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Clinical course and outcome of rheumatoid arthritis-related usual interstitial pneumonia

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Abstract. *Background:* Although the prognosis of interstitial pneumonia in connective tissue disorders is better than that of idiopathic pulmonary fibrosis (IPF), the prognosis of rheumatoid arthritis (RA) related usual interstitial pneumonia (UIP) is controversial. *Objectives:* To determine prognosis, clinical course and prognostic factors of the patients with RA-UIP and compare them to IPF. *Design:* Retrospective review of 84 patients with RA-UIP (biopsy-proven: 30) from two tertiary referral centers. *Results:* The median follow-up period was 33 months. One half of the patients were stable, one third progressed, 17% had acute exacerbation and 6% improved. TLC % predicted was the only significant predictor for the stable group. Among non-AEx patients, 41% was treated due to poor initial lung function or progression of the disease and one half of them improved or had stable lung function. Despite of worse initial lung function, the survival of treated group was similar to untreated group. Age, FVC and change in DLco during 6 months were significant predictors for mortality. The prognosis of RA-UIP was significantly better than that of IPF matched with age, sex, smoking and baseline lung function (median survival, 53 vs. 41 months respectively, p = 0.015). *Conclusions:* In spite of variable clinical course of RA-UIP, overall prognosis of RA-UIP was significantly better compared to IPF. Our data supported the treatment of the patients with significant functional impairments or progression.
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Key words: clinical course; prognosis; rheumatoid arthritis; usual interstitial pneumonia, treatment

Introduction

Rheumatoid arthritis (RA) is a common systemic inflammatory disease affecting 1-2% of the population and almost 50% of patients with RA demonstrate some type of extra-articular manifestation (1-3). Lung disease is the second most common cause of death after cardiovascular disease (4-8). The histopathologic and radiographic appearance of RA-related interstitial lung disease (RA-ILD) is heterogeneous (9-14). Available data suggest that usual interstitial pneumonia (UIP) pattern is more prevalent in RA, whereas nonspecific interstitial pneumonia (NSIP) is the predominant pattern in other connective tissue diseases (CTDs) (9, 10, 13-16). Although the prognosis of UIP in other non-RA CTD was good and similar to that of idiopathic NSIP (15), the prognosis of RA-UIP was reported to be poor and similar to that of idiopathic pulmonary fibrosis (IPF). Therefore, the histopathologic pattern of in-

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terstitial pneumonia may be important in RA. Even in the patients with UIP pattern, the course of individual patients seems to be variable and recent literature suggested that acute exacerbation (AEx) occurred most frequently in RA-ILD among the CTD [17]; however there was not much data about the prevalence of different courses and predictors for future course at the time of diagnosis. Furthermore, corticosteroid therapy with or without immunosuppressant are frequently used in these patients although there was no evidence or guideline of using these toxic therapies. Therefore, we analyzed the clinical course of RA-UIP to evaluate the overall pattern of the clinical course, characteristics of the patients with different courses, the effect of conventional therapy and predictive markers for prognosis. We also compared the survival of the patients with RA-UIP with that of the patients with IPF.

Methods

Study population

This study was a retrospective review of 84 patients seen at the pulmonary department at Asan Medical Center and Pusan Paik Hospital in Korea from 1991 to 2008 due to RA according to the revised criteria of the American College of Rheumatology (18) and UIP according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) Consensus Classification for idiopathic interstitial pneumonia (IIP) (11, 19) (surgical lung biopsy n = 30). Patients with other coexisting CTDs were excluded.

To compare the outcome, 209 patients with IPF were selected from our IPF cohorts (total: 509 patients confirmed diagnosis according to the new ATS/ERS/JRS/ALAT evidence-based guidelines for diagnosis and management of IPF (20), biopsy-proven: 290) seen during the same period at Asan Medical Center by matching the age, sex, history of smoking and initial FVC % predicted. Although 18 among 84 patients with RA-UIP subjects and 83 with IPF were included in our previous studies (10, 15), the previous papers were studied on only survival, whereas the present study focused more on the clinical course of individual patients with RA-UIP. Three among 14 patients with acute exacerbation (AEx) of RA-UIP patients were included in our previous study (17). AEx was defined by the criteria proposed by Collard et al. (21) Briefly, 1) a sudden aggravation of dyspnea within 30 days; 2) newly developed bilateral ground-glass opacity or consolidation; 3) no evidence of pulmonary infection or other known causes, in the patients with known RA-UIP (by biopsy or HRCT evidence of UIP pattern). This study was approved by the Institutional Review Board of the Asan Medical Center (2007-0250) and Pusan Paik Hospital (10-179).

