Interstitial Lung Diseases in Rheumatology Practice: A Single Center Experience

Romatoloji Pratiğinde İnterstitiel Akciğer Hastalığı: Tek Merkez Deneyimi

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ABSTRACT

Objective: Interstitial lung diseases (ILDs) are a heterogeneous group of pulmonary diseases affecting the pulmonary interstitium. ILDs may occur secondary to connective tissue diseases (CTDs) and increase morbidity and mortality due to ventilation impairment. The aim of this study was to reveal the clinical, laboratory and imaging features of CTD-related ILDs (CTD-ILDs) and to analyze the treatment approaches.

Material and Methods: A total of 132 consecutive ILD patients were included in this cohort. Demographic characteristics, laboratory and high-resolution chest computed tomography (HRCT) results and treatments were analyzed.

Results: There were 99 patients with CTD-ILD, the mean age was 54.7±11.6 years, females made up 82.8%, median follow-up time was 48.5 months. There were 96 patients who were followed up for more than six months. The median number of HRCT scans was 3 (1-10) with a median interval of 12.5 months. Most common HRCT findings were ground-glass opacities and interlobular septal thickening. One-third of all scans had a honeycomb pattern. 89.6% of CTD-ILD patients recieved corticosteroids, and 44.8% recieved antimalarials. Azathioprine and cyclophosphamide were the most commonly used immunosuppressive drugs. After treatment, the mean pulmonary function tests did not significantly differ from the baseline (p >0.05). 35% of the patients had improved forced vital capacity (FVC >10% increase) with treatment whereas 31% had decreased values and 34% were stable.

Conclusion: The desired point of the treatment of CTD-ILD patients has not been reached yet even though a significant effort is being made for the diagnosis, treatment and follow up. Novel curative agents are needed for patients with CTD-ILD.

Key Words: Connective tissue diseases, High-resolution computed tomography, Interstitial lung diseases.

ÖZ

Amaç: İnterstitiel akciğer hastalığı(İAH) akciğerlerdeki interstitiel aralığı etkileyen heterojen bir hastalık grubudur. İAH bağ doku hastalıklarına(BDH) sekonder gelişebilir ve solunum yetmezliğinden dolayı sakatlık ve ölüm oranı artar. Bu çalışmanın amacı BDH ilişkili İAH'nın klinik, laboratuvar ve görüntüleme özelliklerini tanımlamak ve tedavi yaklaşımlarını analiz etmektir.

Gereç ve Yöntemler: Bu çalışmaya ardışık gelen 132 İAH hastası alındı. Demografik özellikleri, laboratuvar ve yüksek rezolüsyonlu akciğer tomografisi(HRCT) ve tedavi sonuçları analiz edildi.

Bulgular: BDH ilişkili İAH tanısı alan 99 hasta vardı. Ortalama yaş 54.7±11.6 yıl, kadın oranı %82.8, median takip süresi 48.5 aydı. 96 hastanın takip süresi altı aydan fazlaydı. HRCT taramaları median 12.5 aylık intervaller ile median 3(1-10) kez tekrarlanmıştı. En sık HRCT bulguları buzlu cam opasiteleri ve interlobüler septal kalınlaşmalardır. Hastaların üçte birinde bal peteği paterni vardı. Hastaların %89.6'sı kortikosteroid %44.8'i antimalaryal ajan almıştı. Azatiopürin ve siklofosfamid en sık kullanılan immünosupresif ilaçlardı. Tedavi sonrası ortalama solunum fonksiyon testleri tedavi

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öncesinden farklı değildi (p>0.05). Tedavi ile hastaların %35'inde zorlu vital kapasite düzelmiş (FVC >%10 artış), %31'inde azalmış ve %34'ünde değişmemişti.

Sonuç: BDH ilişkili İAH tanı, tedavi ve takibi için yoğun çaba harcanmasına rağmen tedavide henüz tatmin edici noktaya ulaşılmamıştır. BDH ilişkili İAH hastaları için yeni kür sağlayıcı ajanlara ihtiyaç vardır.

