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Risk factors for interstitial lung disease in rheumatoid arthritis: a cohort study from the KOBIO registry

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Hong Ki Min, Se Hee Kim, Sang-Heon Lee and Hae-Rim Kim

Abstract

Background: Interstitial lung disease (ILD) is a critical extra-articular manifestation of rheumatoid arthritis (RA). However, little is known about the risk factors of RA-ILD.

Objectives: Here, we examined the effect of demographic, clinical, therapeutic, and environmental factors on the incidence of ILD in RA patients using the Korean College of Rheumatology Biologics and Targeted Therapy (KOBIO) registry.

Design: We used data from the KOBIO registry, a multi-center, prospective, observational cohort that included RA patients in South Korea.

Methods: RA patients who used biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) or conventional synthetic (cs)DMARDs, and were enrolled in the KOBIO registry, were examined. Demographic, clinical, and radiographic characteristics, as well as medications, were recorded at baseline and annually thereafter. Kaplan–Meier curves and the log-rank test were used to compare the incidence of ILD between RA patients taking different b/tsDMARDs. Hazard ratios (HRs) were calculated by Cox regression analyses.

Results: In total, 2492 patients (1967 in the b/tsDMARDs group and 525 in the csDMARDs group) were analyzed. The b/tsDMARDs group showed longer disease duration, higher erythrocyte sedimentation rate/C-reactive protein, and higher disease activity score-28 (DAS28) than the csDMARDs group. The incidence of ILD was significantly higher in those taking tumor necrosis factor inhibitors and abatacept than in those taking csDMARDs (log ranked $p < 0.001$). Multivariate Cox regression analysis identified older age (HR = 1.057, $p = 0.001$), male sex (HR = 2.824, $p = 0.007$), time-averaged DAS28 (HR = 2.241, $p < 0.001$), and rheumatoid factor titer (HR = 1.009, $p = 0.007$) as having a significantly increased HR for ILD occurrence.

Conclusion: ILD is a rare but critical extra-articular symptom of RA patients. Therefore, RA patients with the above risk factors should be monitored carefully for ILD development.

Keywords: biologics, DAS28, DMARDs, interstitial lung disease, rheumatoid arthritis, rheumatoid factor

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Correspondence to:
Hae-Rim Kim
Division of Rheumatology, Department of Internal Medicine, Research Institute of Medical Science, Konkuk University Medical Center, Konkuk University School of Medicine, 120-1 Neungdong-ro, Gwangjin-gu, Seoul, Republic of Korea
kimhaerim@kuh.ac.kr

Hong Ki Min
Division of Rheumatology, Department of Internal Medicine, Konkuk University Medical Center, Gwangjin-gu, Seoul, Republic of Korea

Se Hee Kim
Division of Rheumatology, Department of Internal Medicine, Konkuk University Medical Center, Gwangjin-gu, Seoul, Republic of Korea

Department of Rheumatology, Kyung Hee University Hospital at Gangdong, College of Medicine, Kyung Hee University, Seoul, Republic of Korea

Sang-Heon Lee
Division of Rheumatology, Department of Internal Medicine, Research Institute of Medical Science, Konkuk University Medical Center, Konkuk University School of Medicine, Gwangjin-gu, Seoul, Republic of Korea

Introduction

Rheumatoid arthritis (RA) is an autoimmune-mediated systemic inflammatory arthritis[1] with a prevalence of approximately 0.5–2%.[2] Synovitis associated with RA mainly affects the small joints, in which uncontrolled inflammation causes destructive arthropathy.[1] Although the main symptoms of RA are articular, they may be accompanied by other extra-articular complications such as interstitial lung disease (ILD), cardiovascular disease, and osteoporosis.[3] Furthermore, the main cause of mortality in RA patients is not associated with articular symptoms or complications; rather, patients are more likely to die from cancer, cardiovascular

disease, and pulmonary complications.[4,5] ILD is an uncommon but critical pulmonary complication in RA, leading to an increased risk of death.[6,7]