Methods

Clinical data were obtained from medical records. Survival status was available on all patients and obtained from medical records, telephone interviews and/or the record of National Health Insurance of Korea. Baseline clinical parameters were obtained within one month of the initial diagnosis. Because all patients were seen at the ILD clinic in both hospitals, most patients had complete detailed systematic questionnaires on environmental or drugs exposures, and symptoms/signs of CTD according to clinical study protocols for ILD, not only at the time of initial diagnosis but also during follow-up. Dyspnea score was based on Medical Research Council dyspnea scale scores (22).

The biopsy slides were reviewed independently by two pathologists (TVC. and SJJ.) who were blinded to the clinical information, and a consensus on histopathological diagnosis was achieved.

The high resolution computerized tomography (HRCT) images were obtained by using 1-or 1.5-mm collimation at least 10-mm intervals and were reconstructed by using a high-spatial-frequency algorithm. HRCTs were reviewed by one thoracic radiologist (EJC) who was blinded to clinical information. The extent of emphysema, ground glass opacity (GGO), reticulation, consolidation and honeycombing (HC) were scored on a 5 point scale (0 ~ 4) for all lobes. Overall CT pattern was categorized as definite UIP pattern (19), which was defined as reticulation and HC predominantly basal and subpleural distribution with rare or no GGO.

Lung functions were measured according to ATS recommendation (23-25) and the results were expressed as percentages of normal predicted values. Changes in lung function were presented as the per-

centage change of initial value. Improvements and deteriorations were defined as more than 10% changes in forced vital capacity (FVC) and/or more than 15% changes in DL_{CO} (19). Patients who did not satisfied the criteria of improvement or progression were considered as stable.

Statistical Methods

All values are given as mean ± standard deviation or median (range) for continuous variables or percentages for categorical variables. The chi-square or Fisher's exact tests were used for categorical data and the unpaired Student's *t*-test for continuous data. Logistic regression analysis was used to identify significant variables capable of predicting the course of RA-UIP. Survival was evaluated using a Kaplan-Meier approach and the log-rank test. Cox regression analysis was used to identify significant variables predicting survival. A greedy algorithm was used to obtain pairs of subjects by randomly selecting a case patient from the RA group and matching it to four control patients in the IPF group by age (± 5), sex, smoker, and FVC (± 5). P-value less than 0.05 was considered statistically significant (two-tailed). All data analyses were performed using SAS version 9.1 (SAS Institute; Cary, NC).

Results

1. Baseline features of the subjects

Mean age of the subjects was 63 years and 52% were male. The median follow-up period was 33 months. In the majority of the subjects, ILD was diagnosed after RA (63.1%) or concomitantly (28.6%); only 7 patients (8.3%) developed RA during the follow-up for presumptive IPF (table 1). Most of the subjects (86.9%) had definite UIP pattern on HRCT.

Table 1. Baseline clinical features of the subjects

Characteristics	Total
Patient number	84 (100)
Age, years	62.6 ± 10.0
Male	44 (52.4)
Never-smokers	44 (52.4)
Sequence of diagnosis	
RA first	53 (63.1)
ILD first	7 (8.3)
Concomitant	24 (28.6)
Rheumatoid factor, IU/mL*	309 (106 - 611)
C-reactive protein, mg/dL*	0.9 (0.3 - 3.3)
Symptoms at diagnosis	
Dyspnea	60 (71.4)
Cough	69 (82.1)
Duration of dyspnea, (months)*	3.5 (1.0 - 12.0)
Dyspnea score, MRC grade	2.5 ± 0.9
Pulmonary function test (% predicted)	
FVC	75.1 ± 20.7
DLco	66.0 ± 21.8
TLC	83.2 ± 20.5
BAL fluid, %	N = 30
Neutrophils	14.7 ± 11.2
Lymphocytes	21.1 ± 12.6

Data are presented as mean ± standard deviation or No. (%) unless otherwise indicated.
RA, rheumatoid arthritis; ILD, interstitial lung disease; MRC, medical research council; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; TLC, total lung capacity; BAL, bronchoalveolar lavage
* Median value with interquartile ranges in parentheses

2. Treatment

Although there was no pre-defined treatment guideline, the treatments for UIP were mostly given to the patients with respiratory symptoms and reduced lung function (n = 29) or those who presented with AEx (n = 14). For the treatment of RA-UIP (excluding AEx cases), nine patients received corticosteroid alone and 20 patients received corticosteroid and cytotoxic agents (azathioprine: 14, cyclophosphamide: 4, cyclosporine: 2). The initial dosage of corticosteroid was 42.2 ± 17.7 mg for 6.8 weeks (median, interquartile range [IQR]: 2.7 - 12.3 weeks) and the total duration of therapy was 9.2 months (median, IQR: 5.0 - 12.0 months). The treatment for UIP constituted the only treatment for this subset of patients. However, the majority (n = 41) of patients who were not treated for UIP received various combination regimen for RA; low dose steroid (76%), low dose methotrexate (49%) and hydroxychloroquine (66%). For the treatment of AEx cases, nine patients received high dose corticosteroid alone and 5 patients received corticosteroid and cytotoxic agents (azathioprine: 3, cyclophosphamide: 2).

