1 (0.8)	28 (7.5)	10 (1.7)	274 (15.0)
Mean grade (SD)	2.1 (1.0)	1.2 (0.7)	2.1 (1.0)	1.5 (0.8)	2.2 (0.9)	1.6 (0.7)	2.2 (0.9)	1.7 (0.8)	2.5 (1.0)
Exacerbations in the last 3 months, n (%)									
None	2126 (45.4)	45 (100.0)	23 (15.4)	567 (100.0)	265 (25.9)	119 (100.0)	84 (22.5)	578 (100.0)	445 (24.4)
≥ 1	2552 (54.6)	0 (0.0)	126 (84.6)	0 (0.0)	757 (74.1)	0 (0.0)	290 (77.5)	0 (0.0)	1379 (75.6)
Charlson comorbidity index, mean value (SD)	2.2 (1.5)	1.9 (1.0)	2.5 (1.6)	1.9 (1.3)	2.2 (1.6)	1.8 (1.5)	2.3 (1.6)	1.9 (1.4)	2.3 (1.6)

Abbreviations: LABA, long-acting $beta_2$-agonist; LAMA, long-acting antimuscarinic antagonist; ICS, inhaled corticosteroid; SD, standard deviation; FEV_1, forced expiratory volume in 1 second.

Table 2 Factors Independently Associated with Lack of Control of COPD Considering the Therapeutic Option

	LABA or LAMA		LABA + LAMA		LABA + ICS		LABA + LAMA + ICS	
	Odds Ratio (95% CI)	**P**	**Odds Ratio (95% CI)**	**P**	**Odds Ratio (95% CI)**	**P**	**Odds Ratio (95% CI)**	**P**
Post-bronchodilator FEV_1 (% of pred.): <30% versus ≥30%	10.3 (1.1–93.6)	0.039	1.9 (1.3–2.8)	0.002	N.A.	N.A.	1.5 (1.1–2.0)	0.003
Physical activity								
Low/inactive versus high	8.1 (2.4–28.0)	<0.001	4.1 (3.0–5.8)	<0.001	1.8 (0.9–3.6)	0.004	3.7 (2.8–4.9)	<0.001
Moderate versus high	1.5 (0.5–4.6)	0.135	1.5 (1.1–2.0)	0.010	0.7 (0.4–1.4)	0.011	1.7 (1.3–2.2)	0.169
Adherence to inhalers								
Poor versus good	6.6 (2.5–17.8)	<0.001	1.9 (1.4–2.7)	0.002	N.A.	N.A.	2.1 (1.4–3.1)	0.002
Intermediate versus good	0.9 (0.3–2.4)	0.028	1.3 (1.0–1.8)	0.781	N.A.	N.A.	1.3 (1.0–1.7)	0.404
Charlson comorbidity index: ≥2 versus 1	1.5 (1.0–2.1)	0.028	1.5 (1.2–1.9)	<0.001	2.2 (1.3–3.5)	0.002	1.2 (1.0–1.5)	0.038

Abbreviations: LABA, long-acting $beta_2$-agonist; LAMA, long-acting antimuscarinic antagonist; ICS, inhaled corticosteroid; SD, standard deviation; FEV_1, forced expiratory volume in 1 second; 95CI, 95% confidence interval; N.A., not associated (p≥0.05).

(95% CI, 2.4–28.0)] than high physical activity in patients with monotherapy, OR: 4.1 (95% CI, 3.0–5.8) with LABA + LAMA, OR:1.8 (95% CI, 0.9–3.6) with LABA + ICS, and OR: 3.7 (95% CI, 2.8–4.9) with triple therapy. For Charlson comorbidity index (≥2 versus 1), ORs were: 1.5 (95% CI, 1.0–2.1), 1.5 (95% CI, 1.2–1.9), 2.2 (95% CI, 1.3–3.5), and 1.2 (95% CI, 1.0–1.5), respectively. Additional factors were post-bronchodilator FEV_1 (<30% versus ≥30%), and adherence to inhalers (poor versus good) in the monotherapy group, LABA + LAMA, and triple therapy.

Discussion

Clinical control in COPD is assessed to determine the clinical status of patients and optimize their treatments.[6] A patient may be considered controlledif, during follow-up, show minimal or no symptoms, no acute exacerbations have occurred since the last follow-up visit, and no impairment in quality of life has been seen while receiving the current treatment.[17] CAT™ is a one of the most important tools used on GOLD strategy, able to determine how the disease impacts on the life of the patient.[3,12] The present study aimed at complementing the information from the GOLD's therapeutic algorithm by providing the frequency of uncontrolled patients for each therapy option, the sociodemographic and clinical profile of the patient that frequently requires each option, and the features potentially associated with non-control.