Several conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologic/targeted synthetic DMARDs (b/tsDMARDs) have been approved for the treatment of RA. The American College of Rheumatology (ACR), European Alliance of Associations for Rheumatology (EULAR), and the Korean College of Rheumatology (KCR) recommend b/tsDMARDs when RA patients fail to achieve clinical improvement after taking csDMARDs.[8–10] Evidence suggests that bDMARDs not only have antiarthritic effects but also improve prognosis related to extra-articular complications such as cardiovascular disease and osteoporosis.[11–14] The chronic inflammatory status of RA can aggravate cardiovascular complications and reduce bone mineral density.[15,16] Although the pathogenesis of RA-ILD is assumed to be associated with inflammation,[17] the net effects of DMARDs (which suppress inflammation) are not clearly understood.[18] Some case series have suggested that methotrexate (MTX) may induce ILD in RA patients[19]; however, a recent meta-analysis did not find an association between MTX and ILD occurrence.[20] The anti-IL-6 receptor Ab, tocilizumab, does not decrease pulmonary function in RA-ILD patients.[3,21] One study showed that tsDMARDs [i.e. janus kinase inhibitors (JAKi)] may have a positive effect on established RA-ILD.[22] However, the effects of cs/b/tsDMARDs on new-onset ILD in RA patients remain unclear, and thus more studies are needed to identify the risk factors for ILD in RA patients.

The Korean College of Rheumatology BIOlogics (KOBIO) registry, which was established by the KCR in 2012, recruits RA patients who started, reinitiated, or switched to b/tsDMARDs at rheumatology clinics in tertiary hospitals in South Korea.[23] RA patients who only used csDMARDs were also recruited to the KOBIO registry as controls. The KOBIO registry is a nationwide prospective observational cohort in which most university hospital-based rheumatology clinics take part. The registry collects abundant information about demographic, clinical, and radiographic characteristics, as well as treatment responses, at the time of enrollment and collects follow-up data annually; because data collection is ongoing, the KOBIO registry reflects nationwide real-world data from RA patients in South Korea. Also, because it has been running for more than 10 years, the KOBIO registry is suitable for evaluating outcomes of RA patients in South Korea.

Here, we obtained data from the KOBIO registry and examined the incidence of new-onset ILD in RA patients according to type of b/tsDMARDs. Also, we evaluated the impact of demographic and clinical characteristics, medications, and environmental factors on the occurrence of ILD in RA patients.

Patients and methods

Study population

Data from RA patients enrolled in the KOBIO registry from December 2012 to December 2021 were provided by the KOBIO committee of the KCR (ClinicalTrials.gov identifier NCT01965132). Demographic, clinical, laboratory, and radiographic characteristics, as well as medications, place of residence, and disease activity-related data, were collected at baseline, and follow-up data (laboratory and disease activity-related data) were collected annually. The inclusion criteria were as follows: (1) patients who fulfilled the 2010 ACR/EULAR classification criteria for RA,[24] (2) age $>$ 18 years, and (3) no ILD at enrollment. All patients were screened for pulmonary manifestation by chest X-ray at the time of enrollment and were then referred to a pulmonologist when abnormal findings were detected in the chest X-ray. Thereafter, the patients underwent several examinations, such as high-resolution computed tomography (HRCT) of the chest and pulmonary function tests, to define lung involvement. Chest X-rays were then performed annually, and further examinations, such as HRCT, were performed when abnormal findings were detected in follow-up chest X-ray images. Patients who withdrew consent for entity into the KOBIO registry or lacked follow-up data were excluded. RA patients who initiated, restarted, or switched b/tsDMARDs were enrolled in the KOBIO registry as the b/tsDMARDs group, and RA patients who only used csDMARDs were set as a control group (csDMARDs group). The study was conducted according to the principles of the Declaration of Helsinki Good Clinical Practice guidelines. The study protocol and data collection forms were approved by the

institutional review boards of Konkuk University Medical Center (IRB number: KUMC 2022-06-005). All participants provided informed consent prior to enrollment by the treating physician at each rheumatology center. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology statement.[25]