3. Clinical course

At the time of initial diagnosis of UIP, 19 patients and another 8 patients who presented as AEx were treated. After the treatment, only one among

Table 2. Baseline features of patients with different follow-up courses

Characteristicss	Improved	Stable	Progress	AEx	p-value
Patient number	5	37	28	14	
Age, years	45.8 ± 8.3	63.1 ± 10.0	62.1 ± 8.3	68.1 ± 7.8	0.002
Male	3 (60.0)	19 (51.4)	14 (50.0)	8 (57.1)	0.847
Never-smokers	3 (60.0)	19 (51.4)	15 (53.6)	7 (50.0)	0.993
RF, IU/mL	220 ± 182	630 ± 879	482 ± 611	326 ± 216	0.787
CRP, mg/dL	2.2 ± 2.5	1.9 ± 3.0	1.8 ± 3.1	2.0 ± 2.7*	0.814
Dyspnea score	3.5 ± 0.7	2.2 ± 0.6	2.6 ± 1.0	2.0 ± 1.0*	0.126
Initial PFT (% pred)					
FVC	62.2 ± 12.9	80.3 ± 22.4	73.6 ± 19.5	77.7 ± 10.0*	0.246
DLco	59.6 ± 26.4	70.5 ± 23.3	63.0 ± 17.8	83.0 ± 15.6*	0.185
TLC	68.7 ± 12.7	90.3 ± 25.5	76.6 ± 14.0	83.3 ± 3.4*	0.107
Radiologic Pattern	N = 4	N = 35	N = 25	N = 6	
Fibrosis score†	1.8 ± 1.4	1.6 ± 0.9	1.6 ± 0.6	2.0 ± 1.4*	0.677
Total extent	2.0 ± 0.3	1.8 ± 0.8	1.9 ± 0.8	2.0 ± 1.2*	0.728
Atypical UIP	1 (25.0)	2 (5.7)	6 (24.0)	1 (16.7)*	0.077

Data are presented as mean ± standard deviation or No. (%) unless otherwise indicated.
AEx, acute exacerbation; RF, rheumatoid factor; CRP, C-reactive protein; PFT, pulmonary function test; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; TLC, total lung capacity; UIP, usual interstitial pneumonia
* data from patients who first presented with acute exacerbation (n = 8) were excluded.
† Fibrosis score is defined as the sum of reticulation and honeycombing score

19 non-AEx patient deteriorated and died within one year and majority (n = 18) of non-AEx patients improved/stabilized in lung function (in 3 patients, lung function became normalized). However, 9 patients (50%) had a relapse and most of them (n = 8) progressed thereafter.

Among 57 patients who were untreated initially, 32 patients (56.1%) had stable lung function throughout the course (median duration: 44.2 months), 6 patients (10.5%) developed AEx and 19 (33.3%) had slow progression of lung function. Among 10 patients who were treated due to slow progression, 4 patients improved/stabilized, but 6 patients deteriorated despite of treatment.

Acute exacerbation was frequent in RA-UIP; 8 patients presented as AEx at initial diagnosis. Six patients who were not treated initially developed AEx at 21.5 months (median, IQR: 1.9 - 31.8 months) after the diagnosis of RA-UIP. All but one of these 14 patients died at 1.5 months from the onset of AEx (median, IQR 1.0 - 7.0 months).

4. Characteristics of patients with different clinical courses of RA-UIP

The clinical course of the RA-UIP was categorized into 4 groups according to the final lung function; 1) improved, 2) stable, 3) progressed, and 4) AEx group (table 2).

Improved group was younger. Although they had a trend of poor initial lung function (table 2), the changes in FVC and DL_{CO} after 6 months were larger (table 3).

The stable group had a tendency of higher initial lung function with higher frequency of definite UIP pattern on HRCT (p = 0.077). TLC % predicted (odds ratio [OR]: 1.043, 95% CI: 1.003 - 1.084, p = 0.036) was a significant determinant for this stable course on univariate logistic regression analysis (Appendix-table 1).

The progressed group had a tendency of atypical UIP pattern on HRCT (p = 0.077) (table 2) (Appendix-table 2). Among the patients initially untreated, patients with lower TLC had a tendency to progress or AEx (OR: 0.963, 95% CI: 0.925-1.003, p = 0.066) (Appendix-table 3).