Anahtar Sözcükler: Bağ doku hastalıkları, İnterstitiel akciğer hastalığı, Yüksek rezolusyonlu akciğer tomografisi

INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogeneous group of disorders affecting the pulmonary interstitium. Idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis, sarcoidosis and connective tissue disease-associated interstitial lung disease (CTD-ILD) are included in this group (1). A multidisciplinary approach is necessary to evaluate patients with CTD-ILD. Pathologists, pulmonologists, radiologists and rheumatologists should recognize ILDs with their clinical presentations along with any underlying diseases, radiological patterns and pathological findings (2).

The frequency of ILD in patients with CTD varies based on patient selection and diagnostic methodologies for detection. High-resolution chest computed tomography (HRCT) is the most helpful test for diagnosis (3). It is reported that 15% of patients with rheumatoid arthritis (RA) develop ILDs causing restriction in pulmonary functions (4). 11.4-22% of patients with primary Sjögren's syndrome (pSS) (5,6), 7.3% of patients with systemic lupus erythematosus (SLE) (7) have been found to have ILDs. This proportion increases to 90% in patients with systemic sclerosis (SSc) (8). ILD is an important cause of morbidity and mortality in patients with CTD (5, 9-12).

ILDs are classified according to histological patterns (13,14). This classification is used for both idiopathic pulmonary fibrosis (IPF) and CTL-ILD patients even though their treatment options and prognoses are different. However, histopathological sampling is rarely performed. The diagnosis of ILD is usually based on clinical findings and HRCT results. HRCT is the imaging of choice and the results correlate with histopathological findings (15).

Another important topic regarding CTD-ILDs is that there is no consensus on treatment modalities. Randomized controlled trials for SSc-ILD have recently been published (16,17) but information on other CTD-ILDs is not adequate. Corticosteroids and immunosuppressive agents aim to inhibit inflammation (18). Treatment experiences are based on uncontrolled case series and anecdotal reports.

It is difficult to determine the extent of disease severity in CTD-ILDs (13). Pulmonary function tests (PFT) are the most frequent test used for this purpose. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and diffusion capacity of the lung for carbon monoxide (DLCO) are used for monitorization. Reduced FVC levels show advanced disease and more than 10% decrease is related with poor prognosis (19). HRCT also correlates with spirometric measurements and may be used in follow-up (20).

Connective tissue diseases are a principal group of rheumatologic diseases and they constitute an important part of rheumatological practice. Pulmonary symptoms of these patients require a good differential diagnosis and treatment approach. Although there are a number of recent studies focusing on CTD-ILDs, there is no consensus on the diagnosis, follow-up and treatment of these patients. In this study, we aim to present a single rheumatology center clinical experience of patients with ILD. Furthermore, we reported the clinical, laboratory, imaging results and treatment approaches of patients with CTD-ILD.

MATERIAL and METHODS

Study population

This is a cross-sectional study and it was conducted on patients followed-up and treated at a rheumatology clinic of an university hospital between February 2014-January 2015. All consecutive patients diagnosed with ILD were included in this study. The patients' age, sex, history of primary disease, disease duration, age of onset of pulmonary symptoms, previously received treatment, smoking history and physical examination findings were recorded. Diagnosis of CTD was based on current diagnostic criteria at the time of the diagnosis. Rheumatoid factor (RF), anti-nuclear antibody (ANA) titer and pattern, extractable nuclear antibody screen (ENA profile), anti-cyclic citrullinated peptide (Anti-CCP) results, HRCT, PFT, DLCO, bronchoscopy and lung biopsy results were noted. Treatments for both CTD and ILD were recorded, separately. Patients with insufficient data were excluded from the study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients enrolled gave consent to participate. The study was approved by the local ethics committee (Akdeniz University ethics committee) on 11.12.2013 (Number: 308)

Pulmonary functions

Pulmonary involvement was defined based on the presence of pulmonary signs/symptoms and/or impaired PFT and/or abnormal HRCT patterns. PFT values were obtained from patient files. Results were shown as percentages of the predicted value of each parameter for each individual based on the age, gender and height. Pulmonary function was considered abnormal if FVC was <80% and/or FEV_1 <80% of the predicted values. PFT values from the last follow-up visit (last visit) and at the time of diagnosis (baseline) were compared. Percent change of the parameters was calculated to analyze the change in pulmonary functions. ''(Last visit FVC-Baseline FVC)/ Baseline FVC'' and ''(Last visit FEV_1- Baseline FEV_1)/ Baseline FEV_1'' formulas were used. More than 10% increase of FVC and FEV_1 was categorized as improvement, >10% decrease was categorized as deterioration and ±10% changes were categorized as stable disease. Single-breath diffusion capacity of the lung for carbon monoxide (DLCO) was used to assess gas transfer.

