



ISSN: 2277- 7695

TPI 2017; 6(2): 93-96

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www.thepharmajournal.com

Received: 14-12-2016

Accepted: 15-01-2017

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Changes in systemic inflammation markers and severity of symptoms in chronic obstructive pulmonary disease patients receiving adequate basic therapy

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Abstract

Many studies show that systemic inflammation marker levels should be taken into account as a key factor causing extrapulmonary complications and progression of the disease. However, assessment of systemic inflammation severity is not always used in routine medical practice to determine the severity of COPD.

Aim: Determine the severity of systemic inflammation by measuring serum SAA and CRP levels during the stable phase of the disease in COPD patients who received different treatments.

Materials and Methods: We have examined 37 COPD patients. Patients examination included general clinical methods, questionnaires for detecting of severity of symptoms, detecting severity of systemic inflammation by measuring serum SAA and CRP levels. Patients were divided into two subgroups depending on the treatment which they received. Patients of both subgroups were screened twice – at baseline (visit 1) and three months after assignment of adequate standard therapy (visit 2).

Results: If treated inadequately, COPD patients in the stable phase, regardless of severity of their condition, suffer from more intense symptoms, have more relapses over the previous year, and their systemic inflammation levels are higher than in patients who receive long-term therapy adequate to their COPD. Proper three-month COPD treatment helps improve the symptoms to the levels found in patients who receive longer adequate therapy. As soon as three months after initiation, correctly assigned COPD treatment helps reduce systemic inflammation significantly by CRP levels and slightly by SAA levels.

Keywords: COPD, systemic inflammation, C-reactive protein, serum amyloid A

1. Introduction

The key objective of COPD patient management is to achieve long-term stabilisation of the disease and to slow down the progression of symptoms, life-threatening complications and rapid decline in quality of life [8, 9]. This can be achieved by timely prescription of basic medication therapy taking into account the severity of the condition [4, 6].

A comprehensive assessment recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) is important to monitor the efficacy of COPD treatment. [8]. Many studies show that systemic inflammation marker levels should be also taken into account as a key factor causing extrapulmonary complications and progression of the disease [6, 10]. However, assessment of systemic inflammation severity is not always used in routine medical practice to determine the severity of COPD.

It should be noted that even in the stable phase of the pathological process systemic inflammation markers are elevated in COPD patients compared to healthy individuals, however, these markers can return to normal due to the treatment adequate to the severity of the condition [1, 2, 3, 11, 13]. There are publications of studies that assessed changes in systemic inflammation marker levels during exacerbation and after stabilisation of the condition, yet only a small number of the studies investigated changes in systemic inflammation markers during the stable phase of the disease in patients who received different treatments [4, 5, 6].

A large number of systemic inflammation markers are currently being studied in COPD patients but C-reactive protein (CRP) remains the best studied and accessible marker in clinical practice [3, 10]. Researchers are also interested in another, less well understood COPD systemic inflammation biomarker known as serum amyloid A (SAA) protein [11, 12, 13].

Therefore, our study was aimed to determine the severity of systemic inflammation by measuring serum SAA and CRP levels during the stable phase of the disease in COPD patients who received different treatments.

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2. Materials and Methods

We have examined 37 COPD patients (all patients had stage II-IV disease) in a stable pathological process phase (33 (89,18%) men, 4 (10,82%) women; mean age was 63,45±1,18 years, level of forced expiratory volume in one second (FEV₁) was 46,65 [42,00–61,45] % pred.

Patients were divided into two subgroups depending on the treatment which they received: subgroup 1–20 patients, who receiving adequate basic therapy for a long period of time (according to the severity of COPD in accordance with national standards [9]) (men – 18 (92%), women – 2 (8%), the average age was 63,22 ± 1,18 years, FEV₁ – 46.30 [41,00–63,60]% pred., number of exacerbations in the past year was 1 [1–2]). Sub-group 2 consisted of 17 patients who did not receive adequate therapy (did not take medications on a regular basis, or were taking them in inadequate doses), (males was 15 (92%), women–2(8%) (p = 0.863 vs subgroup 1) Average age was 64, 21 ± 1,88 year (p = 0.734 vs subgroup 1), FEV₁ – 40.50 [35,85–49,50]% pred. (p = 0,612 vs subgroup 1) number of exacerbations in the past year was 2 [1–2] (p = 0,033 vs subgroup 1).