Data collection and outcomes

All data from the KOBIO registry were recorded in a web-based data center by the treating physician at each rheumatology center. The baseline data used in the present study comprised age, sex, body mass index (BMI), disease duration before enrollment to the KOBIO registry, smoking history (pack-years), laboratory data [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, rheumatoid factor (RF) level, anticitrullinated protein antibody (ACPA) level], the disease activity score-28 joints based on CRP (DAS28-CRP),[26] the swollen/tender joint count (SJC/TJC), radiographic evidence of erosion on the hands or feet, type of b/tsDMARDs [tumor necrosis factor inhibitor (TNFi), abatacept, tocilizumab, rituximab, or JAKi], and concurrent csDMARDs [MTX, hydroxychloroquine (HCQ), sulfasalazine (SSZ), leflunomide (LEF), tacrolimus (TAC), or glucocorticoids]. Information about the ESR/CRP, DAS28, and whether the b/tsDMARDs were continued or stopped were collected annually. The concentration of air pollutants, particulate matter with an aerodynamic diameter of $\leqslant 10\,\mu m$ (PM10), sulfur dioxide (SO_2), nitrogen dioxide (NO_2), ozone (O_3), and carbon monoxide (CO) were obtained from www.airkorea.or.kr; this website collects and releases atmospheric information collected by regional groups in South Korea. The average values for air pollutants were calculated according to the residential area of each patient, as well as the duration of exposure. The average values of these air pollutants are presented in Supplemental Table S1. The primary outcome was defined as new-onset ILD detected on a chest HRCT scan with confirmation by a pulmonologist. The index date was set as the date on which the RA patients were enrolled in the KOBIO registry. To avoid detection bias, ILD was only considered new-onset ILD when it was detected at least 6 months after the patient was enrolled in the KOBIO registry. The last follow-up date was determined as follows: (1) if ILD occurred: the date when ILD was reported; (2) if ILD did not occur: until 31 December 2021, or the last follow-up date; or (3) if switching or stopping b/tsDMARDs: the last date before switching or stopping the current b/tsDMARDs.

Statistical analyses

Continuous data were compared using Student's *t*-test and expressed as the mean ± SD. Categorical variables were compared using the chi-square test and expressed as numbers and percentages. Kaplan–Meier analysis and the log-rank test were used to compare the incidence of ILD in csDMARDs and each b/tsDMARDs group. Cox regression analysis was used to calculate the hazard ratio (HR) for ILD incidence. Variables with a p value < 0.05 in univariate Cox regression analyses were included in multivariate Cox regression analysis. Time-averaged DAS28 was calculated by dividing the area under the receiver operating characteristics curve for DAS28 by the total number of follow-up days.[27,28] A two-sided p value < 0.05 was considered statistically significant. All statistical analyses were performed using R software (R for Windows 3.3.2; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Comparison of baseline characteristics between RA patients taking csDMARDs and b/tsDMARDs

A total of 2492 patients (1967 patients taking b/tsDMARDs and 525 patients taking csDMARDs) were included in the study. The flow chart showing the inclusion and exclusion process is presented in Figure 1. Disease duration was longer, and the baseline ESR/CRP, DAS28, and SJC/TJC were higher, in the b/tsDMARDs group than in the csDMARDs group. In addition, radiographical evidence of erosion on the hands or feet was more common in the b/tsDMARDs group than in the csDMARDs group. The most common b/tsDMARDs were TNFi (49.1%), whereas the use of MTX was similar between the two groups (84.6 *versus* 82.4%, respectively; $p = 0.259$). HCQ, SSZ, LEF, and TAC were used more frequently by the csDMARDs group than by the b/tsDMARDs group. The baseline characteristics are summarized in Table 1.