High-resolution CT scan findings

HRCT scan abnormalities were categorized according to the classification of patterns described in the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias (14). The presence of honeycombing, cysts, septal and subpleural lines, irregular pleural margins and ground-glass attenuation were considered as indicative of ILD. Other remarkable findings were also noted: traction bronchiectasis, reticular pattern, subpleural linear opacity, consolidation, bullae, centrilobular emphysema, atelectasis, lymphocytic interstitial pneumonitis (LIP) and bronchial wall thickening—and entered into a data sheet independently. The evaluation of the radiological studies was performed according to the definition as reported previously (21).

Statistical analysis

Statistical analysis was performed using the PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, USA). Descriptive statistics, i.e., means, standard deviations, median, minimum, maximum, frequencies, and percentages, were used to describe the study variables. Continuous variables were reported as mean± SD and compared using Student's t-test, and those without normal distribution were reported as median and compared using Mann–Whitney's U-test. Differences in categorical data were analyzed by the Chi-square test. The paired t-test was used to determine if there was a statistically significant change in PFT, and a 95% confidence was calculated for the FVC and FEV_1. P values less than 0.05 were considered significant.

RESULTS

A total of 132 consecutive ILD patients were included in this study. 75% of these patients (n=99) were diagnosed with CTD-ILD. The mean age of the patients was 55.7±11.9 years and follow-up time was 48 (min-max 0-260) months. Age of onset of pulmonary symptoms was 49.9±14.2 years. CTD-ILD was more common in women and the smoking rate was lower than in non-CTD-ILD. Lung biopsy was performed in 11 patients out of the 132 (8.3%) (CTD-ILD 3% vs. non-CTD-ILD 24%, p<0.001). Characteristics of the patients included in the study are presented on Table I.

Table I: Demographic features and pulmonary functions in patients with interstitial lung disease.

	All patients (n=132)	**CTD (n=99)**	**non-CTD (n=33)**	**p***
Female (n, %)	98 (74.2)	82 (82.8)	16 (48.5)	<0.001
Age(y) (Mean±SD)	55.7±11.9	54.7±11.6	58.6±12.6	0.108
Age of onset of symptoms(y) (Mean±SD)	49.9±14.2	47.5±13.6	56.9±13.9	0.001
Follow-up time (Mo) (Median, Min-Max)	48 (0-260)	48.5 (0-260)	12 (0-84)	<0.001
Smoking (Never)(%)	64.2	77.8	27.2	<0.001
Biopsy samples (n, %)	11 (8.3)	3 (3)	8 (24)	<0.001
Number of HRCT (Median, Min-Max)	3 (1-10)	3 (1-10)	1 (1-4)	<0.001
Baseline FVC (% Pred) (Mean±SD)	73.7±19.4	75.1±19.1	72.6±18.3	0.543
The last FVC (% Pred) (Mean±SD)	76.4±20.3	76.8±20.9	74.2±17.3	0.662
Baseline FEV_1 (% Pred) (Mean±SD)	79.3±19.4	78.7±19.2	81.1±20.3	0.571
The last FEV_1 (% Pred) (Mean±SD)	79.5±20.2	80.1±20.9	75.9±15.1	0.471
Baseline DLCO (% Pred) (Mean±SD)	67.0±25.8	64.8±23.2	71.7±30.9	0.431
The last DLCO (% Pred) (Mean±SD)	60.3±24.3	61.4±24.7	50.0±19.7	0.447

***CTD** versus non-CTD, **CTD:** Connective Tissue Diseases, **HRCT:** High-resolution CT, **FVC:** Forced vital capacity, **FEV_1:** Forced expiratory volume in 1 second, **DLCO:** Diffusing capacity of the lung for carbon monoxide.

