M U N I

COMMENTARY TO HABILITATION THESIS[1]

Background. Diffuse parenchymal lung diseases, or interstitial lung diseases (ILDs), are a heterogeneous group of diseases characterized by varying degrees of inflammation and pulmonary fibrosis. In many ILDs etiology is unknown, differential diagnosis is often difficult and disease outcome unpredictable. Therefore, these diseases are a challenge for further research.

Aims.This thesis is a commented set of publications (first author/shared first author, coauthor) published in journals indexed in the Web of Science or Scopus databases. There are six main parts of the thesis which correspond to selected aims. Aim 1. To determine prognostic factors in sporadic form of idiopathic pulmonary fibrosis in relation to clinical course. Aim 2. To perform genetic analyses (studies) in families with familial pulmonary fibrosis (FPF) and suspected genetic predisposition for pulmonary fibrosis; evaluate the effect of antifibrotic treatment in relation to the gene polymorphism MUC5B (mucin5B) rs35705950 and DSP (desmoplakin) rs2076295. Aim 3. To perform genetic studies in sarcoidosis and identify associations of HLA polymorphisms with clinical phenotypes. Aim 4. Early detection of cardiac sarcoidosis in asymptomatic patients with pulmonary sarcoidosis. Aim 5. Biomarkers in idiopathic pulmonary fibrosis and sarcoidosis – their significance for diagnosis and prognosis. Aim 6. Immunodeficiency in differential diagnosis of interstitial lung processes and other autoimmune processes.

Methods. Aim 1. Retrospective study of patients with IPF from the registry of patients of our pulmonary department and EMPIRE database (European MultiPartner IPF Registry) evaluating the influence of clinical characteristics, lung function parameters, chest HRCT findings, and treatment on the prognosis. Aim 2. Whole exome sequencing of FPF case with suspicion of rare Heřmanský-Pudlák syndrome; analysis of MUC5B gene polymorphism rs35705950 and DSP gene polymorphism rs2076295 on clinical course and survival in IPF. Aim 3. Next Generation Sequencing (NGS) in 212 sarcodosis patients to analyze associations of sarcoidosis clinical phenotypes and HLA polymorphisms. Aim 4. Evaluate cardiac magnetic resonance imaging using parametric mapping techniques including T1 relaxation time in 113 consecutive sarcoidosis patients to detect early asymptomatic stages of sarcoidosis of the heart. Aim 5. Analysis of selected markers in EBC (exhaled breath condensate) as a non-invasive

[1] The commentary must correspond to standard expectations in the field and must include a brief characteristic of the investigated matter, objectives of the work, employed methodologies, obtained results and, in case of co-authored works, a passage characterising the applicant's contribution in terms of both quality and content.

examination method in patients with ILD in relation to disease development and comorbidities (gastroesophageal reflux); analysis of the influence of surfactant protein A, protein D, Clara cell protein 16, S100 protein, factor 3 trefoil, prostate secretory protein in blood and bronchoalveolar fluid (BALF) on prognosis of selected ILDs. Aim 6. Analysis of the importance of autoantibodies in vasculitis and systemic connective tissue diseases for the diagnosis and prognosis of ILDs; differential diagnosis of granulomatous processes with description of rare granulomatosis; and analysis of the importance of immunological examinations in differential diagnosis of ILDs.

Results. Aim1. In multivariate analysis, age ≥70 years, interstitial HRCT score ≥3, and change in DLCO of ≥15% at month 12 were confirmed as factors negatively influencing IPF overall survival (OS). DLCO changes over time were shown as a better predictor of mortality compared with FVC (forced vital capacity) changes. Based on this analysis, it is necessary to implement the DLCO analysis into clinical trials and routine practice. During a 2-yr follow-up (841 IPF patients, 45.5% received pirfenidone and 25.9% no antifibrotic treatment), less than a quarter of the patients progressed on pirfenidone as assessed by the decline of ≥10% FVC and ≥ 15% DLCO. On pirfenidone, the DLCO (≥10%) declines at 6, 12, 18 and 24 months' and DLCO (≥15%) declines at 6, 18-and 24-months' follow-up were associated with increased mortality. The DLCO decline showed higher predictive value for mortality than the FVC decline in IPF. In patients with no antifibrotics, FVC and DLCO declines were not predictive for mortality. Pirfenidone increases 5-yr OS over no-antifibrotic treatment (55.9% vs 31.5% alive, P = 0.002). Aim 2. We reported a novel *SFTPA1* (surfactant protein A1) gene variant in a family with idiopathic interstitial pneumonia (IIP). We identified a compound heterozygous genotype in HPS1 gene in the proband. Moreover, we identified a pathogenic frameshift variant c.1189delC; p.(Gln397Serfs*2), resulting in a premature stop codon. This variant has been previously associated with HPS. Furthermore, we characterized previously undescribed nonsense variant c.1507C > T; p.(Gln503*), resulting in a premature stop codon and mRNA degradation through nonsense-mediated decay.

We have found by Next-Generation Sequencing (NGS) in IPF patients from the EMPIRE registry that *MUC5B* and *DSP* genotypes may predict IPF risk in general population. We confirmed overexpression of *MUC5B* rs35705950*T allele (55.2% vs. 20.9%, P<0.001) and *DSP* rs2076295*G allele (80.4% vs. 68.3%, P<0.001) in IPF compared to controls. Carriers of *DSP* rs2076295*G allele profited on nintedanib compared to IPF patients with TT genotype who had a shorter OS (hazard ratio (HR) 7.99; 95% confidence interval (CI)=1.56-40.90;

P=0.013) and a faster decline in lung function (HR 9.42; 95%CI=1.91-46.403; P=0.006). These patients with rs2076295 TT genotype benefit from pirfenidone by prolonged OS (P=0.040; HR=0.35; 95%CI=0.13-0.95) compared to nintedanib. Both associations were confirmed by cross-validation analysis. After stratifying by *MUC5B* rs3570595*T allele carriage, no difference in treatment outcome was observed in nintedanib or pirfenidone (P=0.784).

