CLINICAL CHARACTERISTICS OF PROGRESSIVE PULMONARY FIBROSIS IN PATIENTS WITH AUTOIMMUNE ASSOCIATED ILD

PhD thesis

Tamás Nagy, MD
Károly Rácz Doctoral School of Clinical Medicine
Semmelweis University

Supervisor: Veronika Müller, MD, D.Sc

Official reviewers: Tamás Németh, MD, Ph.D
Szabolcs Bozsányi, MD, Ph.D

Head of the Complex Examination Committee:
András Kiss, MD, D.Sc.

Members of the Complex Examination Committee:
Balázs Antus, MD, D.Sc.
Dorottya Czövek, MD, Ph.D

Budapest
2024

1. INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogenous group of pulmonary conditions, including over 200 subtypes. Several forms are characterized by irreversible fibrotic scarring of the lung parenchyma. Idiopathic pulmonary fibrosis (IPF) is a chronic progressive ILD, associated with a median survival of 3-5 years. ILDs associated with autoimmune features can be subdivided into connective tissue disease-associated ILDs (CTD-ILDs) and interstitial pneumonia with autoimmune features (IPAF), both showing varying rates of progression. Depending on the underlying condition, CTD-ILDs are most frequently associated with systemic sclerosis (SSc), rheumatoid arthritis, or autoimmune myositis. IPAF is characterized by both ILD and autoimmune characteristics without definitive CTD. Important diagnostic requirements are patient history, physical examination, pulmonary function tests (PFTs), autoimmune serology and high-resolution computed tomography (HRCT) imaging. The diagnosis of ILD is established by a multidisciplinary discussion (MDD) team consisting of pulmonology, radiology,

pathology, and rheumatology specialists. Management of ILDs includes pharmacologic and non-pharmacologic therapeutic modalities. Pharmacological treatments include for progressive fibrosing (PF)-ILDs antifibrotics (nintedanib, pirfenidone) and conventional immunosuppressive (ISU) and/or biologic agents for CTD-ILDs. Non-pharmacologic treatment encompasses mainly oxygen supplementation and pulmonary rehabilitation. The progression of ILDs shows a varying course. Progressive pulmonary fibrosis (PPF) is characterized by the presence of at least two out of the three defining criteria, which includes: worsening of respiratory symptoms, physiological deterioration (PFTs), and the increasing extent of fibrosis on HRCT scans – all considered within a 1-year follow-up of any ILD other than IPF. Non-IPF ILDs with disease progression and untreated IPF patients can share a similar course of disease, including worsening respiratory symptoms, lung function deterioration, and increased risk of early mortality. It is important to raise awareness among treating physicians in terms of recognizing progression and, furthermore, to underline the requirement for standardized

diagnosis and management guidelines. Early identification of progression is at utmost importance even among patients with physiologic lung function in order to decrease lung function deterioration and to improve the outcome when administering timely immunosuppression and/or antifibrotic agents.

2. OBJECTIVES

Our aim was to analyze the special population of ILDs with autoimmune features in our single center *CTD-ILD Study* and *SSc-ILD Study*. Primary objectives of this PhD thesis:

1. To describe patient characteristics, clinical symptoms of SSc-ILD patients, and the functional status of *CTD-ILD* and *SSc-ILD Study* subjects.
2. To evaluate HRCT patterns of CTD-ILD and SSc-ILD patients.
3. To investigate the prevalence of functional progression of PPF domain in the Hungarian SSc-ILD populations.
4. To detect possible predictive factors of functional progression in SSc-ILD patients.
5. To analyze applied therapies in the CTD-ILD and SSc-ILD patients. Evaluate the effect of baseline ISU therapy, and the administration of targeted antifibrotic agents.
6. To evaluate adverse events of the applied antifibrotic treatment in the autoimmune associated ILDs in the *CTD-ILD Study*.

3. METHODS

The study design of this PhD thesis consists of two retrospective longitudinal observational studies conducted on predefined patients with CTD-ILD and SSc-ILD. Each case was diagnosed by the MDD at the Department of Pulmonology, Semmelweis University, Budapest, Hungary, taking into consideration HRCT scans, PFTs and/or clinical symptoms. CTD subtypes were evaluated by rheumatologist specialists, according to the current international guidelines.

Patients enrolled in the ***CTD-ILD Study*** (January 2017 - June 2019) were diagnosed with ILD and had a follow-up period of at least 24 months. The two subgroups analyzed were CTD-ILD and IPAF cases. IPAF was diagnosed according to the 2015 American Thoracic Society (ATS) and the European Respiratory Society (ERS) diagnostic criteria. PF-ILD in our study was determined by the functional deterioration as a relative yearly forced vital capacity (FVC) decline of ≥5 % of the predicted value without respiratory symptoms' worsening or HRCT verified fibrosis progression.

