CHARACTERISTICS OF INTERSTITIAL LUNG DISEASES AND FACTORS DETERMINING PROGRESSION - FOCUS ON LUNG DISEASES WITH AUTOIMMUNE FEATURES

PhD thesis

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I. INTRODUCTION

Interstitial lung diseases (ILDs) consist of a heterogenous group of patients (nearly 200 distinct often rare diseases) represented by similar clinical appearances including symptoms, pulmonary function tests (PFT), radiological manifestations. Patients are mostly characterized by mild restrictive ventilatory defect with decreased static parameters in PFT. High-resolution computed tomography (HRCT) is considered the gold standard diagnostic imaging modality. Additionally, bronchoscopic evaluation for bronchoalveolar lavage is often helpful in the diagnosis. Respiratory system involvement may present in any of the connective tissue diseases (CTDs), such as systemic sclerosis (SSc), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), idiopathic inflammatory myopathies (IIM), Sjögren's-syndrome (SS) and ILD might be their most common manifestation. In recent years, many studies have been conducted on cases with interstitial pneumonia with autoimmune features (IPAF). Although idiopathic pulmonary fibrosis (IPF) is the most common type of progressive ILD, the incidence of progressive fibrosing phenotype can occur in other conditions. Progressive pulmonary fibrosis (PPF) has a similar disease course as IPF, with worsening respiratory symptoms, reduced lung function, decreased quality of life, and increased risk of mortality. To diagnose PPF, at least two of the following three conditions must be

met: a worsening of respiratory symptoms within a year, physiological progression (a decline in forced vital capacity (FVC) or capacity of the lungs for carbon monoxide (DLCO) within a year), or radiological progression evident in extent or severity. A multidisciplinary discussion (MDD) is considered to be the diagnostic and management reference standard of ILDs that includes pulmonologists, radiologists and a pathologist, if a histopathologic sample is available.

II. OBJECTIVES

1. Determination of the patient characteristics, clinical symptoms and serological findings in CTD-ILD and IPAF population in Hungary
2. Evaluating the decline in functional stability and estimating the prevalence of PF-ILD* in the CTD-ILD and IPAF population
3. Investigation of factors influencing progression of disease in CTD-ILD and IPAF
4. Determining patient characteristics and clinical symptoms in the Hungarian SSc-ILD population
5. Analysis of HRCT pattern and involvement, lung function abnormalities and serological findings in SSc-ILD
6. Evaluating the distribution of PF-ILD according to treatment subgroups in SSc-ILD and factors of functional decline

*At the time of the studies PPF guideline was still not in place, PF-ILD is representing functional decline as in later PPF guideline.

III. METHODS

3.1. CTD-ILD/IPAF study population

Our first study included ILD patients selected from MDD discussions at Semmelweis University. Data analysis covered the period from January 2017 to June 2019, retrospectively. During this time, our MDD reviewed 511 suspected ILD cases. Among these, 380 subjects (74.4%) were confirmed to have ILD and were categorized into four groups by MDD experts: (1) ILDs with known etiology including mainly CTD-ILD cases and hypersensitivity pneumonitis cases, (2) idiopathic interstitial pneumonias (IIP); (3) granulomatous diseases; and (4) other rare forms. This study focused on ILDs with autoimmune features, including 63 CTD-ILD patients [32 SSc, 13 RA, 6 SLE, 4 IIM, 2 vasculitis], 6 patients with other types of ILD and 44 IPAF patients. CTD diagnosis was set up according to the internationally accepted American College of Rheumatology/European League Against Rheumatism Collaborative Initiative (EULAR-ACR) criteria by rheumatology specialists. IPAF diagnosis was made using the classification criteria proposed by European Respiratory Society (ERS)/ American Thoracic Society (ATS) in 2015.

3.2. SSc study population

In our second retrospective study, we examined SSc-ILD patients discussed at the MDD of Semmelweis University's Department of Pulmonology. Diagnosis and treatment initiation for SSc were conducted by experts at immunological-rheumatological centers in central Hungary, following the EULAR-ACR criteria. All patients were presented and discussed at the MDD. During the evaluation period (January 2017 to June 2019), we identified 54 SSc-ILD patients, of which 42 had longitudinal functional and radiological data until June 2021. Subgroups were formed based on ongoing therapy: patients without treatment (n = 12), patients on immunosuppression (ISU) therapy (n = 21), and patients receiving biological therapy (n = 9).

