Diagnostic and prognostic role of matrix metalloproteinases in patients with chronic obstructive pulmonary disease

BO Basina, L’I Konopkina and GV Kondrateva

Abstract
In GOLD 2017 updated report was pointed that lung function level does not depend on patients’ category of future risk. That is why continuing of COPD additional risk precursors discussion is still actual. COPD is associated with increased numbers of inflammatory cells and fibroblasts and the up-regulation of proteases such as matrix metalloproteinases (MMPs) resulting in fibrosis of small airways and destruction of the parenchyma. But these markers also constitute innovative direct or indirect targets to modify cardiovascular tissue remodelling in atherosclerosis and heart failure. That is why it is important to understand could really MMP-2 and MMP-9 be markers of bronchial inflammation including patients with COPD.

The aim of our work was to determine the role of initial and dynamic levels of inflammatory markers MMP-2 and MMP-9 as indicators of COPD severity, stability and treatment effectiveness.

We observe patients with verified stable COPD. The levels of MMP-2 and -9 in plasma were determined by ELISA. Investigations were done firstly on screening (visit 1). Then correction of basic anti-inflammatory treatment was done according to national and European guidelines. Repeated studies were done on visit 2 (after 3 months of basic treatment), on visit 3 (after 6 months of basic treatment), on visit 4 (after 12 months of regular basic treatment). Comparison group was patients with verified cardiac disease. Control group was healthy people.

In general levels of inflammatory markers MMP-2 and MMP-9 in COPD patients on visit 1 were significantly higher than in control group, but in subgroups they were almost identical. After 3 months of adequate treatment level of MMP-2 dropped slightly, kept at this level for six months, and in one year it decreased significantly and reached the level of the control group. On the base of regular treatment both MMP-2 and MMP-9 decreased from visit to visit and after 12 month they have been normalized. This fact indicates that these markers could be parameters of effective basic treatment in patients with COPD. Increasing of such inflammatory biomarkers as MMP-2 and MMP-9 are useful index of COPD which indicates on needing of regular basic treatment and dynamic decreasing and normalizing of MMP-2 and MMP-9 during basic treatment are signs of successful therapy during their long-term follow-up.

Keywords: Prognostic role, matrix metalloproteinases, chronic obstructive pulmonary disease

1. Introduction
Chronic obstructive pulmonary disease (COPD) is a debilitating disease that is characterized by reduced lung function, breathlessness, decreased productivity, and poor quality of life [13]. Currently, COPD is the only major cause of mortality with a rising death rate and it is estimated that by 2030 COPD will become the fourth leading cause of death worldwide [9, 10]. The natural history of COPD is often marked by periodic exacerbations in which symptoms of breathlessness and sputum production worsen acutely, resulting in emergency visits and hospitalizations [4, 11, 13].

COPD is considered as a chronic inflammatory disease which is non-specific in nature involving the airway, lung parenchyma and pulmonary vessels which progressively leads to decrease in the airflow. Initiating factors for this inflammatory occurrence, which is not normal, are the toxic environmental conditions and the inflammation often remains even after eradication of the disturbing agent. This non-specific inflammation can activate a variety of inflammatory cells like neutrophils and macrophages and release of various inflammatory mediators, such as IL-8, IL-6, and TNF-α est. [3, 7, 12]. These inflammatory mediators destroy the lung architecture and also promote the neutrophil inflammatory response.

