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1. ABSTRACT

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Report date: 09 FEB 2021	Study number: 1237-0070	Version/Revision: Not applicable	Version/Revision date: Not applicable
Title of study:	Non-interventional, cross-sectional, multicenter study to describe the exacerbations profile of COPD patients Treated with ICS in a real-life primary care population in Spain. OPTI Study.		
Keywords:	Chronic Obstructive Pulmonary Disease (COPD), Inhaled corticosteroids (ICS), primary care, exacerbations, GOLD 2019, GesEPOC 2017, Real World Evidence (RWE)		
Rationale and background:	Inhaled corticosteroids (ICS) have proven useful for COPD patients with frequent exacerbations despite optimal bronchodilator treatment. However, ICS has not been proven to reduce mortality, and long-term use is associated with increased side effects. Clinical guidelines have addressed this issue (GOLD 2017 and GOLD 2019) by recommending ICS for patients with $\geq$ two exacerbations or $\geq$ one exacerbation leading to hospital admission [2] [7]. For patients not meeting these criteria, long-acting bronchodilation is preferred. Despite this, 61% of COPD patients are treated with ICS [4]. In 2017, a Spanish consensus in the use of ICS recommended that ICS therapy should be withdrawn in patients without exacerbations in the previous two years [5] [1].		
Research question and objectives:	<u>Primary Objective:</u> - To describe the patient profile for patients treated with ICS at the time of study visit, measured by proportion of patients currently on ICS who did not have moderate/severe exacerbation in the year prior to the study visit. <u>Secondary Objectives:</u> - To describe the patient profile for patients not treated with ICS at the time of study visit. - To assess the proportion and the number (count) of patients with COPD treated with ICS at the time of study visit with or without moderate or severe exacerbations, both in the previous 1 year and previous 2 years before the study visit. - To assess the proportion and the number (count) of patients with COPD not treated with ICS at the time of study visit with or without moderate or severe exacerbations, both in the previous 1 year and previous 2 years before the study visit. - Use of rescue medication.		

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	- Adherence to treatment recommendations according GesEPOC guidelines. - To describe ICS-related adverse events.		
Study design:	A non-interventional, descriptive, cross-sectional cohort, and multicentre study of COPD patients attending Spanish Primary Care centers across the entire territory. The study's design imposed a single study visit, which coincided with patients' regular visits as part of their disease's routine follow-up. After signing the informed consent (if the patient agreed to participate in the study) patients were asked to answer the breathlessness scale (mMRC) and the CAT – COPD Assessment Test at the unique study visit. Other variables needed to answer study objectives were obtained directly from patient medical records. The end of the study visit was the end of the study for each patient.		
Setting:	A total of 185 principal investigators (PI) from Spanish Primary Care centers were planned to participate in the study between September 2018 and January 2020. Finally, only 151 PIs were able to include patients. DBL was done in May 2020.		
Subjects and study size, including dropouts:	922 patients were enrolled, of which 21 were non-eligible; in turn, the Full Analysis Set totaled 901 COPD subjects. Eligible patients had to meet all of the inclusion criteria and not meet any exclusion criteria: Inclusion criteria: - Written informed consent before participation. - Female and male patients ≥ 40 years of age. - COPD diagnosis for more than 2 years before the study visit. - Previously confirmed COPD diagnosis (post-bronchodilator FEV ₁ /FVC ratio <70%) - Clinical data available for 2 years before the study visit. - Ability to complete CAT – COPD Assessment Test. Exclusion criteria: - Current participation in any clinical trial involving a drug or device. - A moderate or severe exacerbation (requiring oral corticosteroid, antibiotics or hospitalisation) during the study visit or within 4 weeks before the study visit.		