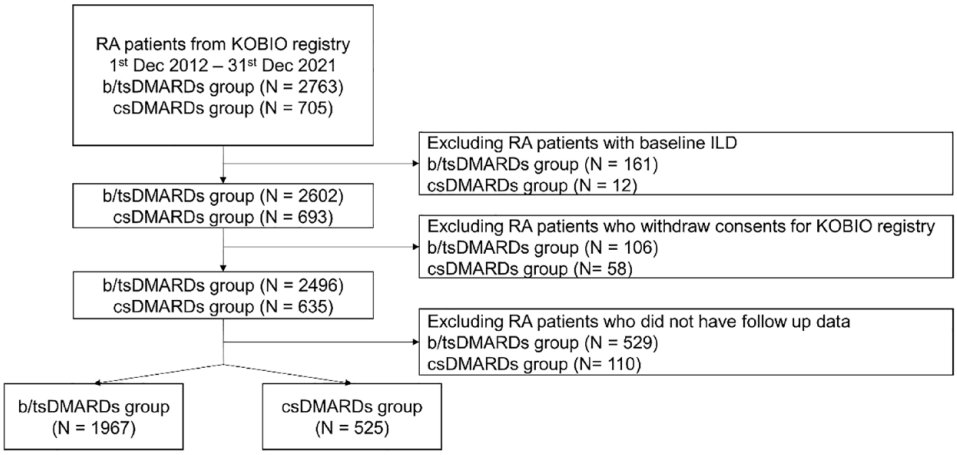

Figure 1. Flow chart showing the patient enrollment process.

Table 1. Baseline characteristics of the enrolled RA patients.

Variables	csDMARDs group (*N* = 525)	b/tsDMARDs group (*N* = 1967)	*p*
Female (*N*, %)	451 (85.9%)	1651 (83.9%)	0.300
Age (years)	54.9 ± 11.8	54.2 ± 12.8	0.237
Disease duration (year)	6.7 ± 6.8	7.8 ± 7.5	0.001
ESR (mm/h)	27.4 ± 21.7	48.4 ± 27.5	<0.001
CRP (mg/dL)	0.6 ± 1.4	2.3 ± 3.4	<0.001
DAS28-ESR	3.3 ± 1.2	5.5 ± 1.1	<0.001
DAS28-CRP	2.7 ± 1.2	4.8 ± 1.1	<0.001
BMI (kg/m^2)	22.7 ± 3.0	22.7 ± 3.5	0.964
Smoking (pack-years)	3.3 ± 10.4	3.5 ± 11.8	0.692
Smoking status			0.690
Nonsmoker	438 (83.6%)	1652 (84.0%)	
Ex-smoker	41 (7.8%)	166 (8.4%)	
Current smoker	45 (8.6%)	149 (7.6%)	
SJC	1.9 ± 3.4	6.6 ± 5.4	<0.001
TJC	2.6 ± 4.6	8.6 ± 6.8	<0.001
Type of b/tsDMARDs			
TNF inhibitors*		966 (49.1%)	
Abatacept		238 (12.1%)	
Tocilizumab		478 (24.3%)	

(Continued)

Table 1. (Continued)

Variables	csDMARDs group (*N* = 525)	b/tsDMARDs group (*N* = 1967)	*p*
Rituximab		19 (1.0%)	
JAK inhibitors**		266 (13.5%)	
MTX	444 (84.6%)	1620 (82.4%)	0.259
HCQ	190 (36.2%)	179 (9.1%)	<0.001
SSZ	59 (11.2%)	118 (6.0%)	<0.001
LEF	161 (30.7%)	238 (12.1%)	<0.001
TAC	65 (12.4%)	116 (5.9%)	<0.001
Systemic glucocorticoid	375 (71.4%)	1672 (85.0%)	<0.001
Daily dose of glucocorticoid (mg/day, equivalent to prednisolone)	4.4 ± 3.4	5.3 ± 3.2	<0.001
Erosion on hands	103 (24.8%)	617 (36.9%)	<0.001
Erosion on feet	84 (27.8%)	432 (33.9%)	0.052
RF positive	417 (81.0%)	1566 (82.6%)	0.416
RF titer (IU/mL)	144.3 ± 287.1	136.6 ± 231.4	0.577
ACPA positive	370 (84.7%)	1418 (85.7%)	0.628
ACPA titer (U/mL)	196.8 ± 478.5	219.1 ± 372.6	0.365
Residence			
Seoul City	305 (58.1%)	1065 (54.1%)	
Incheon City	5 (1%)	24 (1.2%)	
Gyeonggi-do Province	41 (7.8%)	153 (7.8%)	
Chungcheong-do Province	52 (9.9%)	138 (7.0%)	
Cheonan City	0	60 (3.1%)	
Gyeongsangbuk-do Province	18 (3.4%)	200 (10.2%)	
Busan City	0	35 (1.8%)	
Gyeongsangnam-do Province	18 (3.4%)	34 (1.7%)	
Jeollanam-do Province	19 (3.6%)	64 (3.3%)	
Jeollabuk-do Province	67 (12.8%)	185 (9.4%)	
Jejudo Island	0	9 (0.5%)	

