ORIGINAL ARTICLE

Role of inhaled corticosteroids in the exacerbation rate of moderate chronic obstructive pulmonary disease

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ABSTRACT

Aim To analyse frequency of chronic obstructive pulmonary disease (COPD) exacerbation in patients on therapy with inhaled corticosteroids (ICS) and relevant factors that influence the rate of COPD exacerbations in a subgroup of moderate illness, like FEV1, comorbidities and other concomitant therapy.

Methods The study included patients with moderate COPD with at least 10 pack-years history of smoking and accompanying cardiovascular comorbidity. Demographic data, frequency of exacerbations and information about proscribed treatments – ICS alone or in combination with long acting beta agonist (LABA), were collected from medical records for the previous 12 months from the index date.

Results Data were collected for 210 patients (170 males) with the mean age 65.63±8.66 years, 72 of which were treated with a fixed combination of long acting beta blocker (LABA) and ICS. Significantly more frequent exacerbations were detected in patients using ICS $p<0.0001$) and having higher Modified British Medical Research Council (mMRC) score $p=0.004$). No statistically significant difference was registered related to ratio of FEV_1/FVC ($p=0.121$) or a number of cardiovascular comorbidities per patient ($p=0.969$).

Conclusions: Our results present a small contribution to the current scientific discussion about the use of ICS in COPD treatment. Further prospective studies are needed to confirm the impact of ICS on the frequency of COPD exacerbations.

Key words: chronic obstructive pulmonary disease, inhaled corticosteroids, exacerbations

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is preventable and treatable long-term disease characterized by progressive airway obstruction. Common risk factors of COPD are tobacco smoking and airway pollution. The problem of underdiagnosis and under-treatment of COPD has been recognized for a while (1-3) and it seems that more than 70% of patients at the moment of first diagnosis already have moderate to severe COPD (2).

According to the Global Strategy for the Diagnosis, Management and Prevention of COPD by Global Initiative for COPD updated in 2017 (4) treatment goals are reduction of symptoms, reduction of severity and frequency of exacerbations, improvement of exercise tolerance and health status. Inhalation therapy is preferred in the COPD treatment (4). The first option for the management of shortness of breath in patients with occasional dyspnea is short acting bronchodilator (SABA). Prescription of long-acting bronchodilators (LABD) is expected in the case of progression of the disease with decline of forced expiratory volume in 1st second (FEV1). Recommended treatment options are long-acting beta-2 agonists (LABA) and long-acting muscarinic agonists (LAMA). Nevertheless, adherence to maintenance therapy seems to be low in COPD patients (4).

According to the latest update of GOLD (2017) (5) long-term mono-therapy with inhaled corticosteroids (ICS) is not recommended, while long-term treatment with ICS/LABA may be considered in patients with frequent exacerbations despite LABA treatment. The ICS and LABA/ICS have been shown to reduce the frequency of COPD exacerbations (1,5). Lung function, health status and reduction of exacerbations are better in patients using ICS combined with a LABA than in patients treated with ICS alone (4,6). Long-term use of ICS is associated with high prevalence of oral candidiasis, hoarse voice and skin bruising (7). Also, introduction of ICS in patients with FEV1<60% of predicted contributes to reducing frequency of exacerbations but is also associated with increased risk of pneumonia (4). Recent European Medicines Agency`s (EMA) Pharmacovigilance Risk Assessment Committee (PRAC, 2016) review suggested an increased risk of pneumonia with ICS and found no difference between different products (8).

New options for COPD treatment and uncontrolled asthma, mostly for overlap syndrome (the term has been subject to changing in recent few years) are biological therapy with monoclonal antibodies and first experiences are positive (6,7). Widespread use of LAMA could be one of the commonest treatments of COPD in future (10-11). Use of biomarkers is another additional guide for performing an adequate treatment of COPD as much as possible (11,12)

The aim of this study was to investigate the use of ICS in practice of moderate COPD treatment in Bosnia and Herzegovina and factors that influence rate of exacerbations in a subgroup of moderate COPD patients. Spirometry parameters, comorbidity and cardiovascular risk were investigated as potential factors for COPD exacerbation.