To our knowledge, this is the first study evaluating the lack of clinical control considering the target and the therapeutic option. Our study included patients from the CLAVE study,[9] which involved those with severe disease. Most of them (416 in the dyspnea and 1986 in the exacerbation pathway) were receiving triple therapy. The frequency of control in the dyspnea pathway (assessed with CAT™) was higher than the non-control in all medication groups; in contrast to found in the exacerbation pathway (assessed with CAT™ and exacerbations in the last 3 months), where non-control was more prevalent than control.

GOLD guidelines provide recommendations to uncontrolled patients depending on the pathway.[3] In the dyspnea pathway, the combination of LABA + LAMA is recommended for patients with persistent breathlessness or exercise limitation receiving a LABA or LAMA in monotherapy. For uncontrolled patients taking LABA + ICS, the escalation to triple therapy can be considered or, if ICS was inadequate, to LABA + LAMA. Other causes of dyspnea, the inhaler technique, physical activity and the adherence should also be investigated.[3] In the exacerbation pathway, the escalation to LABA + LAMA or LABA + ICS is recommended in patients with persistent exacerbations receiving monotherapy. With recurrent exacerbations on LABA + LAMA, and depending on blood eosinophils, the recommendation is to escalate to triple therapy (if eosinophils ≥100 cells/μL) or to add roflumilast or azithromycin (if <100 cells/μL). Similarly, triple

therapy is recommended in patients with further exacerbation on LABA + ICS or, if inadequate response to ICS, to LABA + LAMA. Finally, an uncontrolled patient receiving triple therapy may consider one of the three following options: add roflumilast, macrolide, or stopping ICS.[3] Using this step-up approach, we hope to get better control results. However, the medication was positively correlated with the number of uncontrolled patients, which might be probably explained by the severity bias from the observational nature of the study, since those patients with a more severe condition (lower FEV1, higher dyspnea score) used a more intensive treatment (triple therapy).

On the other hand, in our study, factors associated with non-control of COPD were in agreement with those proven to participate in disease severity, ie declined pulmonary function, low levels of physical activity (or inactivity), poor adherence to inhalers, and higher presence of comorbidities.[18–22] Indeed, both physical activity level and Charlson comorbidity index were significant factors of non-control presented in all medication groups. Low physical activity levels have been associated with a greater lung function impairment, incidence of comorbidities (such as cardiovascular diseases, diabetes, hypertension, depression), and thus with a higher risk for all-cause mortality.[20,21] In our study, the probability of non-control was up to 8.1 times higher in patients with low/intermediate activity level receiving LABA or LAMA in monotherapy, compared with those with high physical activity level. Comorbidities are frequent in COPD patients.[18] They complicate the therapeutic approaches and contribute greatly to poor health outcomes.[23] In our cohort of patients, when evaluating comorbidities as a continuous variable (Charlson comorbidity index ≥2 versus 1), the risk for COPD non-control was up to 2.2 times higher in patients receiving LABA + ICS. Bronchodilators represent the keystone in the COPD control, as they improve pulmonary function and reduce symptoms and exacerbations.[24] However, the adherence to medications is especially poor, with non-adherence rates of 50–80%.[25,26] The non-adherence of bronchodilators has been correlated with greater risk for morbimortality, higher number of hospitalizations, and impaired quality of life.[19] In our study, patients receiving LABA or LAMA in monotherapy with poor adherence to the medication had 6.6 times higher probability of non-control than those with good adherence. Finally, airway obstruction (determined by FEV_1) has been associated with disease progression and is indicative of poor clinical control.[22] In our study, a patient receiving LABA or LAMA in monotherapy with FEV_1 <30% of predicted had 10.3 times higher likelihood of non-control than those with FEV_1 ≥30%. It is interesting to note that active smoking was not among factors associated with non-control, since it is one of the most important factors impacting on the natural history of the disease.[27] The main limitation of the present study is its post-hoc design, not specifically designed to fulfil primary and secondary endpoints. Nevertheless, it has an exploratory nature (the correlation between therapeutic options, clinical control, and patient characteristics). Observations must be subsequently checked in further, properly designed, prospective clinical trials with large cohort of patients.

Conclusions

In conclusion, regarding the management of the disease, there are still room for improvement in the COPD control. From the pharmacological perspective, every step in treatment have a pool of uncontrolled patients in which a step-up could be considered according to the GOLD's follow-up pharmacological treatment algorithm.

Abbreviations

COPD, Chronic obstructive pulmonary disease; GOLD, Global Initiative for chronic obstructive lung disease; CI, confidence interval; CATTM, COPD assessment test; ICS, inhaled corticosteroid; LABA, long-acting beta2-agonist; LAMA, long-acting antimuscarinic antagonist; SD, standard deviation; FEV1, forced expiratory volume in the first second.

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Data Sharing Statement

Data is available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

Procedures were approved by the Research Ethics Committee of the Hospital Clinic of Barcelona (Spain) and were in accordance with the Declaration of Helsinki. All participants provided informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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