ABSTRACT

The role of biomarkers obtained from serum, sputum, BALF and lung tissue samples in assessing the activity and targeting therapy of chronic inflammatory and fibrotic diseases of the lungs and bronchi

Introduction

Chronic inflammatory and fibrotic lung and airway diseases represent a heterogeneous group of respiratory tract diseases, both with an initial inflammatory background. Crucial differences in its etiopathogenesis and location significantly influence its clinical manifestation. Considering an extensive progression in science, it is obvious that there is certain heterogeneity among inflammatory processes as well as in etiopathogenesis within the differential diagnosis. Nowadays the aim is to choose best-targetted therapy based on specific endotypes and phenotypes.

Aims

The aim of this study is I) to provide a comprehensive overview of biomarkers of chronic inflammatory and fibrotic lung and bronchi disorders II) to asses a diagnostic role of biomarkers in clinical practice as well as the role of biomarkers when deciding a type of phenotypically targeted therapy in patients with severe refractory asthma.

Methods

The work (ad II) is divided into two parts.

In the first part, we correlated levels of serum biomarkers, biomarkers in induced sputum, bronchoalveolar lavage fluid and ENT findings including nasal biopsies before and after systemic glucocorticotherapy treatment in the group of severe asthmatics. There are three papers/studies dealing with this issue.

The second part is geared towards monitoring the effect of targeted therapy based on phenotypization due to biomarkers. The second part involves 4 papers/studies. Two studies focus on the evaluation of the effect of omalizumab therapy, one study focuses on the role of periostin in the selection of targeted therapy, and the last study evaluates the effect of bronchial thermoplasty.

Statistical analyses used predominantly the Chi-square test, the Spearman correlation coefficient, the Kaplan-Maier algorithm, Friedman's ANOVA, and the Cox regression model;

Results

In the first part, we obtained samples of induced sputum (IS) and bronchoalveolar lavage fluid (BALTE) from 29 patients with severe refractory asthma and compared the applicability of flow cytometry and routine cytological (DCC) and immunocytochemical (ICC) methods to determine the cell profile of the obtained samples. We found out that the flow cytometry method is not suitable for IS and BALF evaluation and that cytological and immunocytochemical method remain the gold standard. Furthermore, we compared samples from IS, BALF and nasal biopsy (NB) in 30 patients before and after treatment of 40mg prednisone/day/1 month. We detected a close relationship between eosinophilic inflammation (EOS) in the upper and lower respiratory tract. We also detected correlation in eosinophil counts presented in NB and IS, but we did not detect any correlation in eosinophil counts in NB and BALTE. The value of ECP in NB correlated with findings in IS and BALTE. After 4 weeks of systemic glucocorticoid therapy, there was a significant reduction in eosinophil counts in IS, BALF and ECP and FENO values. There was not detected any correlation between EOS in NB and FENO before and after administration of systemic glucocorticotherapy. The last study of this first part focused in more

detail on the use of ENT findings (128 patients) in the phenotyping of severe asthmatics. We confirmed the importance of nasal polyposis as a marker of eosinophilia in the lower respiratory tract and its correlation with disease severity and certain specific asthma phenotypes.

In the second part, we confirmed an excellent effect of omalizumab therapy in patients with severe IgE-mediated asthma phenotype in the Czech Republic (114 patients) during the 2-year follow-up in the registry. In another related study with 10year follow-up, we detected significant benefits in patients from our center for severe asthma (55 patients) and in the subgroup of patients with bronchopulmonary aspergillosis. We found that the production of serum periostin is significantly associated with a modality of treatment and the presence of chronic rhinosinusitis with nasal polyps (48 patients). The last pilot study (6 patients) confirmed the satisfying effects of bronchial thermoplasty, the non-pharmacological treatment of asthma, in preselected patients according to functional biomarkers.

Conclusion

Key and practical biomarkers for more precise severe refractory asthma phenotyping, which are essential when selecting targeted therapy, are: total and specific IgE, ECP, peripheral blood eosinophilia, sputum and nasal biopsy eosinophilia, presence and degree of nasal polyposis and reversibility of bronchial obstruction. Serum periostin seems to be a promising biomarker of the phenotype of Th-2 high pathway in asthma and chronic rhinosinusitis with nasal polyps. Cytological and immunocytochemical slide methods seem to be the gold standard in determining the cell profile of induced sputum and bronchoalveolar lavage samples.