PATIENTS AND METHODS

Patients and study design

The retrospective research included smokers/former smokers with moderate COPD and cardiovascular comorbidity. Data were collected during the period 2011- 2015 in five Cantons of the Federation of Bosnia and Herzegovina (Sarajevo, Zenica-Doboj, Herzegovina-Neretva, Tuzla and Una-Sana Canton). The data were extracted from patients' medical documentation in local healthcare services in departments of lung diseases.

Methods

Moderate COPD diagnosis was defined according to the GOLD spirometry criteria ($FEV_1 \geq 50\%$ and $\leq 70\%$ of predicted) (13). To consider a patient for inclusion in the study requirements were: a smoker or a former smoker with cardiovascular comorbidity, airway obstruction reversibility confirmed by pre-bronchodilator test, post-bronchodilator ratio of FEV_1 and forced expiratory capacity (FEV_1/FVC) of ≤ 0.70 and the Modified British Medical Research Council score (mMRC2 or higher) (14)

Cardiovascular comorbidities reviewed at inclusion were: coronary artery disease (CAD), previous myocardial infarction (MI), peripheral vascular disease (PAD), previous cerebrovascular accident (CVA) or transitory ischemic attack (TIA) or a combination of two of the following: ventricular arrhythmia (VA), diabetes mellitus

(DM), arterial hypertension (AH) and treated hypercholesterolemia (C).

Patients were excluded in the case of lung cancer or other significant chronic respiratory diseases, suspected or confirmed alpha-1 trypsin deficiency and congestive heart failure (HF) class IV according to the New York Heart Association (15).

Data on exacerbations and proscribed treatments were collected for the period of previous 12 months from the index date. Also, composite variable cardiac comorbidity was formed and included following comorbidities: CAD, MI, HF and VA.

Statistical analysis

Descriptive data were presented as arithmetic mean and standard deviation (SD), while frequencies were expressed as percentages for measured spirometric parameters. Due to differently sized groups and measuring variables mostly at nominal level non-parametric χ^2test was chosen for detecting statistical significance at the level of $p<0.05$. For strength statistics the Cramer's V test was used in the case of a significant χ^2 test result.

RESULTS

The study included 210 patients, of which 170 (81%) were males. The average age of enrolled patients was 65.63±8.66 years, while the average body mass index (BMI) was 27.91±4.68. Most of them were past smokers (Table 1).

Table 1. Characteristics of 210 patients with moderate chronic obstructive pulmonary disease (COPD)

Characteristics/ Clinical information	No (%) of patients
Smoking status	
Past	131 (62.4)
Current	79 (37.6)
Exacerbations	
No	149 (71)
Change of treatment	43 (20.5)
Hospitalization	18 (8.5)
mMRC	
score 2	159 (75.7)
score 3	51 (24.3)
Cardiac comorbidity	
Yes	83 (39.5)
No	128 (60.5)

mMRC, Modified British Medical Research Council

Median number of cardiovascular comorbidities per patient was 3 (range 1 to 7). The most common comorbidities were cardiovascular diseases (Figure 1).

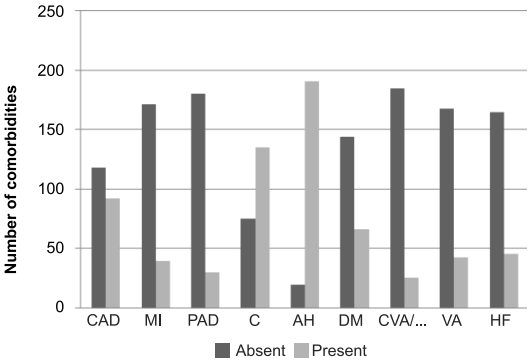

Figure 1. Distribution of patients with different types of cardiovascular comorbidity
CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral artery disease; C, cerebral stroke; AH, arterial hypertension; DM, diabetes mellitus; CVA/TIA, cerebrovascular transitory ischemic attack; VA, ventricular arrhythmia; HF, heart failure

All patients were prescribed short acting beta agonists (SABA) for the use as needed. Eighty-nine (42.4%) patients were treated with a fixed combination LABA/ICS, while 16 (7.6%) used ICS mono-therapy (Figure 2). During different periods of the previous year only 3 (1.4 %) patients used both, either ICS as mono-therapy or ICS/LABA. A total of 96 (45.7 %) were prescribed LABD, mostly in fixed combination with ICS, while 11 (5.2%) used LABA as a mono-therapy and 3 (1.4 %) patients used LAMA (Figure 2).