5. Outcome of patients with RA-UIP

The median survival of all RA-UIP patients was 55.9 months. Improved and stable group had a better outcome compared to other groups (table 3, fig. 1A). Among the non-AEx group, there was no difference in outcome between treated and untreated group in spite of poor baseline lung function of treated group. (table 4, fig. 1B). No difference in outcome was found among different treatment regimens (data not shown).

Table 3. Comparison of lung function changes and outcome among patients with different follow-up courses

Characteristicss	Improved	Stable	Progress	AEx	p-value
Patient numbers	5	37	28	14	
Treatment	5 (100)	9 (22.0)	15 (62.5)	14 (100)	< 0.001
PFT change, % *					
FVC, 6 mo	18.3 ± 4.0	4.9 ± 10.0	0.3 ± 16.6		0.043
DLco, 6 mo	10.0 ± 1.0	9.7 ± 21.2	-2.8 ± 21.2		0.202
FVC, 12 mo	15.2 ± 9.0	3.4 ± 10.8	-1.9 ± 15.6		0.041
DLco, 12 mo	17.9 ± 12.3	5.1 ± 26.3	-5.0 ± 26.0		0.154
Survival period, mo					< 0.001
Mean	NA	112.6	62.8	15.0	
(95% CI)		(85.7 - 139.4)	(43.1 - 82.5)	(7.1 - 22.8)	
Median	NA	NA	51.0	3.8	
(95% CI)			(0 - 104.6)	(0 - 26.4)	
Cause of death	N = 0	N = 14	N = 19	N = 13	< 0.001
DP	0	0	7 (36.8)	10 (76.9)	
Infection	0	5 (35.7)	9 (47.4)	2 (15.4)	
Malignancy	0	2 (14.3)	0	0	
CVD	0	2 (14.3)	1 (5.3)	0	
Unknown	0	5 (35.7)	2 (10.5)	1 (7.7)	

Data are presented as mean ± standard deviation or No. (%) unless otherwise indicated
AEx, acute exacerbation; PFT, pulmonary function test; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; mo, months; NA, not applicable; CI, confidence interval; DP, disease progression; CVD, cardiovascular disease
* PFT change (%) = [last FVC (or DLco) – initial FVC (or DLco)]/ initial FVC (or DLco) x 100

Table 4. Comparison of baseline features, outcome and cause of death between untreated and treated patients

Characteristics	Untreated	Treated*	p-value
Patient number	41	29	
Age	64.5 ± 9.2	57.1 ± 9.9	0.003
Dyspnea	26 (63.4)	24 (82.8)	0.078
FVC, % predicted	83.1 ± 21.3	67.0 ± 17.0	0.003
DL_{CO}, % predicted	70.8 ± 23.3	60.3 ± 17.2	0.085
TLC, % predicted	91.9 ± 23.8	70.6 ± 10.0	< 0.001
Survival period, mo			0.583
Mean	103.3	108.8	
(95% CI)	(77.7 - 128.8)	(70.8 - 146.9)	
Median	93.8	84.4	
(95% CI)	(29.1 - 158.5)	(43.8 - 125.0)	
Cause of death	N = 17	N =16	0.008
DP	2 (11.8)	5 (31.3)	0.171
Infection	5 (29.4)	9 (56.3)	0.119
Malignancy	2 (11.8)	0	
CVD	2 (11.8)	1 (6.3)	
Unknown	6 (35.3)	1 (6.3)	

Data are presented as mean ± standard deviation or No. (%) unless otherwise indicated.
FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; TLC, total lung capacity; CI, confidence interval; DP, disease progression; CVD, cardiovascular disease
* Patients with acute exacerbation were excluded in this analysis (n=14)

In all patients, the main causes of death were disease progression (37.0%) and respiratory infection (34.8%); however, no patients in improved or stable group died of UIP, whereas 7 patients of progressed (36.8%) and 10 patients of AEx group (76.9%) died of UIP. Among the treated patients, infection seems to be a more frequent cause of death compared to untreated group although statistically insignificant (p = 0.119).

6. Prognostic factors for mortality in patients with RA-UIP

Among the significant predictors on univariate analysis, multivariate analysis showed only age, FVC% predicted and change in FVC or DLco during 6 months were significant independent predictors for mortality.

7. Comparison of outcomes between patients with RA-UIP and those with IPF

RA-UIP group had significantly better outcome than the patients with IPF matched by age, sex, history of smoking and initial FVC% (median survival: 52.6 vs. 40.9 months, p = 0.015) (fig. 2). In all patients with UIP pattern, the presence of RA was a significant independent prognostic factor (hazard ratio: 0.641, 95% CI: 0.394 - 1.009, p = 0.018).