*TNFi: Etanercept (*n* = 276), Infliximab (*n* = 201), Adalimumab (*n* = 340), Golimumab (*n* = 149).
**JAKi: Tofacitinib (*n* = 149), Baricitinib (*n* = 112), Upadacitinib (*n* = 5).
ACPA, anticitrullinated protein antibody; b/tsDMARDs, biologic or targeted synthetic disease-modifying antirheumatic drugs; BMI, body mass index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DAS28, disease activity score 28 joints; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HCQ, hydroxychloroquine; JAKi, janus kinase inhibitor; LEF, leflunomide; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; SSZ, sulfasalazine; TAC, tacrolimus; TJC, tender joint count; TNFi, tumor necrosis factor inhibitor.

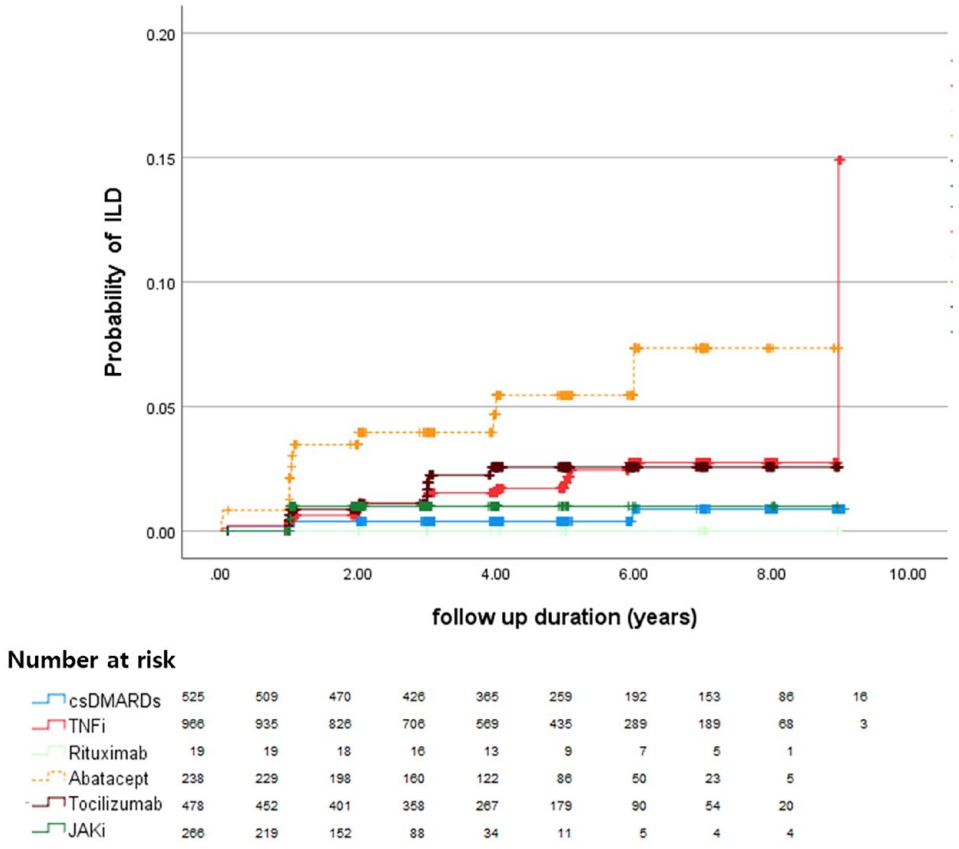

Figure 2. Kaplan–Meier curves showing ILD incidence according to the use of csDMARDs or b/tsDMARDs. b/tsDMARDs, biologic or targeted synthetic disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ILD, interstitial lung disease.