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Variables and data sources:	Data used for this study was extracted from clinical charts or measured at the study visit. Variables obtained from clinical charts included: • COPD diagnosis and characteristics; • COPD treatment, with or without ICS; • number and type of exacerbations in the last two years; • socio-demographic and clinical characteristics; • rescue and concomitant medication; • commonly ICS-related adverse events; and • comorbidities (COTE index, asthma and atopy history). Variables measured at the study visit included the patients' questionnaires (mMRC and CAT). And these variables were autocalculated according the information recorded in the eCRF: GOLD 2019 spirometric classification, GOLD 2019 patient group and BODEx.		
Statistical Methods:	Continuous variables were summarized using mean, standard deviation (SD), median and quartiles, minimum and maximum and number of valid and missing cases. Categorical variables were summarized with number of valid cases and column percentage over the total valid responses. The two-sided 95% confidence interval was presented for primary and secondary outcomes. P-values were provided as descriptive representations of the data, since no confirmatory testing was planned. All analyses were conducted using SAS Enterprise Guide version 7.15. The primary analysis consisted of the proportion of patients, currently on ICS, who did not have or had moderate/severe exacerbations in the year prior to the study visit, so current treatment with ICS was presented according to the presence or not of moderate/severe exacerbations in the previous 365 days. The primary analysis was performed for the patients in the FAS currently receiving ICS, understanding that these patients could make inappropriate ICS use.		

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		The use of ICS was analyzed using number of patients in each category and percentages (absolute and relative frequencies). The 95% confidence intervals were provided based on Wald's (Normal Approximation) method for each group. Percentages were compared using Chi-Square test or Fisher's exact test. Secondary analyses were conducted as follows: - ICS use in the two years prior to the study visit Number and proportion and 95%CI of patients with COPD treated with ICS at the time of study visit with or without moderate or severe exacerbations in the previous 2 years before the study visit was presented for the FAS population. - Moderate or severe exacerbations in COPD Number (count) of moderate or severe exacerbations in the previous 1 and 2 years before the study visit in COPD patients according to ICS use at time of study visit was presented for the FAS population. At an exploratory level, negative binomial regression, using backward selection procedures with p-value <0.05 to stay in the model, was used for modelling discrete-count variables, as the number of moderate or severe exacerbations (counts), both for first and second previous years. - General patient profile for COPD patients Descriptive statistics were used for describing the patient profile, including sociodemographic, clinical variables, exacerbations, COPD characteristics, comorbidities and treatments. This analysis was performed for the FAS. - Rescue medication use Number and percentage of patients who used rescue medication (global and for each treatment) in the last year and in the last two years was described in the FAS population. This percentage was calculated using as denominator the FAS set and was stratified by ICS treatment at the study visit.	

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	- Adherence to GesEPOC 2017 treatment recommendations guidelines Number and percentage of adherent patients (considered to be treated according to the GesEPOC 2017 guidelines) was presented. This analysis was performed for the FAS population and described according to the number of exacerbations in the last year prior to study visit. - ICS-related adverse events Number and percentage of patients with commonly ICS-related adverse events were reported. This analysis was performed for the FAS population. No interim analysis was conducted.		
Results:	Primary outcome The full analysis set included 901 eligible COPD patients treated within the Spanish national health system's primary care, of which 80.4% (n=724) were males and 19.6% (n=177) were females, mean age of 70.97 (9.82) years, 99.2% were Caucasian (n=894) and 47.9% (n=432) were currently treated with ICS. Within ICS treated patients, a significant proportion of patients (62.5%) had not experienced moderate/severe exacerbations in the year before the study visit. Secondary outcomes FAS population was used for secondary outcomes. Patients treated with ICS experienced a considerably higher proportion of moderate or severe exacerbations both in the year prior and 2 years prior to the study visit (37.5% and 46.8%, respectively), when compared to non-currently treated ICS patients (16.6% and 22.8%, respectively). The proportion of patients who did not experience moderate or severe exacerbations during the two years prior to the study visit totaled 53.2% among ICS-treated patients, and 83.4% and 77.2% among non-ICS treated patients during the year and two years prior to the study visit, respectively.		