Clinical diagnosis of COPD was formulated in accordance with Order No.555 of the Ministry of Health of Ukraine dated June 27, 2013 [9].

All patients were in a stable phase of COPD for at least two previous months.

All patients signed informed consent forms for participation in the study.

Patients of both subgroups were screened twice – at baseline (visit 1) and three months after assignment of adequate standard therapy (visit 2).

Patients examination of both subgroups included general clinical methods (review of complaints, case history, life history), assessment of clinical symptoms. To assess dyspnea severity we used the modified British Medical Research Council (mMRC) scale recommended for COPD patients and containing 5 grades of dyspnea [8, 9]. The global effects of the disease on patient's daily life were measured with the 8-items COPD Assessment Test (CAT) with possible total score from 0 to 40. For symptoms assessment we also used St. George's Respiratory Questionnaire (SGRQ) (domain 'symptoms') [7].

Pulmonary ventilation function was assessed with a morning fasting computer-based spirometry study by using Master Screen Body/Diff system (Jager, Germany). Levels of forced expiratory volume in one second (FEV₁) and forced vital

capacity (FVC) as percentage of the predicted value as well as the FEV₁/FVC ratio were calculated. Reversibility of bronchial obstruction was measured by the change in FEV₁ absolute value (mL) after inhalation of 400 µg of a short-acting β₂-agonist (salbutamol).

Plasma C-reactive protein (CRP) (mg/L) was measured as a systemic inflammation marker by immunoturbidimetric technique. Values of SAA, other systemic inflammation marker, was analyzed in duplicate using a sandwich enzyme immunoassay kit (HK333, Human SAA Hycultbiotech (Netherlands)).

During visit 1 COPD treatment was corrected to patients of subgroup 2 in accordance with the severity of COPD and national standards. [9] We did not change therapy to patients of subgroup 1 because their treatment was corresponded with disease severity.

For statistical analysis of the results we used biometric analysis methodology supported by STATISTICA 6.1 software. Normal distribution was analysed by the mean value and mean error while non-normal distribution was analysed by the median and quartiles (Me [25–75]).

3. Results and Discussion

The data analysis showed that patient groups were comparable in their age and gender at Visit 1 though there were significantly lower relapse rates in subgroup 1 over the past year, which seems to be the result of the long-term adequate basic therapy. The patient subgroups were similar in terms of lung ventilation function measured as FEV₁. This can be explained by the fact that initially both subgroups included patients with ventilation disorders varying from stage 2 to stage 4 according to the GOLD classification [8].

Analysis of severity of COPD symptoms showed that at baseline both patient subgroups were similar in their dyspnea levels as assessed with the mMRC scale, however the subgroups were different in terms of severity of symptoms according to the CAT and SGRQ scores (the 'symptoms' domain). This may be due to the fact that the CAT and SGRQ scores are more focused on COPD symptoms while mMRC scale only measures dyspnea levels. Patients in subgroup 2 had significantly higher severity of COPD symptoms than those in subgroup 1. This lower severity of symptoms in subgroup 1 seems to be the result of the long-term adequate basic therapy (see Table 1).

Table 1: Comparison of symptoms severity and severity of systemic inflammation between subgroups at visit 1

Variables	Subgroup 1 (n=20) visit 1	Subgroup 2 (n=17) visit 1	p
mMRC (score)	1 [1–2]	1 [1–3]	0,502
CAT (score)	15 [11–20]	20 [13–27]	0,021
SGRQ (domain 'symptoms')	44,1 [34,2–59,2]	63,2 [50,1–81,7]	0,031
CRP (mg/l)	4,04 [3,72–4,83]	11,30 [9,0–16,60]	0,000
CAA (ng/l)	220,97 [192,75–247,52]	666,66 [345,63–1346,15]	0,000

It was also found that in subgroup 2 baseline systemic inflammation levels measured by both (CRP and SAA) study markers were significantly higher than in subgroup 1, which may indicate positive effects of the long-term adequate therapy on systemic inflammation in COPD patients (see Table 1). It should be noted that in subgroup 2 baseline systemic inflammation markers were roughly three times higher than in subgroup 1.

At the next stage, we compared changes in severity of systemic inflammation symptoms in both patient groups.

It was established that COPD symptoms levels in subgroup 1 assessed by the mMRC, CAT and SGRQ scores (the 'symptoms' domain) did not change significantly.