Incidence of ILD according to type of b/tsDMARDs and factors predictive of ILD in RA patients

The mean follow-up duration in the csDMARDs and b/tsDMARDs groups was 5.2 ± 2.4 and 4.2 ± 2.2 years, respectively. A total of 30 cases of new-onset ILD were reported during total follow-up; two cases occurred in the csDMARDs group, 14 cases in the TNFi group, six cases in the abatacept group, six cases in the tocilizumab group, and two cases in JAKi group. No ILD occurred in the rituximab group. The incidence rate of ILD was 0.07 per 100 person-years (PYs) in the csDMARDs group, 0.31 per 100 PYs in the TNFi group, 0.61 per 100 PYs in the abatacept group, 0.29 per 100 PYs in the tocilizumab group, and 0.30 per 100 PYs in the JAKi group. Kaplan–Meier curve analysis revealed that the probability of ILD occurrence was higher in the TNFi, abatacept, and tocilizumab groups than in the csDMARDs group (Figure 2). Univariate Cox regression analyses identified older age, male sex, higher time-averaged DAS28, history of smoking (pack-years), RF titer, and TNFi or abatacept use (when compared to csDMARDs user) as having a significantly increased HR for ILD occurrence. Neither air pollutant concentration (PM10, SO_2, NO_2, O_3, and CO) nor concurrent use of csDMARDs was associated with ILD occurrence (Table 2). Multivariate Cox regression analysis of variables that were significant in univariate analysis identified older age (HR = 1.057, $p = 0.001$), male sex (HR = 2.824, $p = 0.007$), higher time-averaged DAS28 (HR = 2.241, $p < 0.001$), and higher RF titer (per 10 IU/mL, HR = 1.009, $p = 0.007$) as being significantly associated with an increased HR for ILD occurrence (Table 2).

Discussion

The present study reveals an association between various demographic, clinical, laboratory, and environmental characteristics, as well as type of medication, and the incidence of new-onset ILD in RA patients. The incidence of ILD differed between the csDMARDs and b/tsDMARDs

Table 2. Univariate and multivariate Cox proportional regression analysis of factors associated with new-onset ILD in patients with RA.

Variables	Univariate			Multivariate*		
	HR	95% CI	*p*	HR	95% CI	*p*
Age	1.069	1.033–1.107	<0.001	1.057	1.022–1.093	0.001
Male sex	3.222	1.755–5.914	<0.001	2.824	1.335–5.972	0.007
Disease duration (years)	1.017	0.972–1.065	0.461			
BMI	1.085	0.988–1.193	0.088			
PM10 (per 1 μg/m^3)	0.993	0.863–1.142	0.916			
SO_2 (per 0.001 ppm)	1.598	0.584–4.369	0.361			
NO_2 (per 0.01 ppm)	1.237	0.776–1.972	0.371			
O_3 (per 0.01 ppm)	0.523	0.187–1.469	0.219			
CO (per 0.1 ppm)	1.736	0.455–6.620	0.419			
Baseline erosion on hands	1.386	0.635–3.025	0.413			
Baseline erosion on feet	1.105	0.461–2.644	0.823			
Time-averaged DAS28-CRP	2.459	1.750–3.455	<0.001	2.241	1.551–3.236	<0.001
Smoking (pack-years)	1.024	1.015–1.034	<0.001	1.002	0.970–1.028	0.426
RF titer (per 10 IU/mL)	1.008	1.003–1.013	0.002	1.009	1.002–1.015	0.007
ACPA titer (per 10 CU)	1.003	0.999–1.007	0.179			
Type of b/tsDMARDs						
csDMARDs	(reference)			(reference)		
TNFi	4.896	1.082–22.170	0.039	2.970	0.621–14.200	0.173
Abatacept	9.572	1.871–48.980	0.007	5.351	0.851–28.706	0.076
Tocilizumab	4.610	0.900–23.600	0.067	3.016	0.561–16.218	0.199
JAKi	5.968	0.802–44.390	0.081	3.681	0.478–28.324	0.211
Rituximab	NA			NA		
csDMARDs						
MTX	1.014	0.388–2.649	0.977			
HCQ	0.815	0.284–2.341	0.704			
LEF	0.500	0.152–1.650	0.255			
SSZ	1.610	0.488–5.315	0.434			
TAC	0.389	0.053–2.857	0.353			
Glucocorticoids	1.549	0.538–4.456	0.417			