3.3. Methodology and statistical analysis of the studies

A detailed medical history and physical examination were conducted at baseline for each case. Baseline measurements of body mass index (BMI), PFT, HRCT, arterialized capillary blood gases, and 6-minute walk test (6MWT), HRCT scans were performed at the time of ILD diagnosis. PFTs included measurements of FVC, forced expiratory volume in 1 second (FEV1), FEV1/FVC, and total lung capacity (TLC) following ATS and current ERS guidelines. DLCO and KLCO was also determined. Blood

sampling included detection of autoantibodies. Long-term follow-up involved pulmonary and rheumatology controls based on individual disease requirements, including PFT measurements and HRCT. In both studies PF-ILD was determined by an annual relative FVC decline of ≥5% along with worsening clinical symptoms or fibrosis progression on HRCT. The follow-up period lasted at least 24 months for all cases in the CTD-ILD/IPAF study and at least 31 months in the SSc study.

In both studies, analysis was performed using the GraphPad software, Microsoft Excel and SPSS v25. Parametric variables are expressed as mean ± standard deviation. Normality was examined with Kolmogorov–Smirnov test. Student's t-test for normally distributed data; a Mann–Whitney U-test was used for evaluation the differences between subgroups. Comparison of categorical variables was implemented with Chi squared test and two-tailed Fisher's exact test. The additional statistical methods used in the articles included Cox proportional hazards regression model, the odds ratio, plot analysis and correlation performing by logarithmic transformation. A p-value <0.05 was defined as statistically significant.

IV. RESULTS

4.1. Determination of the patient characteristics, clinical symptoms and serological findings in the CTD-ILD and IPAF population in Hungary

In our first study 107 patients with autoimmune featured ILD fulfilled the inclusion criteria. They were divided into CTD-ILD (N=63) and IPAF (N=44) subgroups. The average age was 63.8 ± 13.9 years and there was a female predominance (70.1%) in the whole study population. There was a balanced smoking exposure in the IPAF subgroup, while two thirds of patients in the CTD subgroup considered themselves non-smokers. In the whole population the most common symptoms were dyspnea (69.1%), crackles (58.9%), cough (58.6%). In summary, significantly more patients suffered from dyspnea, weight loss, crackles in the IPAF group. No serological differences were detected between the two groups.

4.2. Evaluating the decline in functional stability and estimating the prevalence of PF-ILD in the CTD-ILD and IPAF population

Total of 34 CTD-ILD (23.5% males; mean age 58.42 ± 13.01 years) and 25 IPAF (48.0% males; mean age 69.0 ± 12.5 years) patients had longitudinal functional data

during the observation period. The annual FVC decline from baseline was more pronounced among IPAF cases in comparison to the CTD-ILD cases (-53.1 ± 0.3 ml vs. 16.7 ± 0.2 ml; p=0.294). However, 68.0% were at least stable in the IPAF subgroup as compared to 82.4% in the CTD-ILD subgroup (p=0.200). 14 patients fulfilled our PF-ILD criteria: 6 cases in the CTD-ILD subgroup (RA (N=3), SSc (N=2), other (N=1)) and 8 in the IPAF subgroup.

4.3. Investigation of factors influencing progression of disease in CTD-ILD and IPAF

In our study, we detected possible prognostic factors for functional progression of disease (PF-ILD) in autoimmune mediated ILDs. These factors include malignancy as a comorbidity, anti-SS-A antibody positivity, and post-exercise pulse increase at the 6MWT.

4.4. Determining patient characteristics and clinical symptoms in the Hungarian SSc-ILD population

In our second investigation 54 patients fulfilled the inclusion criteria and out of these, 42 patients had follow-up data. They were divided in 3 subgroups according to therapy: no treatment, ISU, or biological. The SSc-ILD population had a mean age of 58.7 years. In the whole population a female predominance was present (87.0%) and 74.1% of the subjects were non-smokers. The average

BMI was in normal range in the no treatment subgroup (23.6 kg/m2). On the other hand, overweight was noted in both the ISU (25.0 kg/m2) and in the biological treatment subgroups (26.4 kg/m2). Respiratory symptoms, like dyspnea and crackles were present in the largest proportion, followed by Raynaud's phenomenon and joint pain and finger clubbing.