In GOLD 2017 updated report was pointed that lung function level does not depend on patients’ category of future risk [5]. That is why continuing of COPD additional risk precursors discussion is still actual.
COPD is associated with increased numbers of inflammatory cells and fibroblasts and the up-regulation of proteases such as matrix metalloproteinases (MMPs) resulting in fibrosis of small airways and destruction of the parenchyma [6]. But from the other side members of the MMP family share sequence homology, act on interstitial protein substrates, acutely participate in inflammatory processes and chronically mediate tissue remodelling. MMPs are important in vascular remodelling, not only in the overall vasculature architecture but also, more importantly, in the advancing atherosclerotic plaque. MMP activation modifies the architecture of the plaque and may directly participate in the process of plaque rupture. MMPs also participate in cardiac remodelling following myocardial infarction and development of dilated cardiomyopathy. Soluble MMPs are now potential biomarkers in delineating cardiovascular risk for plaque rupture and coronary risk. They also constitute innovative direct or indirect targets to modify cardiovascular tissue remodelling in atherosclerosis and heart failure [8]. That is why it is important to understand could really MMP-2 and MMP-9 be markers of bronchial inflammation including patients with COPD. That is why the aim of our work was to determine the role of initial and dynamic levels of inflammatory markers MMP-2 and MMP-9 as indicators of COPD severity, stability and treatment effectiveness.

2. Materials and methods

We observe 50 patients with verified stable COPD. On screening (visit 1) we found that from them 27 patients with GOLD III-IV use inadequate and not enough anti-screening (visit 1) we found that from them 27 patients with COPD patients on visit 1 were significantly higher than in the control group (table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Main group</th>
<th>Control group</th>
</tr>
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<tbody>
<tr>
<td>MMP-2, cu</td>
<td>134,8±8,8*#</td>
<td>92,5±4,10</td>
</tr>
<tr>
<td>MMP-9, cu</td>
<td>167,1±18,1*#</td>
<td>103,1±5,55</td>
</tr>
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Notes: * - p<0,05 with control group;

According to the analysis of correlation, neither connection between the level of MMP-2 and disease severity (r=0,146; p=0,213), no between levels of MMP-2 and FEV1 (post) (r=0,103; p=0,381) was determined. Between the levels of MMP-9, on the one hand, and the severity of the disease and the level of FEV1 (post) on the other, correlation hasn’t been established (r=0,038; p = 0,748 and r=0,078; p=0,510 respectively). At the same time the level of MMP-2 had a close correlation with the level of MMP-9 (r=0,4666, p=0,00003), indicating a unit direction of system inflammation markers changes in patients with COPD. After 3 months of adequate treatment level of MMP-2 dropped slightly, kept at this level for six months, and in one year it decreased significantly (p<0,05).

3. Results

On visit 1 the condition of patients was stable. Complains and results of physical examination corresponded to the stages of disease: dyspnea, cough with expectoration of viscous sputum, decrease in efficiency. Mean FEV1 (post) was 37,5±1,61% pred.

Levels of inflammatory markers MMP-2 and MMP-9 in COPD patients on visit 1 were significantly higher than in control group (table 1).

Table 1: Initial levels of biomarkers in patients with COPD

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That is why it should be considered what the dynamic changes of plasma levels of MMP-2 can be used as a prognostic factor of further progression of COPD during long-term observation of patients, but only on the base of prolonged (per 1 year) adequate treatment. Plasma levels of MMP-9 in patients during screening similar levels of MMP-2 were significantly higher (almost on 70%) than in the control group. Gradually, from one visit to the next the level of this parameter was declined steadily (p<0,05).

That is why it should be consider what the dynamic changes of plasma levels of MMP-9 can be used as a prognostic factor for long-term follow-up starting from the earliest stages. So on the base of regular treatment both MMP-2 and MMP-9...
decreased from visit to visit and after 12 month they have been normalized (table 2). This fact indicates that these markers could be parameters of effective basic treatment in patients with COPD.

4. Conclusions
1. Increasing of such inflammatory biomarkers as MMP-2 and MMP-9 are useful index of COPD, which indicates on needing of regular basic treatment;
2. Dynamic decreasing and normalizing of MMP-2 and MMP-9 during basic treatment are signs of successful anti-inflammatory therapy;
3. Determining of levels of markers of systemic inflammation (MMP-2 and -9) can be used as additional parameters for assessment of clinical stability in patients with COPD during their long-term follow-up.

5. Reference
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