The inclusion criteria of the ***SSc-ILD Study*** consisted of a physiologic PFT (FVC >80% predicted) and a follow-up period of at least 12 months. The underlying SSc was previously diagnosed in immunological-rheumatological centers. IPF patients with normal FVC served as benchmark progressive cohort from our center included into the European Multipartner IPF Registry (EMPIRE) diagnosed by the 2011 ATS/ERS guideline. Functional decline of PPF diagnosis was established as functional deterioration regarding the annual ≥ 5% predicted FVC decline and/or ≥10% predicted of diffusing capacity of the lungs for carbon monoxide (DL_{CO}) decline, without other criteria of worsening symptoms and/or HRCT verified fibrotic progression in a 1-year follow-up period.

Clinical and functional parameters of treatment data were registered and analyzed at baseline and at each follow-up. Patient characteristics included smoking history, body mass index, symptoms, and comorbidities. Detailed functional tests were conducted and included PFTs [FVC, forced expiratory volume in 1 s (FEV_1), total lung capacity (TLC), DL_{CO}, transfer coefficient of the lung for carbon monoxide (KL_{CO})], arterial blood gas test

(ABG) and 6-minute walk test (6MWT). HRCT scan patterns at baseline were recorded. Gender-age-physiology (GAP) index - including sex, FVC, and DL_{CO} - was calculated for every patient. ISU and/or antifibrotic treatment was analyzed, while antifibrotic related adverse events were described in more detail.

Statistical analysis. Continuous variables were expressed as mean ± standard deviation or median ± interquartile range and were compared with Student's t-test or Mann–Whitney U-test, depending on the variable's distribution. The Kolmogorov–Smirnov test was used to test for normality. Categorical variables were presented as percentages (%) expressed for the whole study population (all patients) or subgroups, as indicated, and were then evaluated using the Pearson's chi-square test or the two-tailed Fisher's exact test, depending on the distribution. A *p*-value of <0.05 was defined as statistically significant. Multiple logistic regression analysis was used for progression analysis in the *SSc-ILD Study*. Parameters assessed included age (continuous variable), sex (male/female), smoking history (present/absent), cough (present/absent), pulmonary hypertension (PH)

(present/absent), baseline PFTs - FVC, TLC, DL_{CO}, KL_{CO} (% of the predicted value as continuous variables) - and treatment (applied/none). Outcome was defined as observed progression until the end of the first year of follow-up (progression/ stable-improved).

4. RESULTS

Patient characteristics, clinical symptoms of SSc-ILD patients compared to respective comparators, and the functional status of *CTD-ILD* and *SSc-ILD Study* subjects

In the *CTD-ILD Study,* besides the mild restrictive dysfunction (reduced TLC and decreased DL_{CO} and KL_{CO}), a notable difference could not be detected between CTD-ILD and IPAF study groups, having taken into consideration PFTs, ABGs, and 6MWT parameters.

In the *SSc-ILD Study* SSc-ILD group was notably younger, predominately included females; while, on the other hand, positive smoking history and obesity were more common in IPF patients.

ILD related respiratory symptoms, such as dyspnea, cough, and crackles; were more frequently present in the IPF group, while Raynaud's phenomenon was only associated with SSc-ILD. The vast majority of patients presented with GAP stage I. The proportion of PH and gastro-esophageal reflux disease (GERD) among the two groups were similar. Regarding PFTs, IPF patients had

significantly lower TLC, and decreased DL_{CO} values; however, SSc-ILD patients had notably reduced KL_{CO} parameters. Statistical significance was not found in the 6MWT data, including the distance recorded, post-exercise tachycardia, desaturation, and the Borg scale.

HRCT patterns of CTD-ILD and SSc-ILD patients

In the *CTD-ILD Study,* the non-specific interstitial pneumonia (NSIP) pattern was notably more predominant in CTD-ILD patients, as compared to IPAF cases (p<0.001); however, probable (p) usual interstitial pneumonia (UIP) pattern was more frequently observed in IPAF patients (p=0.001). SSc-ILD patients were more commonly associated with the NSIP pattern, and the predominant HRCT pattern was found to be UIP/ pUIP in the IPF group in the *SSc-ILD Study*.

Prevalence of functional progression in the Hungarian SSc-ILD population

During the follow-up period, one-third of the SSc-ILD patients (n=11) presented with functional progression, while this value was 30.2% (n=16) among IPF cases. The decline in the functionally progressive SSc-ILD subgroup

was notably higher than in the stable/improved SSc-ILD subgroup (-153.9 (-278.3 to -121.4) mL/year vs. -26.2 (-75.4 to -1.6) mL/year, p=0.017).