Discussion

Our study showed that the clinical course of RA-UIP was highly variable. About one half of the

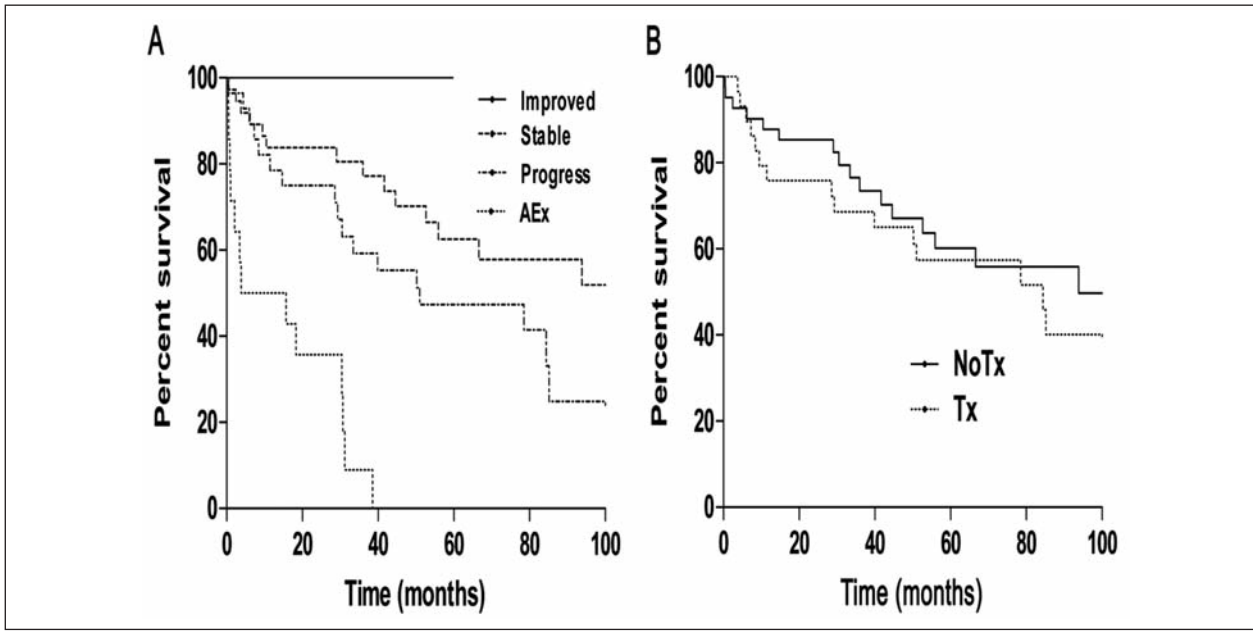

Fig. 1. A. Comparison of the survival curves among RA-UIP patients with different follow-up courses (AEx = acute exacerbation). B. Comparison of the survival curves between RA-UIP patients with and without treatment (Tx = treatment, AE group was not included in treatment group)

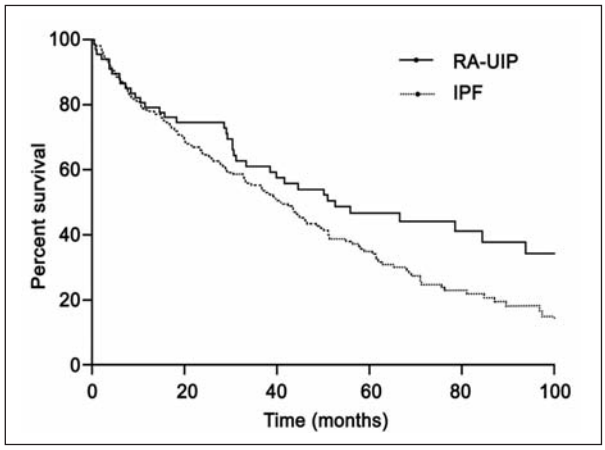

Fig. 2. Comparison of the survival curves between RA-UIP and IPF patients

patients were stable throughout the course, one third had progression of the disease irrespective to treatment and only 6% of the patients improved. AEx was not uncommon (17%) and found either at the time of initial presentation or during follow-up. TLC was a significant predictor for stable course. Among non-AEx group, 40% of the patients were treated due to poor initial lung function or progression of the disease and one half of them had improvement or stabilization of lung function. In spite of worse pre-treatment lung function of treated group, there was no difference in survival between treated and untreated group. Age, FVC and 6 months change in FVC or DLco were significant predictors for mortality. Although the overall prognosis of RA-UIP was poor, it was significantly better compared to IPF.