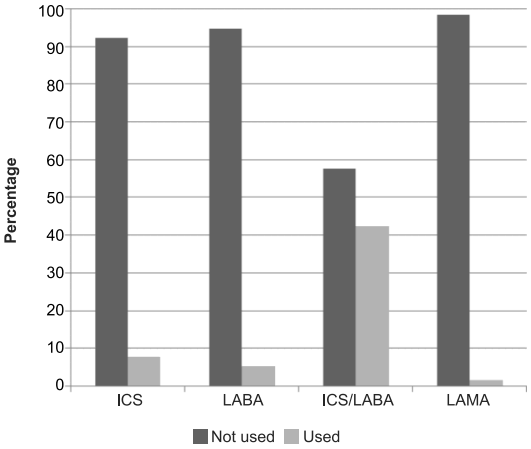

Figure 2. Use of inhalation maintenance therapy during previous 12 months
ICS, inhaled corticosteroid; LABA, Long Acting Beta Agonists; LAMA, Long Acting Muscarinic Activators

Exacerbation in previous 12 months had been significantly more frequent in the group of patients treated with ICS, in fixed combinations or monotherapy, compared to those not treated with ICS (51 vs. 10; $p<0.0001$). Detected Cramer's V value was 0.449 ($p<0.0001$) (Figure 3).

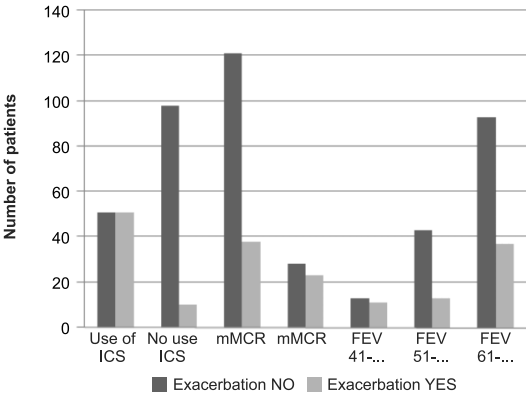

Figure 3. Exacerbations of chronic obstructive pulmonary disease (COPD) according to the use of inhaled corticosteroids (ICS), different Modified Medical Research Council score (mMRC), and different forced expiratory volume in 1st second (FEV_1/FVC)

Average FEV_1/FVC was 61.14±6.93 and according to it the patients were classified in three groups (41-50%, 51-60%, 61-70%). No significant difference was found between frequency of exacerbations and FEV_1/FVC (p=0. 121), while significant difference was found for mMRC score (p= 0.004). Detected Cramer's V value was 0.200 (p=0.004) (Figure 3).

No significant difference was detected between exacerbations frequency and factors such as sex (p = 0357), age below/over 60 years (; p=0.680), BMI below/over 25 p=0.971), current smoking status (p=0.741), presence of cardiac comorbidity (p=0.112) or a number of cardiovascular comorbidities per patient (p=0.969).

DISCUSSION

Our results showed significantly more frequent exacerbations in patients treated with ICS and in patients with higher mMRC score, while no significant difference was found in relation to to FEV1/FVC. One of the primary goals in the COPD management is prevention of exacerbations which often lead to introduction of antibiotics, change of treatment or hospitalization (16,17). Hospitalizations are considered to be the major drivers of high costs of COPD management (2,15), that account for up to 86% of direct medical costs (14,15). Different factors are identified to influence likelihood of exacerbations including older age, chronic mucus hypersecretion and decreased FEV1, or comorbidities like heart failure, lung cancer, diabetes, dyslipidemia and hypertension (1). Also, quitting smoking has been recognized as an important factor in COPD management (1,14,16).