Possible predictive factors of functional progression in SSc-ILD patients

In the *SSc-ILD Study,* multiple logistic regression analysis of subjects confirmed cough and PH as prognostic factors for functional progression in SSc-ILD patients (odds ratio: 36.2 (95% confidence interval (CI): 1.8–711.9) and 36.4 (95% CI: 1.1–1184.9)). Dry cough was predominant in both functionally progressive subgroups (SSc-ILD: 85.7% vs. IPF: 71.4%).

Applied ISU and/or antifibrotic therapy modalities in the CTD-ILD and SSc-ILD patients

In the *CTD-ILD Study,* conventional ISU treatment was administered in 36 cases (CTD-ILD: n=22; IPAF: n=14) as either monotherapy or in combination. During the follow-up period, ISU agents were initiated in 25 patients (CTD-ILD: n=18; IPAF: n=7) as mono- or combined therapy. Antifibrotics were combined with ISU treatment in PF-ILD, while notably more IPAF patients received

antifibrotics (5 CTD-ILD- vs. 13 IPAF patients, p=0.007). Maintenance dosages included nintedanib 150 mg twice daily, and 801 mg pirfenidone three times daily. Antifibrotics showed clinical benefit in 72.2% of the cases, regarding improved or stabile lung function parameters. Among SSc-ILD patients, ISU treatment was used in 26 cases, and 9 patients received biological therapy, including 7 patients receiving combined treatment. In the analyzed group, antifibrotic therapy was not used.

Adverse events of antifibrotic treatment in the *CTD-ILD Study*

Antifibrotics (nintedanib n=17, pirfenidone n=2)-associated adverse events were mild and temporary, primarily manifesting as gastrointestinal symptoms such as nausea, vomiting, diarrhea, and heartburn. Adverse events were typically alleviated by reducing the dosage of antifibrotic agents and initiating supportive medications. In one case, an increase in liver enzyme levels prompted switching from nintedanib to pirfenidone.

5. CONCLUSIONS

This PhD thesis focused on the functionally progressive ILD population: ILD-s with autoimmune features (CTD-ILD and IPAF) and IPF.

1. In the *SSc-ILD Study* PH and GERD, as comorbidities, presented similarly in the two populations, and functional parameters were similar in the *CTD-ILD Study*. Although, IPF patients had a notably more restrictive PFT (decreased TLC) and reduced CO diffusion (DL_{CO}), KL_{CO} was significantly lower in patients with SSc-ILD, suggesting a worse diffusion per lung units.
2. NSIP was the predominant pattern in definitive autoimmune ILDs, similarly to the *CTD-ILD* and *SSc-ILD Study*; however, the UIP associated pattern dominated in IPAF and IPF cases.
3. Although, similar proportions of patients presented with PPF in the analyzed SSc-ILD and IPF subgroups, antifibrotics were introduced only in IPF patients; however, ISU and/or biologic

treatment was applied exclusively in SSc-ILD patients.

4. In SSc-ILD patients with physiologic PFTs, the presence of cough showed an increased risk for PPF development, possibly posing as a prognostic factor for functional decline. Furthermore, PH was found to be a negative prognostic factor for PPF in SSc-ILD patients.
5. Baseline treatment data of the *CTD-ILD Study* showed that administering ISU treatment with or without antifibrotic agents resulted in stable or improved lung functions. In the *SSc-ILD Study*, patients receiving ISU and/or biological-therapy displayed better functional outcomes, which highlights the importance of early and specific SSc therapy.
6. In the *CTD-ILD Study*, administered antifibrotics were associated with tolerable gastrointestinal adverse events, similar to clinical trials.

6. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

Publications related to the present PhD thesis:

1. **Nagy T**, Toth NM, Palmer E, Polivka L, Csoma B, Nagy A, Eszes N, Vincze K, Bárczi E, Bohács A, Tárnoki ÁD, Tárnoki DL, Nagy G, Kiss E, Maurovich-Horvát P, Müller V. Clinical Predictors of Lung-Function Decline in Systemic-Sclerosis-Associated Interstitial Lung Disease Patients with Normal Spirometry. *Biomedicines*, 2022 Aug 31;10(9):2129. doi: 10.3390/biomedicines10092129. PubMedPMID: 36140231, PubMed PMCID: PMC9495755. (Q1)

2. Nagy A†, **Nagy T**†, Kolonics-Farkas AM, Eszes N, Vincze K, Barczi E, Tarnoki AD, Tarnoki DL, Nagy G, Kiss E, Maurovich-Horvat P, Bohacs A, Müller V. Autoimmune Progressive Fibrosing Interstitial Lung Disease: Predictors of Fast Decline. Front Pharmacol. 2021 Dec 22;12:778649. doi: 10.3389/fphar.2021.778649. PubMed PMID: 35002713 PubMed PMCID: PMC8727590. (Q1)

†shared first authorship