Patients with at least 6 months of follow-up were selected to analyze PFT changes. Ninety-six patients with CTD-ILD were followed up for more than 6 months (Table II). 80.2% of these patients were female and the mean age was 54.5±11.9 years. Median follow-up time was 48 (Min-Max: 6-260) months. 69.9% of patients had never smoked. Raynaud's phenomenon was detected in 52.4% of the subjects, ANA positivity was present in 73%. RF was detected in 37 of 67 patients (39.7%), anti-CCP positivity in 25.7%, and ANCA positivity in 33.3% of the patients analyzed during follow-up.

A total of 404 HRCTs were performed for 96 patients and the median HRCT number per patient was 3 (Min-max:1-10). The follow-up time (months)/Times HRCT performed ratio was calculated. HRCT scans were repeated at 12.5 (Min-max:3-66) month periods.

Table II: General characteristics of CTD-ILD patients with follow-up period of 6 months and above(n=96).

Female (n, %)	77 (80.2)
Age (y) (Mean±SD)	54.5 ± 11.9
Follow-up time (Mo) (Median, Min-Max)	48 (6-260)
Smoking (Never)(%)	69.9
Raynaud's Phenomenon (%)	52.4
Antinuclear antibodies (%)	73.0
Rheumatoid factor (%)	39.7 (27/68)
1. Anti-cyclic Citrullinated Peptide (%)	25.7 (9/35)
2. Anti-neutrophil cytoplasmic antibody(%)	33.3 (11/33)
Connective tissue disorders (n=99)	
Systemic sclerosis	44
Primary Sjögren's syndrome	29
Rheumatoid Arthritis	14
Systemic Lupus Erythematosus	7
Mixed connective tissue disease	2
HRCT per patient (Median, Min-Max)	3 (1-10)
The median duration of HRCT imaging (mo)	12.5 (3-66)
Baseline FVC- The last FVC (n=92)	(74.9±18.5)- (76.6±20.4) **1.81 (95% CI (-1.63- 5.25)) p:0.298**
Baseline FEV_1- The last FEV_1 (n=92)	(78.7±18.9) – (79.5±20.2) **0.86 (95% CI (-2.05- 3.76)) p:0.559**
Baseline DLCO- The last DLCO (n=19)	(66.7±23.0) –(64.4±22.7) **-2.36 (95% CI (-11.31- 6.57)) p:0.585**

CTD: Connective Tissue Diseases, **HRCT:** High-resolution CT, **FVC:** Forced vital capacity, **FEV_1:** Forced expiratory volume in 1 second, **DLCO:** Diffusing capacity of the lung for carbon monoxide.

Table III: HRCT findings.

Parenchymal lesions	**(%)**	**Non- parenchymal**	**(%)**
Ground-glass opacities	70.3	Mediastinal lymphadenopathy	29.7
Interlobular septal thickening	70.3	Pleural disease	15.3
Nodules	43.2	Pulmonary arterial trunk	10.8
Bronchiectasis	36.0	Esophageal abnormalities	6.3
Honeycomb pattern	33.3		
Reticular abnormalities	14.4		
Geographic pattern	12.6		
Discrete cysts	12.4		
Emphysema	8.1		
Lymphoid Interstitial Pneumonia(LIP)	1.8		

Pathological findings from HRCTs were categorized as parenchymal and non-parenchymal (Table III). The most common parenchymal findings were ground-glass opacities and interlobular septal thickening. A honeycomb pattern was seen in one-third of the patients. Non-parenchymal findings detected on HRCT images were lymphadenopathy, pleural, pulmonary artery and esophageal abnormalities. SSc was the most common underlying problem in patients with CTD-ILD. Ground-glass opacity, interlobular septal thickening, honeycomb pattern, bronchiectasis and parenchymal nodules were seen in all CTDs. A honeycomb pattern was more common in patients with RA (50%) than in any other CTD (SSc: 27%, pSS: 31%, SLE: 29%). Pathological intrathoracic lymphadenopathy (>1 cm) was more commonly in patients with pSS. LIP pattern was seen in only 2 patients: one patient with pSS and another with SLE. HRCT findings of patients with CTDs are presented on Table IV.