Comorbidities significantly contribute to severity of the disease. Cardiovascular diseases are considered to be the common and important comorbidities in COPD patients (4). Comorbidities may influence mortality and frequency of hospitalizations as it was shown in the presented study. The association of COPD and cardiovascular comorbidities has gained attention recently when impact of COPD on mortality and morbidity after myocardial infarction (MI) was detected in the research of Andell et al. (2014) (17). Older age and smoking contribute to both of these diseases, while COPD exacerbation was detected to be associated with increased risk of MI (17).

The most frequently observed cardiovascular comorbidities in our study population are in accordance with the results of Blanchett et al. (5). Authors identified hypertension (65%), diabetes, coronary heart disease (20%), myocardial infarction (14%) and stroke (16%) as the most common comorbidities, with the average number of chronic comorbidities per patient of 3.7 to 9. In our study the percentage is lower, three per patient. Also, our study registered frequency of hospitalizations that is in accordance with results of retrospective analysis of Dalal (15). This study was conducted in the USA and has shown that approximately 90% of patients with COPD diagnosis did not have inpatient or Emergency department visit during the study year.

The effect of ICS on airway inflammation in COPD is not considered to be pronounced (18). One of the large scale clinical studies that raised the question whether prolonged use of an ICS provides benefit over the use of bronchodilators alone was Towards a Revolution in COPD Health (TORCH) trial (n = 6112) (16). TORCH trial showed that salmeterol (50 mg twice daily) reduced the rate of hospitalizations due to COPD exacerbation by 18%, while addition of fluticasone propionate (500 mcg twice daily) was not noted to add significant further benefit (16). Also, the effects of withdrawal of ICS from COPD treatment has been explored. Nadeem et al. conducted a systematic review of ICS withdrawal studies and found no conclusive evidence that the withdrawal of ICS had an effect on the frequency or number of exacerbations (19. 20). Widespread

use of new forms of LAMA is subject of many recent clinical trials (21, 22)

In conclusion, the benefits of the use of ICS in the treatment of COPD are currently under review and our results provide a small contribution to this discussion. The results of the presented study indicate some dependency between frequency of exacerbations and the use of ICS. No statistically significant difference was detected related to registered FEV_1/FVC ratio, while statistically significant difference was attributed to the score on mMRC, as a validated scale for measuring dyspnea. Both variables indicate the level of severity of the disease. Also, the severity of dyspnea measured by validated scale should significantly correlate with FEV_1/FVC ratio, as an objective measure of airflow obstruction (23-27).

Recent trials refer to more exacerbations of COPD after the use of ICS, but further research is needed to position the role of ICS in the treatment of COPD and confirm possible influence on the incidence of disease exacerbations. Position of LAMA as a potential cause of COPD exacerbation should be included in the analysis too.

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Competing interests: None to declare.