*All variables with *p* values < 0.05 in univariate Cox regression analysis were entered into multivariate analysis.
ACPA, anticitrullinated protein antibody; b/tsDMARDs, biologic or targeted synthetic disease-modifying antirheumatic drugs; BMI, body mass index; CI, confidence interval; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; DAS28, disease activity score 28 joints; DMARDs, disease-modifying antirheumatic drugs; HCQ, hydroxychloroquine; HR, hazard ratio; ILD, Interstitial lung disease; JAKi, janus kinase inhibitor; LEF, leflunomide; MTX, methotrexate; NA, not available; PM10, particulate matter with an aerodynamic diameter of ⩽10 μm; ppm, parts per million; RA, rheumatoid arthritis; RF, rheumatoid factor; SSZ, sulfasalazine; TAC, tacrolimus; TNFi, tumor necrosis factor inhibitor.

groups. Cox regression analysis identified older age, male sex, higher time-averaged DAS28, and higher RF titer as being associated with an increased HR for ILD occurrence. The results of this prospective cohort study are meaningful because they are derived from real-world nationwide data.

Although several case reports published in the early 2000s suggested that csDMARDs and bDMARDs may be associated with ILD in RA patients,[29,30] the link remains debatable. Studies evaluating risk factors for ILD in RA patients are relatively uncommon, and most examined the effects of DMARDs on prognosis or progression of ILD in RA patients already diagnosed as RA-ILD.[31–35] A study of data from American insurance claims suggests that the risk for RA-ILD in patients who used TNFi is comparable with that of patients who used different bDMARDs.[36] Another retrospective cohort study revealed that TNFi users had a risk for RA-ILD occurrence comparable with that of csDMARDs users.[37] Similar to previous studies, we also found that the bDMARD subtype was not associated with an increased risk of new-onset ILD in multivariate regression analysis (Table 2). A recent retrospective study showed that among RA patients, tofacitinib users have a lower risk of ILD than adalimumab users.[38] In addition, the incidence rates of ILD in RA patients who used JAKi are relatively low at 0.18 per 100 PYs for tofacitinib users[39] and 0.17 per 100 PYs for baricitinib users.[40] In the present study, the number of patients in the JAKi group was relatively smaller than the number of patients in the TNFi group, and various JAKis (tofacitinib, baricitinib, and upadacitinib) were included. Furthermore, a previous study[38] did not include RA patients who only used csDMARDs, whereas we employed csDMARDs users as a reference group when comparing the risk of ILD occurrence.

Older age, male sex, high ACPA/RF titers, and smoking are known risk factors for ILD in RA patients.[36,41,42] One study published a risk nomogram model for RA-ILD, which showed that male sex, current smoking, RF titer, CRP, and matrix metalloproteinase-3 (MMP-3) levels discriminate ILD in RA patients.[43] Some of the results in the present study are consistent with these findings. Multivariate Cox regression analysis revealed that the HRs for older age, male sex, and higher RF titer were significant predictors of ILD development. The degree of cigarette exposure, measured in pack-years, was the only significant factor in univariate Cox regression analysis but not in multivariate analysis (Table 2). The non-significance of smoking history in multivariate Cox regression analysis may be due to higher cigarette exposure in male RA patients than in female RA patients (19.3 ± 22.8 *versus* 0.5 ± 2.6 pack-years, respectively; $p < 0.001$). Further studies with larger sample sizes and a bias-controlled prospective clinical trial will be required to firmly establish predictors of ILD development in RA patients.