Aim 3. HLA-B*08:01:01, HLA-DRB1*15:01:01, HLA-DRB1*03:01:01, HLA-DQA1*05:01 and HLA-DPB1*01:01:01 occurred with higher frequency in sarcoidosis compared to healthy subjects. Presence of LS associated with HLA-DRB1*03:01, by contrast HLA-DRB1*11:01 and HLA-DQA1*05:09 were more common in patients with progressing disease (stages III, IV). HLA-DRB1*09:01, HLA-DQA1*01:04 and HLA-DQB1*05:03 were more frequent in extrapulmonary sarcoidosis while HLA-DRB1*01:01 and HLA-DPB1*01:01 were overrepresented in patients without extrapulmonary manifestation.

Aim 4. The new MR method using parametric mapping techniques that can differentiate cardiac muscle diffusion processes or more accurate assessment of overall and regional cardiacfunction by evaluating myocardial strains did not show cardiac involvement in 113 patients with pulmonary sarcoidosis.

Aim 5. We have identified that selected ions –most notably sodium, butyrate, and propionate – were elevated in EBC samples of subjects suffering from GERD/EER (gastroesophageal reflux disease, extraesophageal reflux). In addition, pH was also elevated in both patient groups compared to healthy subjects. The ionic analysis and simultaneous pH measurement offer a simple, cheap, fast and non-invasive approach in GERD/EER diagnostics. These parameters of EBC sample alone are not yet able to distinguish the type, severity or the stage of GERD/EER, but can help in pre-selecting the subjects most likely suffering from GERD/EER that may require further confirmatory diagnosis by pH-MII measurement. It is demonstrated that the analysis of EBC samples obtained from patients with various respiratory diseases (chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, sarcoidosis, cystic fibrosis) is feasible in less than five minutes and the ionic profile can be compared with the group of healthy individuals. The analysis of the ionic profile of EBC samples provides a set of data in which statistically significant differences among the groups of patients could be observed for several clinically relevant anions (nitrite, nitrate, acetate, lactate). The developed collection system and method provides a highly reproducible and fast way of collecting and analyzing EBC, with future applicability in point-of-care diagnostics.

In ILDs, seven significant correlations were found: 1) BALF PSP94 level correlated with prognosis of sarcoidosis (P=0.035); 2) BALF SP-D level with pulmonary functions in IPF (P=0.032); 3) BALF SP-D and TFF3 with IPF mortality (P=0.049 and 0.017, respectively); 4) serum TFF3 level with COPD mortality (P=0.006,); 5) serum SP-A with pulmonary functions impairment in IPF (P=0.011); 6) serum SP-D level was associated with HRCT interstitial score in IPF (P=0.0346); and 7) serum SP-A was associated with staging of COPD according to spirometry (P<0.001). Moreover, our analysis showed that some biomarker levels differed significantly among the diseases: 1) BALF SP-D level differed between sarcoidosis and IPF; 2) serum SP-A level differed among IPF, sarcoidosis, COPD and was also different from healthy controls; 3) serum S100A6, S100A11 levels differed among IPF, sarcoidosis, COPD from healthy controls 4) serum SP-D, CC16, TFF-3 levels distinguished IPF patients from healthy controls; and 5) serum CC16, TFF3, PSP94 distinguished COPD patients from healthy controls. Our study shows that some of selected biomarkers should have prognostic value in the analysed lung disorders.

Aim 6. The work on autoimmune processes, immunodeficiencies and connective tissue diseases summarizes comprehensive recommendations for diagnosis and therapy, including immunological examinations and the importance of autoantibodies.

Conclusion. Our work find out the clinical importance of some parameters (DLco) in IPF; positive effect of pirfenidone on survival in IPF; the importance of MUC5B and DSP polymorphisms in IPF with positive trend of nintedanib treatment in *DSP* rs2076295*G carriers and pirfenidone in *DSP* rs2076295 TT genotype; the importance of PSP94 protein in sarcoidosis, and TFF in IPF. Moreover, we described new pathogenic variant of *SFTPA1* gene in FPF and *HPS1* gene in Heřmanský-Pudlák syndrome. We have also proposed recommendations for diagnosis and treatment of FPF. NGS in patients with sarcoidosis confirmed some of the previously described associations of HLA as well as new associations of HLA-DPB1 or HLA-DQA1 polymorphisms with disease clinical course. Moreover, we have developed a collection system and a method providing a highly reproducible analysis of exhaled breath condensate. We conducted pilot studies analyzing markers of oxidative stress and other biomarkers to diagnose gastroesophageal reflux as a frequent comorbidity in pulmonary diseases.

Key words: biomarkers, genetics, immunology, diffuse parenchymal lung disorders, interstitial lung diseases, exhaled breath condensate, clinical characteristics, sarcoidosis, therapy, prognosis

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Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
NA	100	100	NA

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NA	100	70	NA

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NA	100	100	100

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NA	100	100	NA

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Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
NA	100	90	NA

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[3] Bibliographic record of a published scientific result, which is part of the habilitation thesis.

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Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
100	100	100	100

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100	100	100	100

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100	100	100	100

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NA	100	95	NA

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Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
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Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
100	100	100	100

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NA	100	94	NA

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Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
100	100	100	100

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50	50	40	50

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NA	100	100	NA

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NA	100	100	NA

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Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
NA	100	85	100

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Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
NA	100	100	100

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NA	100	100	100