REFERENCES

1. Guariscio JA, Ray MS, Finch KC, Self HT. The clinical and economic burden of chronic obstructive pulmonary disease in USA. Clinicoecon Outcomes Res 2013; 5235-45
2. Blanchette MC, Gross JN, Altnam P. Rising costs of COPD and the potential for maintenance therapy to slow the trend. Am Health Drug Benefits 2014; 7:98-106.
3. Dal Negro R. Optimizing economic outcomes in the management of COPD. Int J Chron Obstruct Pulmon Dis 2008; 3:1-10.
4. Punekar SY, Landis HS, Wurst K, Lee H. Characteristics, disease burden and costs of COPD patients in two year following initiation of long-acting bronchodilators in UK Primary Care. Respir Res 2015; 16:141.
5. Global Initiative for Chronic Obstructive Lung Disease. Pocket Guide to COPD Diagnosis, Management and Prevention. A Guide for Healthcare Professionals, 2017 Edition. Global Initiative for Chronic Obstructive Lung Disease, Inc. http://goldcopd.org (10. Aug.2017)
6. Chupp GL, Bradford ES, Albers FC, Bratton DJ, Wang-Jairaj J, Nelsen LM, Trevor JL, Magnan A, Ten Brinke A. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomized, double-blind, placebo-controlled, parallel group, multicentre, phase 3b trial. Lancet Respir Med 2017; 5:390-400.
7. Dekhuijzen PNR, Batsiou M, Bjermer L, Bosnic-Anticevich S, Chrystyn H, Papi A, Rodríguez-Roisin R, Fletcher M, Wood L, Cifra A, Soriano JB, Price DB. Incidence of oral thrush in patients with COPD prescribed inhaled corticosteroids: Effect of drug, dose, and device. Respir Med 2016; 120:54-63.
8. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax 2013; 68:1029–36
9. Mullerova H, Maskell J, Meeraus WH, Galkin D, Albers FC, Gait C. Characterization of COPD patients treated with inhaled triple therapy containing inhaled corticosteroids [ICS], long-acting beta2-agonists [LABA], and long-acting muscarinic antagonists [LAMA] in the UK. Am J Respir Crit Care Med 2017; 195:A4986.
10. Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agusti A, Paggiaro P, Wedzicha JA, Singh D. Blood eosinophils: a biomarker of response to extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2015; 192:523-5.
11. Pavord ID, Lettis S, Locantore N, Pascoe S, Jones PW, Wedzicha JA, Barnes NC. Blood eosinophils and inhaled corticosteroid/long-acting β-2 agonist efficacy in COPD. Thorax 2016; 71:118-25.
12. Bafadhel M, Davies L, Calverley PM, Aaron SD, Brightling CE, Pavord ID. Blood eosinophil guided prednisolone therapy for exacerbations of COPD: a further analysis. Eur Respir J 2014; 44:789–91.
13. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. Updated 2010. http://www.goldcopd.com (12 Aug 2017)
14. Launois C, Barbe C, Bertin E, Nardi J, Perotin JM, Dury S, Lebargy F, Deslee G. The modified Medical Research Council scale for the assessment of dyspnea in daily living in obesity: a pilot study. BMC Pulmonary Medicine 2012; 12:61.
15. American Heart Association. Classes of Heart Failure. https://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp?appName=MobileApp (10 Aug 2017)
16. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007; 356:775-789.

17. Andell P, Koul S, Martinsson A, Sundstrom J, Jernberg T, Smith JG, James S, Lindahl B, Erlinge D. Impact of chronic obstructive pulmonary disease on morbidity and mortality after myocardial infarction. Open Heart 2014; 1:e000002.
18. Horse F, Kiljander T, Lehtimaki L. Annual costs of chronic obstructive pulmonary disease in Finland during 1996-2006 and prediction model for 2007-2030. NPJ Prim Care Respir Med 2015; 25:15015.
19. Dalal AA, Christensen L, Liu F and Riedel AA. Direct costs of chronic obstructive pulmonary disease among managed care patients. Clinicoecon Outcomes Res 2010; 5:341-9.
20. Shina SS, Gurm HS. The double jeopardy of chronic obstructive pulmonary disease and myocardial infarction. Open Heart 2014; 1:e000010.
21. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, Chanez P; MENSA Investigators. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014; 371:1198-207.
22. Nadeem NJ, Taylor SJ, Eldridge SM. Withdrawal of inhaled corticosteroids in individuals with COPD - a systematic review and comment on trial methodology. Respir Res 2011; 12:107.
23. Dhanalakshmi D, Savya S, Kumar S, Krishna Murthy MG, Sowmya J. Relationship between dyspnea MMRC Scale and Forced Expiratory Volume in First Second (FEV1) in chronic obstructive pulmonary disease. Sch J App Med Sci 2016; 4:3544-7.
24. Bhanurekha B, Sasisekhar TVD, Saireddy Y, Indrakeela Girish M. Correlation of MRC dyspnoea scale and forced expiratory volume in first second (FEV1) in chronic obstructive pulmonary diseases. IOSR Journal of Dental and Medical Sciences 2013; 7:55-7.
25. Yancey S, Albers F, Gunsoy N, Harris S, Keene ON. Effect of mepolizumab on exacerbations in asthma patients with features common in COPD. Am J Respir Crit Care Med 2017; 195:A4683.
26. Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Singh D. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomized controlled trial. Lancet 2017; 389:1919-29.
27. Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Martin UJ. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. Respir Med 2012; 106:257–68.