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	The mean (SD) number of moderate or severe exacerbations was 0.72 (1.23) during the year prior to the study visit and 1.27 (1.99) during the two years prior to the study visit for ICS treated patients, and 0.26 (0.77) and 0.43 (1.25) for non-ICS treated, respectively. The mean (SD) BMI of ICS treated patients was 28.4 (5.3) Kg/m², and 31.5% were obese or severely obese, compared to non-ICS treated patients (mean (SD) of 28.4 Kg/m² (5.1)) and 32.3% were obese or severely obese. Regarding smoking habits, among ICS treated patients, 28.8% were smokers and 62.8% ex-smokers, while 33.5% of non-ICS treated patients were smokers and 57.6% ex-smokers. ICS treated patients in comparison to non-ICS treated ones, tended to have a longer COPD diagnosis, with a mean (SD) time of 10.2 years (6.1) and 8.9 years (5.5), respectively. ICS treated patients held higher proportions of all GesEPOC 2017 phenotypes (Exacerbator with emphysema COPD: 12.9% in ICS-treated compared to 6.8% in non-ICS treated; Exacerbator with chronich bronchitis: 28.0% in ICS-treated compared to 17.6% in non-ICS treated; Asthma-COPD overlap syndrome: 27.8% in ICS-treated compared to 5.7% in non-ICS treated), except for non-exacerbators (31.2% in ICS-treated and 69.9% in non-ICS treated). ICS treated patients had twice as high proportion as non-ICS treated patients in GOLD 2019 III-IV categories (24.4% and 3.6%, compared to 12.9% and 1.5%, respectively) (spirometric classification using FEV₁). Similarly, the same occurred among GOLD 2019 D patients (38.4% of the ICS treated patients compared to 16.8% of the non-ICS treated ones, respectively). In terms of functional capacity, a higher proportion of ICS treated patients had a higher impact from their disease, as summarized by a mean (SD) BODEx of 1.93 (1.72) compared to 1.15 (1.21) in non-ICS treated, a mean (SD) CAT 16.06 (8.03) compared to 12.96 (7.25) of non ICS treated, and a higher proportion of mMRC grade 2 and above (53.7% compared to 37.7% in non-ICS treated).		

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	The proportion of patients with elevated blood eosinophils (both in terms of the 3.6 % cut point for percent values (p75) and the 300 cel/μl threshold for count values) was higher among patients currently treated with ICS (31.6%) compared to non-ICS treated patients (26.2%). Among COPD patients, the most common treatment patterns were LAMA+LABA (35.1%) and LAMA+LABA in combination with ICS (35.2%). COPD treatment in patients with ICS-use were mostly LABA+LAMA+ICS combinations (73.4%), while the majority of non-ICS treated patients were treated with LAMA+LABA (67.4%). The proportion of patients requiring rescue medication use was considerably higher among ICS treated patients, both in the year (63.9% compared to 41.4% among non-ICS treated, p<0.001) and two years prior to the study visit (65.7% compared to 43.9% among non-ICS treated, p<0.001). Salbutamol was the most frequently prescribed medication, irrespective of ICS use both in the year and two years prior to the study visit (proportion of SABA use in the 2 years prior to the syudy visit: ICS treated 58.6%, and non-ICS treated 35.4%). Treatment for a considerable proportion of patients could be considered non-adherent to the GesEPOC 2017 guidelines at the time of the study visit. Non-adherence (encompassing both lack of ICS when recommended or use of ICS when not recommended) was observed for 34.7% of patients, of which the majority of non-adherence corresponded with use of ICS when not recommended. Non-adherent patients represented 63.9% of ICS treated patients. The proportion of patients with histoy of ADRs commonly related to ICS use during the 2-years before the study visit was 1.6% and the frequency of serious ICS-related ADRs was 0.3%. No ADRs associated with BI drugs were reported in the study (N=441 patients exposed to BI drugs).		
Discussion:	This study describes ICS-treatment patterns in a nationwide COPD cohort treated within primary care, in which all regions of Spain were represented. Overall, of the 901 eligible patients, 47.9% (n=432) were currently treated with ICS. A significant proportion of these patients (62.5%) did not experience moderate/severe exacerbations in the previous		

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		year, although those patients could have experienced exacerbations the year before the ICS was first prescribed. Considering the total population, treatment for a considerable proportion of them could be considered non-adherent to the GesEPOC 2017 guidelines at the time of the study visit, varying by GesEPOC phenotype and risk stratification. Non-adherence, which encompassed both lack of ICS when recommended and use of ICS when not recommended, was observed for 34.7% of patients. Among these, the majority of non-adherence corresponded with use of ICS when not recommended, and represented 63.9% of ICS treated patients. In these patients, ICS use should be reviewed in order to consider if withdrawal is appropriate. Among GesEPOC phenotypes, non-adherence was highest in both GesEPOC Exacerbators phenotypes - with emphysema COPD (42.0%), and - with chronic bronchitis COPD (44.3%). In conclusion, within a primary care setting, ICS prescription continues to be generalized and significantly higher than expected, considering the treatment recommendations provided by the clinical guidelines. De-implementation strategies, which account for the possible drivers for ICS-misuse observed in the study, may be appropriate to improve overall COPD patient care.	
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Names and affiliations of principal investigators:		The coordinating investigators were the following: 	