PFT results at the time of diagnosis (baseline) and the last visit were compared using paired t-tests. Some of the patients did not have records from the time of diagnosis and these patients were excluded from analysis. 91 patients with complete PFT records were analyzed, but only 19 patients had records of DLCO results at the time of diagnosis. The median interval between the first and last follow-up PFT results was 36 (min-max:0-150) months. Mean changes in FVC, FEV_1 and DLCO were not statistically significant (p >0.05) (Table II). 51 out of 91 patients with sufficient PFT records had increased FVC (mean±SD:13.2±10.8), whereas 40 (44%) had decreased values (mean±SD:-12.4±9.7). FEV_1 was increased in 50 patients (55%) (mean±SD:10.5±9.5), while 41 patients (45%) had reduced FEV_1 (mean±SD:-10.6±8.5). Classification of disease progression according to FVC and/or FEV_1 changes was as improvement (>10% increase), deterioration (>10% decrease) and stable (±10% change). The rates of improved, deteriorated and stable patients according to FVC values were similar but nearly half of the patients were stable according to FEV_1 (Table V). Also it was shown that FVC and FEV_1 results correlated well in ILD patients (kappa:0.554, p<0.001).

Treatment modalities were administered by the physician according to the clinical conditions or response to drugs and/or the side effects. 89.6% of patients with CTD-

Table IV: HRCT patterns of respiratory involvement in connective tissue disease.

	SSc (n=44)		pSS (n=29)		RA (n=14)		SLE (n=7)		MCTD (n=2)	
	n	%	n	%	n	%	n	%	n	%
Ground-glass opacities	35	80	16	55	10	71	5	71	2	100
Interlobular septal thickening	30	68	23	79	8	57	4	57	2	100
Honeycomb pattern	12	27	9	31	7	50	2	29	1	50
Bronchiectasis	15	34	10	34	5	36	5	71	1	50
Nodules	21	48	14	48	5	36	3	43	2	100
Emphysema	5	11	1	3	2	14	1	14	-	-
Reticular abnormalities	3	7	5	17	4	29	2	29	-	-
Discrete cysts	6	14	3	10	2	14	-	-	1	50
Geographic pattern	7	16	4	14	1	7	-	-	-	-
LIP	-	-	1	3	-	-	1	14	-	-
Lymphadenopathy	8	18	12	41	5	36	2	29	-	-
Pleural thickening	6	14	5	17	1	7	-	-	-	-

SSc: Systemic sclerosis, **pSS:** primary Sjögren syndrome, **RA:** Rheumatoid arthritis, **SLE:** Systemic Lupus Eritematozus, **MCTD:** Mixed connective tissue disease, **LIP:** Lymphoid Interstitial Pneumonia.

Table V: Pulmonary function test outcomes of patients after treatments.

	Number of patients		
	Improvement	Stable	Worsening
FVC	32 (35%)	31 (34%)	28 (31%)
FEV_1	26 (28.5%)	39 (43%)	26 (28.5%)

FVC: Forced vital capacity, **FEV_1:** Forced expiratory volume in 1 second.

ILD (n=96) received corticosteroids and 44.8% received hydroxylchloroquine sulphate. Eighty-four patients received at least one immunosuppressive agent. Only 2 patients used four different immunosuppressives. Most of the patients (n=22) who received azathioprine (AZA) as the first drug did not need a second immunosuppressive agent, and patients who needed a second drug received CYC (5 out of 10 patients). Patients who received CYC as the first drug mostly received AZA (n:16) as the second drug for maintenance treatment. Treatment choices are presented on Table VI.

DISCUSSION

National registries and multicenter studies have shown that CTD-ILDs constitute 7-21% of all ILDs (22-25). All patients diagnosed with ILD should be evaluated for potential CTD-ILD by a rheumatologist. In this cross-sectional study, we evaluated demographic and clinic parameters of patients with ILD in a rheumatology clinic and detected that 75% of these patients were diagnosed with CTD-ILD.