Previously published data on the clinical course of RA-UIP are limited and at times contradictory. Several studies, including recent epidemiological studies reported that the median survival of RA-ILD was 2.6 - 3.5 years, similar to that of IPF (7, 8, 26). Furthermore, Gochuico et al. reported that even preclinical asymptomatic ILD was progressive in RA (27). However, Gabbay et al. found the detected radiologic abnormalities was clinically significant in only a minority of the patients (28). And other studies suggested that the outcome of RA-ILD is variable (29, 30) and this variability may be due to different histopathologic pattern. In RA, UIP pattern seems to be the most prevalent pattern in contrast to other CTDs (9, 10, 13, 31), and several studies showed worse survival of UIP pattern compared to non-UIP even in RA (9, 10, 14, 15); however, the number of the subjects in these studies was too

small. Recently Kim et al (16) reported that in patients with RA-ILD, definite UIP pattern on HRCT was associated with worse survival (HR 2.3; p = 0.05), almost similar to IPF. Therefore it is important to know the prognosis of RA-UIP and our present study with larger number of RA-UIP patients showed significantly (p = 0.015)better survival compared to IPF matched with the age, gender, smoking and lung function. And this was confirmed by the presence of RA was the independent prognostic factor among the patients with UIP pattern.

However we found that the course of even in UIP pattern only was variable; one half of the subjects were stable throughout the course without treatment. Preserved lung function in our stable group may be argued as that these might represent merely an early stage of the disease. However, their lung function was stable for median 45 months and the mean survival was 113 months without proven mortality due to UIP progression, suggesting that the duration of follow-up was long enough and they might be a specific subgroup (or phenotype) rather than a merely early detection. Considering toxic side effects of present therapies in these patients, it is important to predict the course and in our study, TLC was a significant determinant factor for this stable group.

Although high dose corticosteroid/ immunomodulatory therapy are frequently used in these patients, not many studies have evaluated the response to therapy. In our study, initial therapy was given to the minority of the patients with poor lung function and majority (95%) of treated patients improved or stabilized. Although half of the patients in the treated group had relapse, the effect was sustained in the other half. As a whole, there was no difference in the survival between the treated and untreated group. However, considering the poor initial lung function of the treated group (table 4), this similar outcome may actually suggest treatment response (fig. 1B). Our study suggests that patients with preserved lung function may not need treatment, whereas the therapy may be beneficial to the patients with low lung function or who have progressive disease.

Our study confirmed that AEx is not infrequent (17%) in RA-UIP. AEx was reported in RA-ILD primarily in UIP pattern (15, 17, 26, 30) and Akira et al. reported that AEx was noted in 43% of patients presented as reticulation with or without honeycombing on HRCT (26). Our data showed that low TLC had a tendency to predict AEx or disease progression among the untreated patients (Appendix-table 3) and Dawson et al. also reported that TLC was a significant predictor for disease progression in RA-ILD (OR, 0.085; p = 0.024) (30).

HRCT findings were also helpful in prediction. Although the number of patients with atypical UIP pattern on HRCT was small (n = 10, all had histopathologic confirmation by SLBx), most of them (70%) had progression of disease (n = 6) or AEx (n = 1). And total extent and extent of reticulation on HRCT were significant predictors for survival (table 5).

The present study had several limitations. The major limitation is related to the retrospective design and the fact that the majority of the subjects were seen in pulmonary department due to respiratory symptoms. Early asymptomatic patients might not be included, although some of our subjects had only mildly reduced lung function. However, our study

Table 5. Prognostic factors for the mortality in patients with RA-UIP using a Cox regression model

Predictors	Hazards Ratio	95% CI	p-value
Univariate Analysis			
Age	1.054	1.018 - 1.092	0.003
Male	1.753	0.911 - 3.374	0.093
Never-smokers	0.841	0.442 - 1.599	0.597
Rheumatoid factor	1.000	0.999 - 1.000	0.304
C-reactive protein	1.144	1.023 - 1.280	0.018
FVC, % predicted	0.985	0.969 - 1.001	0.072
DLco, % predicted	0.996	0.978 - 1.014	0.629
TLC, % predicted	0.982	0.957 - 1.007	0.163
FVC change, 6 months	0.961	0.925 - 0.998	0.041
DLco change, 6 months	0.953	0.923 - 0.984	0.003
HRCT			
Total extent	1.527	1.015 - 2.298	0.042
Emphysema	1.210	0.696 - 2.101	0.499
GGO	1.236	0.605 - 2.526	0.561
Consolidation	1.882	0.683 - 5.188	0.221
Honeycombing	1.627	0.816 - 3.242	0.167
Reticulation	2.494	1.131 - 5.501	0.023
Atypical UIP pattern	1.098	0.419 - 2.873	0.849
Treatment	1.212	0.610 - 2.407	0.584
Multivariate Analysis			
Age	1.155	1.044 - 1.277	0.005
FVC, % predicted	0.957	0.926 - 0.989	0.010
FVC change, 6 months	0.936	0.879 - 0.998	0.043
DLco change, 6 months	0.953	0.920 - 0.988	0.009

FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; TLC, total lung capacity; HRCT, high resolution computed tomography; GGO, ground glass opacity; UIP, usual interstitial pneumonia

clearly showed that even among patients with respiratory symptoms and/or reduction in lung function, at least a half of them had stable course without specific treatment. A second limitation was the inclusion of patients with definite UIP pattern on HRCT without SLBx, which could be a potential cause of misclassification. Although more than 95% of case of definite UIP pattern on HRCT are confirmed as UIP on SLBx in IIP (32), that correlation has not been verified in RA-ILD. Although the proportion of the subject performed SLBx was small, among 73 with definite UIP pattern on HRCT all cases who undergone SLBx (n = 19) showed UIP pathologically. Most studies showed good correlation between definite UIP pattern on HRCT and histopathologic UIP (13, 16) and worse survival of the patients with definite UIP pattern on HRCT by Kim et al. suggested correlation between HRCT-UIP and pathological UIP pattern. Third limitation was the bias by different treatment regimens. However, there was no difference in the treatment regimen between patients who deteriorated and those who were improved/stable among treatment group (data not shown). Another limitation was relatively short median follow-up period of all patients (33 months), but the median follow-up period of stable (44.6 months) and even progressive group (36.6 months) was long enough to reveal the natural course, outcomes, and response to treatment in RA-UIP patients. Despite of these limitations, this is the largest study on RA-UIP and provides important information on the clinical course, response to treatment, and prognostic predictors.

In conclusion, our study showed the course of RA-UIP was variable from stable to acute exacerbation. Significant portion of the patients (mostly with higher initial TLC) had stable course without treatment. Similar survival despite of poor initial lung function of treated patients supported the treatment of patients with significant functional impairments or progression of the disease. Although overall prognosis of RA-UIP was poor, it was significantly better than that of IPF. Further prospective study in larger number of the patients is required.

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References

1. Bharadwaj A, Haroon N. Interstitial lung disease and neuropathy as predominant extra-articular manifestations in patients with rheumatoid arthritis: a prospective study. Med Sci Monit 2005; 11: CR498-502.
2. Carmona L, Gonzalez-Alvaro I, Balsa A, et al. Rheumatoid arthritis in Spain: occurrence of extra-articular manifestations and estimates of disease severity. Ann Rheum Dis 2003; 62: 897-900.
3. Horton MR. Rheumatoid arthritis associated interstitial lung disease. Crit Rev Comput Tomogr 2004; 45: 429-40.
4. Lamblin C, Bergoin C, Saelens T, et al. Interstitial lung diseases in collagen vascular diseases. Eur Respir J Suppl 2001; 32: 69s-80s.
5. Toyoshima H, Kusaba T, Yamaguchi M. Cause of death in autopsied RA patients. Ryumachi 1993; 33: 209-14.
6. Young A, Koduri G, Batley M, et al. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology (Oxford) 2007; 46: 350-7.
7. Bongartz T, Nannini C, Medina-Velasquez YF, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010; 62: 1583-91.
8. Koduri G, Norton S, Young A, et al. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. Rheumatology (Oxford) 2010; 49: 1483-9.
9. Hakala M, Paakko P, Huhti E, et al. Open lung biopsy of patients with rheumatoid arthritis. Clin Rheumatol 1990; 9: 452-60.
10. Lee HK, Kim DS, Yoo B, et al. Histopathologic pattern and clinical features of rheumatoid arthritis-associated interstitial lung disease. Chest 2005; 127: 2019-27.
11. Tanaka N, Kim JS, Newell JD, et al. Rheumatoid arthritis-related lung diseases: CT findings. Radiology 2004; 232: 81-91.
12. Tansey D, Wells AU, Colby TV, et al. Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. Histopathology 2004; 44: 585-96.
13. Yoshinouchi T, Ohtsuki Y, Fujita J, et al. Nonspecific interstitial pneumonia pattern as pulmonary involvement of rheumatoid arthritis. Rheumatol Int 2005; 26: 121-5.
14. Yousem SA, Colby TV, Carrington CB. Lung biopsy in rheumatoid arthritis. Am Rev Respir Dis 1985; 131: 770-7.
15. Park JH, Kim DS, Park IN, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. Am J Respir Crit Care Med 2007; 175: 705-11.
16. Kim EJ, Elicker BM, Maldonado F, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2010; 35: 1322-8.
17. Park IN, Kim DS, Shim TS, et al. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. Chest 2007; 132: 214-20.
18. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315-24.
19. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2002; 165: 277-304.
20. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011; 183: 788-824.
21. Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2007; 176: 636-43.

22. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. Chest 1988; 93: 580-6.
23. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J 2005; 26: 720-35.
24. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005; 26: 319-38.
25. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J 2005; 26: 511-22.
26. Akira M, Sakatani M, Hara H. Thin-section CT findings in rheumatoid arthritis-associated lung disease: CT patterns and their courses. J Comput Assist Tomogr 1999; 23: 941-8.
27. Gochuico BR, Avila NA, Chow CK, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med 2008; 168: 159-66.
28. Gabbay E, Tarala R, Will R, et al. Interstitial lung disease in recent onset rheumatoid arthritis. Am J Respir Crit Care Med 1997; 156: 528-35.
29. Fuld JP, Johnson MK, Cotton MM, et al. A longitudinal study of lung function in nonsmoking patients with rheumatoid arthritis. Chest 2003; 124: 1224-31.
30. Dawson JK, Fewins HE, Desmond J, et al. Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis. Ann Rheum Dis 2002; 61: 517-21.
31. Kim EJ, Collard HR, King TE. Rheumatoid arthritis-associated interstitial lung disease: the relevance of histopathologic and radiographic pattern. Chest 2009; 136: 1397-405.
32. Flaherty KR, Thwaite EL, Kazerooni EA, et al. Radiological versus histological diagnosis in UIP and NSIP: survival implications. Thorax 2003; 58: 143-8.

Appendix - Table 1. Predicting factors for the stable group using a logistic regression model

Predictors	Odds Ratio	95% CI	p-value
Univariate Analysis			
Age	1.035	0.986 - 1.087	0.164
Male	0.993	0.388 - 2.541	0.989
Never-smokers	0.880	0.343 - 2.254	0.789
Rheumatoid factor	1.000	1.000 - 1.001	0.406
C-reactive protein	0.997	0.818 - 1.216	0.980
Dyspnea	0.365	0.121 - 1.104	0.074
FVC, % predicted	1.020	0.996 - 1.045	0.102
DLco, % predicted	1.019	0.993 - 1.045	0.157
TLC, % predicted	1.043	1.003 - 1.084	0.036
FVC change, 6 mo	1.009	0.962 - 1.059	0.706
DLco change, 6 mo	1.028	0.991 - 1.067	0.138
Atypical UIP pattern	0.190	0.036 - 1.003	0.050
Multivariate Analysis			
TLC, % predicted	1.039	0.997 -1.082	0.070

CI, confidence interval; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; TLC, total lung capacity; mo, months; UIP, usual interstitial pneumonia

Appendix-Table 2. Predicting factors for the progressive group using a logistic regression model

Predictors	Odds Ratio	95% CI	p-value
Univariate Analysis			
Age	1.012	0.964 - 1.061	0.641
Male	0.909	0.349 - 2.367	0.845
Never-smokers	1.049	0.402 - 2.735	0.922
Rheumatoid factor	1.000	0.999 - 1.001	0.624
C-reactive protein	0.995	0.812 - 1.220	0.964
Dyspnea	2.556	0.805 - 8.110	0.111
FVC, % predicted	0.990	0.967 - 1.013	0.390
DLco, % predicted	0.987	0.962 - 1.012	0.311
TLC, % predicted	0.971	0.937 - 1.006	0.106
FVC change, 6 mo	0.962	0.911 - 1.016	0.160
DLco change, 6 mo	0.987	0.962 - 1.012	0.311
Atypical UIP pattern	3.789	0.851 – 16.868	0.080

CI, confidence interval; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; TLC, total lung capacity; mo, months; UIP, usual interstitial pneumonia

Appendix-Table 3. Predicting factors for the progression or development of acute exacerbation among patients who were initially untreated using a logistic regression model

Predictors	Odds Ratio	95% CI	p-value
Univariate Analysis			
Age	0.995	0.936 - 1.058	0.878
Male	1.273	0.445 - 3.639	0.653
Never-smokers	0.814	0.286 - 2.322	0.701
Rheumatoid factor	1.000	0.999 - 1.001	0.714
C-reactive protein	1.121	0.871 - 1.441	0.375
Dyspnea	2.000	0.654 - 6.118	0.224
FVC, % predicted	0.983	0.956 - 1.011	0.226
DLco, % predicted	0.991	0.965 - 1.018	0.521
TLC, % predicted	0.963	0.925 - 1.003	0.066
FVC change, 6 mo	0.989	0.941 - 1.039	0.650
DLco change, 6 mo	0.968	0.931 - 1.006	0.102
Atypical UIP pattern	2.175	0.333 - 14.221	0.417

CI, confidence interval; FVC, forced vital capacity; DLco, diffusing capacity for carbon monoxide; TLC, total lung capacity; mo, months; UIP , usual interstitial pneumonia