Abstract

INTRODUCTION
In recent years there has been a lot of evidence that asthma is etiopathogenetically widely heterogeneous inflammatory disease. Simultaneously with this knowledge, there are new therapeutic possibilities of severe asthma, ie. targeted biological therapy, which reflects their inflammatory heterogeneity. A prerequisite of rational indications of this treatment requires closer asthma phenotyping using available biomarkers.

AIM
The aim of submitted work is as follows:
A) Overview of diagnostics and treatment of asthma in the world and in the Czech Republic with focus on monitoring the effect of targeted therapy of severe asthma selected on the basis of phenotyping using biomarkers.
B) The work is divided into three parts.
1. In the first part it is about evaluating the effect of treatment with anti IgE antibody omalizumab in the Czech Republic since 2007.
2. In the second part, the relationship between the specific allergic profile of patients to the results of treatment with omalizumab in the Czech Republic is examined in detail.
3. The third part deals with the benefit of the periostin investigation in the selection of targeted therapy.

METHODS
In the first part of our work we performed a retrospective post-hoc analysis of patient data with severe refractory asthma from 10 centers in the Czech Republic from 2007 to 2018 treated with omalizumab, which there was enough data relating to treatment results. The treatment effect was evaluated by GETE (Global evaluation of treatment effectiveness), main monitored parameters are the number of severe exacerbations, dose of used systemic steroid, frequency of daily and night symptoms, consumption of relief medication. Data collection had mixed design (cross-sectional and longitudinal).
In the second part, we performed retrospective post-hoc analysis of the same patient set as in part 1, where there was enough data on allergic profile of patients. We compared the results of treatment for subgroups of patients polysensitized (sensitization to at least 3 perennial allergens) with monosensitized to individual allergens or partially polysensitized patients (combinations of individual allergens, but up to 2 perennial).
In the third part, we participated in a study that examined selected clinical parameters that could influence periostin levels in patients with asthma.
Statistical analyzes used predominantly Chi-square test, Mann-Whitney test, T-test, Friedman's ANOVA and Cox regression model, for all analyzes were marked as a statistically significant $P < 0.05$.

RESULTS
1) Data of 279 patients were analyzed (58.3% of women, mean age 52.9 years). Omalizumab treatment presented an 82.8% response rate. Introduction of anti IgE treatment significantly reduces the amount of severe exacerbations, the dose of used system steroids and a number of symptoms of about half
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2) Data of 279 patients were evaluated as in part 1.
We have not shown differences in the representation of individual aeroalergens between responders and non-responders, however we identified the subgroup of responders (polysenzibilized to at least 3 perennial aeroalergens) with better response to treatment (OR = 2.217, p = 0,02).

3) Serum periostin levels were generally decreased in omalizumab-treated asthma patients in comparison to conventionally treated patients (p = 0.025), but there was no overall difference in periostin levels between patients with/without CRSwNP (p = 0.087). We confirmed a significant reduction in periostin levels in patients without concurrent CRSwNP only in the omalizumabtreated subgroup (p = 0.017) in contrast to patients treated by conventional therapy (p = 0.530). Conversely, lower levels of serum periostin in omalizumab-treated patients were discernible only if CRSwNP was not present (p = 0.005), in contrast to patients with CRSwNP (p = 0.386)

CONCLUSION
The Czech Republic became the first country worldwide, where in national recommendations it was established in 2015: phenotyping asthma based on the continuity of clinical manifestations with closer characteristics of inflammation, namely the presence of eosinophilia and allergy, resulting in three basic phenotypes: 1. Eosinophilic allergic, 2. Eosinophilic non-allergic and 3. Non-eosinophilic, non-allergic asthma, which is targeting today's biological treatment either against the IgE antibody or against cytokines regulating the amount and activity of eosinophils.

In the Czech Republic, there is a network of centers of diagnostics and treatment of severe asthma, allowing data collection and evaluation of biological treatment efficiency. In our work we document the high success rate of biological treatment, specifically in patients treated with omalizumab, it is 82.8% of responders.
By analyzing data from the CAR registry, we also confirmed the findings and results of numerous studies, that additive therapy omalizumab is a highly effective tool for treating patients with severe allergic asthma.

Basic biomarkers with the greatest practical impact in biological treatment of severe asthma continue to remain total and specific IgE and eosinophilia in peripheral blood.

According to our knowledge, our study is first worldwide, which provides data on the effects of sensitization by specific allergens or combinations thereof to the results of treatment in patienst with severe allergic asthma treated with omalizumab. Although our conclusions have not shown differences in frequency of presentation of individual allergens between responders or non- responders, however we found that mono- or oligosensitised patients have less likely successful treatment than polysensitised patients, who can represent a different subgroup of allergic diseases.

In our work, we have shown that omalizumab reduces the level of periostin, but the periostin levels are not reduced in the treatment of omalizumab in the presence of chronic rhinosinusitis with nasal polyps (CRSwNP). Although the interpretation of the results is limited due to the small amount of patients examined, our results support the view that allergic patients with CRSwNP can represent a pathogenetically different form of illness.