Previous studies have revealed that ILDs are more common in males, but CTD-ILDs are more common in females (22-26). Females are also prone to other autoimmune diseases as well (6, 15, 27, 28). We think that both CTD and CTD-OLD are more frequent in females.

Exposure to cigarette smoke is an important factor for lung injury. Previous or current exposure to cigarettes is seen in patients with ILDs and the exposure rate is especially high in patients with IPF (22,25). In our previous study (6), we showed that cigarette exposure increases ILD development in patients with pSS. In this cohort, 64.2% of the patients with ILD, especially CTD patients, had no previous exposure. This result may be interpreted as indicating ILD may develop independently from smoking in patients with CTD.

Two most important approaches to the diagnosis of ILD are HRCT and histopathologic evaluation. In 2002, the American Thoracic Society/European Respiratory and Society classified the histopathological findings matched with HRCT findings (14). Although this classification is proposed for idiopathic interstitial pneumonias, it is commonly used in the classification of CTL-ILDs as well. Although all mentioned patterns are seen in CTD-ILD, their frequency differs from the idiopathic form, i.e. usual interstitial pneumonia (UIP) is more common than non-specific interstitial pneumonia (NSIP) in RA patients; however, NSIP is more common than UIP in other CTDs. LIP is a common pattern in pSS patients (29). The most common HRCT results in our cohort were ground-glass opacities and interlobular septal thickening (70.3%). HRCT also revealed extraparenchymal findings such as lymphadenopathy, pleural, pulmonary artery and esophageal abnormalities (Table III, IV).

This study revealed that HRCT is an important parameter for follow-up in patients with ILD, and the technique was repeated at median intervals of 12.5 months. There are no published data on when HRCT should be periodically repeated in patients with IPF or CTD-ILD. Minimum or optimum time to repeat a HRCT to spot a difference in patients with ILD is not defined and it can be a topic of a discussion at any setting. In our clinical practice, HRCT scans were repeated when there was a suspicion of ILD progression or the treatment was changed due to treatment failure.

Histopathology is important for both diagnosis and prognosis, but studies have shown that the ratio of patients who have undergone biopsies is low (22-24, 30, 31). Only 8.3% of our patients underwent biopsy and lung biopsy was more commonly carried out in patients that could not be diagnosed with CTD (3% with CTD vs. 24% without CTD). The low ratio of patients who underwent biopsy can be explained on the basis that patients received the ILD diagnosis if a known CTD diagnosis was present and typical HRCT findings were seen. Another reason is that

Table VI: Drugs for the treatment in patients with CTD-ILD.

Corticosteroids	86 (89.6%)							
Antimalarials	43 (44.8%)							
Immunosuppressive	**First (n=84)**		**Second (n=44)**		**Third (n=13)**		**Fourth (n=2)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Azathioprine	32	38.1	17	38.6	6	41.2	-	-
Cyclophosphamide	31	36.9	7	15.9	-	-	-	-
Methotrexate	16	19.0	10	22.7	3	23.0	-	-
Mycophenolate mofetil	1	1.2	7	15.9	3	23.0	2	100
Rituximab	1	1.2	3	6.8	1	7.7	-	-
Leflunamide	3	3.6	-	-	-	-	-	-

biopsy is an invasive and costly procedure. A need for biopsy is further diminished since HRCT results correlate with histopathologic findings. HRCT results have a good correlation with histopathologic patterns (32,33) and the positive predictive value is >90% (15). Additionally, HRCT can be repeated and can be easily compared whereas repeating a biopsy is impractical.

FVC and DLCO are the best tests to predict prognosis in ILDs. A decrease of more than 10% in FVC or 15% in DLCO at 6 months is considered as "significant decline" and is a marker of poor prognosis (19,34). In patients with more than 6 months of follow-up, mean FVC and DLCO values were lower from baseline as expected. After treatment, the mean FVC and DLCO values were not different. However after categorizing patients according to percent changes in PFTs; changes in FVC show 1/3 of included patients improved (>10% increase), 1/3 deteriorated (>10% decrease) and 1/3 were stable.