4.5. Analysis of HRCT pattern and involvement, lung function abnormalities and serological findings in SSc-ILD

Nonspecific interstitial pneumonia morphological pattern (less than 20% of lung involvement) was present in most cases on HRCT, proceeded by usual interstitial pneumonia (UIP) and probable (p) UIP pattern (equal involvement below and above 20). Analysis of PFT showed a mild restrictive functional decline. Annual FVC decline was prominent in the no treatment subgroup (−10.2 ± 13.0%) in contrast to patients who were on ISU (−3.9 ± 5.1%) or biological treatment (−1.04 ± 7.8%). Patients receiving biological treatment showed the lowest degree of annual FVC decline. There was no significant difference in PFT results between the 3 observed subgroups. However, in the treated subgroups annual FVC declined only in a moderate rate compared to the no treatment subgroup. Among the 14 antibodies tested in this study, the most frequently occurring were the following: ANA, anti-SCL-70, anti-

chromatin and anti-cytoplasmatic antibodies. Anti-SCL-70 was significantly more predominant in the ISU subgroup.

4.6. Evaluating the distribution of PF-ILD according to treatment subgroups in SSc-ILD and factors of functional decline

In our study out of 42 patients who possessed longitudinal data, 15 patients fulfilled our PF-ILD criteria. During-follow up the remaining 27 patients were stable, and no traits of functional decline were identified. PF-ILD was detected in the highest percentage in the no treatment subgroup (41.7%), while three-quarters of subjects were stable or showed improvement during adjusted treatments. Based on our plot analysis being overweight (BMI >= 25 kg/m2, established by the definition of WHO) and absence of anti-SCL-70 antibodies proved to be a favoring factor for functional stability. More than the half of the patients (55.6%) receiving biological treatment were overweight, while patients in the no treatment subgroup were the least affected (25%). For stable SSc-ILD patients a significantly higher BMI was characteristic compared to PF-ILD cases (25.71 kg/m2 vs. 22.9 kg/m2; p=0.03). A clear negative correlation was explored between baseline BMI and annual FVC decline ($r = -0.97$, $r2 = 0.93$, $p < 0.001$).

IV. CONCLUSIONS

1. In our study we determined patient characteristics, clinical symptoms and serological findings in the CTD-ILD and IPAF population in Hungary. The average age was 63.8 ± 13.9 years and there was a female predominance (70.1%) in sex. Smoking status was equally distributed in IPAF population, while CTD-ILD patients were more frequently non-smokers. Most commonly observed symptoms were dyspnea (69.1%), crackles (58.9%), cough (58.6%). There were no serological differences between the two groups.

2. During follow-up out of the 59 patients 14 (23.7%) fulfilled our PF-ILD criteria, while 68% of IPAF and 82.4% of CTD-ILD patients had stable disease.

3. Factors supporting functional progression in autoimmune featured ILDs (both CTD and IPAF) were malignancy, anti-SS-A antibody positivity and post-exercise pulse increase at the 6MWT.

4. Patient characteristics and clinical symptoms of the Hungarian SSc-ILD population were additionally described. Patients had a mean age of 58.7 ± 13.3 years and were mainly nonsmoking women. Patients on ISU and biological treatment had a slight over normal excess in BMI. Dyspnea, crackles, Raynaud's phenomenon, joint

pain, and finger clubbing proved to be typical clinical signs and symptoms.

5. Our study analyzed the HRCT pattern, lung function abnormalities and serological findings in SSc-ILD. NSIP with less than 20% was the most common radiological pattern, followed by UIP and pUIP. Baseline PFT data showed a mild restrictive pattern. Functional decline appeared mainly in untreated patients, while those who received therapy were more stable during the follow-up.

6. Our study evaluated the distribution of PF-ILD according to treatment subgroups in SSc-ILD and factors predicting functional decline: out of 42 patients 15 fulfilled the PPF criteria of functional decline- with the highest proportion in untreated cases (41.7%). Total of 27 patients were stable during follow-up, mainly on adjusted treatment. Overweight (BMI >= 25 kg/m2) and the absence of anti-SCL70 positivity have been confirmed as favoring factors of functional stability.

V. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

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