Higher time-averaged DAS28 was also an independent predictor for the ILD occurrence of RA. This finding is noteworthy because the time-averaged DAS28 reflects the degree of disease activity control during follow-up. The time-averaged DAS28 also predicts cardiovascular disease and TNFi maintenance in RA patients.[27,28] Therefore, we assume that sustained, well-controlled disease activity not only is beneficial for pain control but also prevents extra-articular complications such as ILD and cardiovascular disease.

Air pollutants have been suggested as an environmental risk factor for idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, and reduced lung function.[44] Indeed, an incremental increase of $10\,\mu g/m^3$ NO_2 is associated with a 7.93% increase in the incidence of IPF,[45] and regions with higher concentrations of particulate matter with an aerodynamic diameter of $\leqslant 2.5\,\mu m$ (PM2.5) are associated with a higher incidence of IPF.[46] One population-based retrospective cohort study showed that a concentration of PM10 above $30\,\mu g/m^3$, and PM2.5 above $20\,\mu g/m^3$, increases the risk of autoimmune disease by 12% and 13%, respectively.[47] Also, exposure to higher NO_2 concentrations is associated with the incidence of systemic lupus erythematosus.[48] However, another study showed that air pollutants (PM10, PM2.5, SO_2, NO_2, and CO) do not increase the risk of ILD in patients with autoimmune diseases, including RA, systemic lupus erythematosus, systemic sclerosis, inflammatory myositis, and primary Sjögren's syndrome.[49] Furthermore, the concentration of O_3 is negatively associated with the incidence of ILD in patients with autoimmune disease.[49] Similar to a previous study, we found that air pollutants did not increase the HR for ILD in RA patients. The present study and a previous study[49] report a non-significant, or even negative, association between air pollutants and ILD development in patients with autoimmune disease; however, further

studies are required to clarify the impact of air pollutants on ILD development in these patients.

This study has several limitations. One intrinsic limitation is that the KOBIO registry is an observational cohort. We excluded preexisting RA-ILD patients in the analysis; however, the discriminating association between each DMARD and preexisting ILD was impossible in the present study. The results from observational studies should be confirmed in well-designed clinical trials. Second, the incidence of ILD was relatively small. To minimize bias, we tried to follow the rule of 10, that is, events per variable close to 10 were entered into multivariate Cox regression analysis.[50,51] Third, the present study did not include several biomarkers and susceptible genes related to ILD development in those with RA, which were suggested by recent studies.[41,43,52–54] Suggested biomarkers such as MMP and KL-6, or the susceptibility gene *MUC5B*, are not included as survey items in the KOBIO registry. Fourth, the concentration of air pollutants was calculated based on annual average values for each major city or province; this is because the KOBIO registry records information about the residents in terms of major cities or provinces in South Korea. More detailed information about the residents may increase the accuracy of the data regarding exposure to air pollutants. In addition, the PM2.5 values were collected only after 2015, whereas the KOBIO registry started in 2012; therefore, we could not examine PM2.5 in the present study. Fifth, the severity and pattern of ILD were not recorded in the KOBIO registry.

Conclusion

In conclusion, we compared the incidence of ILD in RA patients taking different b/tsDMARDs. We found that several factors (age, sex, time-averaged DAS28, and RF titer) were associated with an increased risk of ILD. ILD is an uncommon but potentially fatal complication in RA patients; therefore, RA patients at high risk of new-onset ILD should be monitored carefully.

Declarations

Ethics approval and consent to participate

The study protocol and data collection forms were approved by the institutional review boards of Konkuk University Medical Center (IRB number: KUMC 2022-06-005). All participants provided informed consent prior to enrollment by the treating physician at each rheumatology center.

Consent for publication

Not applicable.

Author contributions

Hong Ki Min: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Se Hee Kim: Data curation.

Sang-Heon Lee: Data curation.

Hae-Rim Kim: Conceptualization; Funding acquisition; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data are available upon reasonable request.

ORCID iD

Hong Ki Min https://orcid.org/0000-0003-1147-1046

Supplemental material

Supplemental material for this article is available online.

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