There is no consensus on the treatment approach of CTD-ILDs. Immunosuppressives are commonly used for treatment. Randomized controlled trials on this subject are insufficient. Most profound research on treatment is on patients with SSc-ILD (18). Corticosteroids are most commonly used drugs in both induction and maintenance treatment (35), and can be combined with AZA, MMF, cyclosporine or CYC. Consistent with the literature, 90% of our CTD-ILD patients received corticosteroids and 45% of patients used anti-malarials for the treatment of underlying CTD rather than ILD. In addition to corticosteroids, different immunosuppressants are used in the treatment of CTD-ILD. The most common drugs were AZA and CYC. 45% of patients received CYC for induction treatment. Randomized placebo-controlled (17,36), randomized unblinded (37, 38), retrospective (39-41) and open-label (42-56) studies exist on this subject. Both oral and intravenous CYC treatment showed improvement or stability on FVC. However, since CTD-ILD is a chronic process, it is not possible to use CYC in the long term due to side effects. In clinical practice, alternative immunosuppressants are used if the patient is CYC unresponsive, or CYC is used for a maximum period or dose. AZA was chosen for maintenance treatment. In the literature, AZA is chosen in maintenance treatment after more potent immunosuppressants are used for induction (42). In our cohort, AZA use is common as the first drug of choice (38% as the first drug). AZA is used for the treatment of underlying CTD and it is thought to be effective for ILD as well; clinical and HRCT findings of ILD are mild; patients with SLE and pSS were previously exposed to CYC due to other organ involvement.

MMF is another immunosuppressive agent for the treatment of CTD-ILD. A randomised controlled, double-blind study has reported been reported to compare the efficacy and safety of MMF and oral cyclophosphamide in patients with symptomatic SSc-ILD (57). It was detected that MMF showed non-inferiority to CYC and was safer in SSc-ILD patients. Observational studies on MMF in patients with SSc-ILD have also been published (58-60). Improvement in both FVC and DLCO was shown with MMF maintenance after CYC induction treatment (61). Fischer et al. reported efficacy of at least 6 months of MMF use in patients with non-SSc CTD-ILD (including RA, SLE, pSS, MCTD, DM) (62). They revealed that FVC and DLCO improved significantly in patients with non-UIP, but FVC and DLCO remained stable in patients with UIP. MMF use was relatively low in our cohort. In our opinion, the evidence of the efficacy of MMF in the treatment of CTD-ILD has been reported, recently. MMF use is notable in patients with CTD-ILD, especially in patients refractory to CYC and AZA. Recent reports also showed rituximab as a treatment option of ILD cases refractory to other treatment options (63). Significant improvement after rituximab treatment was shown in 33 CTD-ILD patients. In our clinic, similar to MMF, rituximab use is increasing, especially in patients with RA-ILD.

The literature is not clear on the use of methotrexate in patients with CTD-ILD. Meta-analysis results on RA patients show a mild increase of pulmonary diseases including ILD (64). In patients with SSc, methotrexate is shown to ameliorate dermatological involvement but results on ILD are controversial. It has been shown that DLCO values remain stable (65) or with statistically insignificant improvement (66). In our clinic, methotrexate was chosen in some patients with SSc-ILD.

There are several limitations of our study. First, HRCT findings were not classified as active alveolitis or chronic fibrotic changes Also, the extent of disease severity was not evaluated from HRCT scans. Secondly, efficacy of immunosuppressive drugs was not evaluated separately. Since this study was not designed prospectively, there were no standards on evaluation of treatment response. Each physician decided on treatment response on his/her own using the clinical findings and laboratory results. Due to this design, treatment response was evaluated by comparing parameters from the time of diagnosis and last follow-up. These results should be interpreted as reflections of daily practice. Lastly, DLCO data was insufficient. Decrease of DLCO is important in the prognosis of ILD.

In conclusion, the results of this study reflect daily practice for the management of CTD-ILD patients. HRCT is an often used imaging technique and median HRCT repeating time is 12.5 months. It is also noted that available treatment options did not change mean PFT values and treatment response is not satisfactory. Only one third of the patients had >10% improvement in FVC after being

treated with current immunosuppressive drugs. The use of MMF and rituximab have increased in recent years. There is need for more effective therapeutic drugs in patients with CTD-ILD.

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