FEV₁ in subgroup 1 did not show any significant changes and was 45.1 [41–58.9] (p=0.301 vs Visit 1).

Analysis of changes in systemic inflammation markers showed that at Visit 2 CRP levels in subgroup 1 were significantly lower than at baseline. It should also be noted that CRP levels in patients who received long-term adequate therapy were lower than standard reference values and close

to 3 mg/mL, which can be a favourable predictive index (see Table 2) as some studies showed that COPD patients with relatively high CRP levels (> 3 mg/mL) have higher hospital admission and mortality rates than patients with CRP levels < 3 mg/mL [11]. No similar significant changes in SAA levels

were found in subgroup 1 (see Table 2). SAA seems not to respond to prescribed treatment, and there is evidence that, unlike CRP, SAA levels are lowered even by immunosuppressive (including corticosteroid) therapy [14].

Table 2: Dynamics of symptoms severity and markers of systemic inflammation in patients of subgroup 1

Variables	Subgroup 1 (n=20)		
	visit 1	visit 2	p
mMRC (score)	1 [1–2]	1 [1–2]	0,248
CAT (score)	15 [11–20]	12 [10–16]	0,214
SGRQ (domain 'symptoms')	44,1 [34,2–59,2]	36,7 [27,8–43,3]	0,151
CRP (mg/l)	4,04 [3,72–4,83]	3,24 [2,49–3,81]	0,024
CAA (ng/l)	220,97 [192,75–247,52]	220,36 [175,42–279,83]	0,479

The adjustment in subgroup 2 therapy according to the severity of the condition was accompanied by a statistically significant decrease in severity of COPD symptoms assessed

by the CAT and SGRQ scores while dyspnea levels measured by the mMRC scale remained the same (see Table 3).

Table 3: Dynamics of symptoms severity and markers of systemic inflammation in patients of subgroup 2

Variables	Subgroup 2 (n=17)		
	visit 1	visit 2	p
mMRC (score)	1 [1–3]	1 [1–2]	0,479
CAT (score)	20 [13–27]	15 [12–18]	0,003
SGRQ (domain 'symptoms')	63,2 [50,1–81,7]	38,6 [31,7–46,5]	0,041
CRP (mg/l)	11,30 [9,0–16,60]	4,90 [4,32–6,87]	0,001
CAA (ng/l)	666,66 [345,63–1346,15]	317,79 [217,34–1179,49]	0,772

At Visit 2, FEV₁ level in subgroup 2 was 43.5[39.5–59.0] (p=0.789 vs Visit 1), therefore, no statistically significant improvement in FEV₁ was noted in Group 2 during the study period.

As for severity of systemic inflammation in subgroup 2, after three months of adequate therapy (at Visit 2) CRP levels were significantly lower than at baseline (see Table 3). At the same time, SAA changes median in subgroup 2 was nearly twice lower but statistically insignificant, unlike PSA. It should be noted, given these data, that SAA is much slower to respond to therapy, which is not the case with CRP. This means that systemic inflammation severity assessment only by CRP levels may be insufficient.

Comparison of COPD symptoms and systemic inflammation levels in both patient subgroups at Visit 2 showed that symptoms in subgroup 2 reached subgroup 1 levels after three months of adequate therapy. The Mann-Whitney U test was used to compare the two patient groups at Visit 2 by dyspnea levels as assessed with the mMRC scale (p=0.236 in the patient groups at Visit 2), and severity of COPD symptoms measured with the CAT score (p=0.267) and the SGRQ score (the 'symptoms' domain) (p=0.643)).

Though patients in subgroup 2 had been receiving three-month COPD treatment adequate to their condition, systemic inflammation decreased significantly in such patients yet remained higher than in subgroup 1. CRP and SAA levels in subgroup 2 remained higher than in subgroup 1 (p=0.011, p=0.023, respectively) (see Table 2, 3). A longer period of adequate therapy seems to be needed for a more significant improvement of systemic inflammation.

4. Conclusion

1. If treated inadequately, COPD patients in the stable phase, regardless of severity of their condition, suffer from more intense symptoms, have more relapses over the previous year, and their systemic inflammation levels

are higher than in patients who receive long-term therapy adequate to their COPD.

2. Proper three-month COPD treatment helps improve the symptoms to the levels found in patients who receive longer adequate therapy.
3. As soon as three months after initiation, correctly assigned COPD treatment helps reduce systemic inflammation significantly by CRP levels and slightly by SAA levels.

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