Uncovering risk factors for adverse events and infections in rheumatoid arthritis and rheumatoid arthritis with interstitial lung disease under treatment with biologics or targeted synthetic DMARDs: insights from the KOBIO Registry

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Abstract

Objective

This study aimed to identify the risk factors associated with overall adverse events (AEs) and infections in patients with rheumatoid arthritis (RA) and comorbid interstitial lung disease (ILD), receiving biologic or targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs), using data from the Korean College of Rheumatology Biologics registry.

Methods

We analysed data from a cohort of 2,266 adult patients with RA who received b/tsDMARDs, including 169 patients with comorbid ILD. We identified the risk factors for overall AEs and infections in both the all RA group and the subgroup of patients with RA-ILD and investigated the impact of infections on mortality in patients with RA-ILD.

Results

Among all patients with RA, 45.7% withdrew b/tsDMARDs, whereas among those with RA-ILD, a higher proportion of 57.4% withdrew their treatment regimen. The main reason for withdrawing b/tsDMARDs in the RA-ILD group was AEs, with infections accounting for the largest proportion of reported AEs. In multivariable analysis of the risk factors for overall AEs and infections in the RA-ILD group, older age was identified as a risk factor for overall AEs (odds ratio [OR], 3.01; p=0.014), and only a current smoking status was identified as a risk factor for infections (OR, 2.11; p=0.035).

Conclusion

Patients with RA-ILD exhibited a higher rate of b/tsDMARDs withdrawal due to overall AEs and infections than those with RA without ILD. In the RA-ILD group, older age was identified as a risk factor for overall AEs, whereas a current smoking status was identified as a risk factor for infections.

Key words

rheumatoid arthritis, interstitial lung disease, biologic agent, adverse event, infection

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Received on December 19, 2023; accepted in revised form on March 15, 2024.

Competing interests: none declared.

Introduction

The coexistence of interstitial lung disease (ILD) and rheumatoid arthritis (RA), referred to as RA-ILD, presents challenges in treatment and management, adding complexity to patient care (1). Despite the availability of effective treatments for RA, such as conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs (bDMARDs), and target-synthetic DMARDs (tsDMARDs), the optimal treatment approach for RA-ILD remains uncertain (2). Each patient with RA-ILD presents with a unique disease phenotype, and their response to treatment varies, highlighting the need for personalised care (3-4).

Systemic inflammation and disease activity are believed to have a greater impact on the development and progression of ILD in patients with RA compared to factors such as sex, smoking, and RA serological status. Various research findings support this statement, leading rheumatologists to strive to achieve and maintain remission or low disease activity in patients with RA-ILD (5). A common treatment approach involves initiating therapy with non-pulmonary toxic csDMARDs and short-term or low-dose glucocorticoids before transitioning to bDMARDs or tsDMARDs (6, 7). However, using bDMARDs or tsDMARDs in RA-ILD is challenging because of the increased risk of respiratory complications. Due to known potential adverse effects such as mortality and ILD progression associated with specific b/tsDMARDs, rituximab or abatacept is favored in RA-ILD patients, with tocilizumab or Janus kinase (JAK) inhibitors serving as alternatives (8, 9).

The retention rates of b/tsDMARDs remain lower in patients with RA-ILD compared to the overall RA population (10). Based on our previous research, we have concluded that the primary reason for the low retention rates of b/tsDMARDs in patients with RA-ILD is adverse events (AEs) (10). Additionally, discontinuation of therapy due to ILD progression associated with b/tsDMARDs has been reported in other studies focusing on RA-ILD (11). Nintedanib has shown efficacy in progressive RA-ILD, with other antifibrotic therapies like pirfenidone also being explored. While these treatments hold promise, they cannot replace DMARDs (12). In light of these findings, selecting suitable b/tsDMARDs is paramount for managing disease progression in RA-ILD.

Therefore, this study aimed to identify the types of AEs associated with the use of bDMARDs or tsDMARDs in patients with RA-ILD and determine the associated risk factors, using data from the Korean College of Rheumatology Biologics (KOBIO) registry. Additionally, we conducted an analysis focusing on infections that could have a significant impact on the prognosis of patients with RA-ILD. We compared the frequency of infections occurring during the use of b/tsDMARDs with the factors affecting these infections in the overall RA population.

Materials and methods

Study population

The KOBIO registry is a nationwide, multicenter, web-based, observational cohort study launched in 2012 (10). This study is an extension of our previous research on patients with RA-ILD using data from the KOBIO registry (8). Patients, aged >18 years, with RA who met either the 1987 American College of Rheumatology (ACR) or 2010 ACR/European League Against Rheumatism classification criteria and initiated or switched to bDMARDs or tsDMARDs were enrolled (14, 15). The patients underwent annual follow-up assessments by individual investigator.

Ethics approval for the KOBIO registry was obtained from the institutional review boards (IRB) of all 58 participating institutions. Ethics approval for this study and the use of the KOBIO registry data was granted by the IRB of the researchers' affiliated hospitals (AJIRB-MED-21-450). The study was conducted in accordance with the principles of the Declaration of Helsinki. All the patients provided written informed consent to participate in the study.

Data collection

The clinical information of the enrolled patients was collected from data up-

loaded to the KOBIO web server (http://www.rheum.or.kr/kobio/) between December 2012 and December 2021 (13). Clinical data on demographics, previous or current medications, comorbidities, and extra-articular manifestations, were extracted from this data source. Laboratory results, including rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody positivity, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin, and hematocrit, were also collected. The number of tender and swollen joints, pain visual analogue scale (VAS) score, and patient and physician global assessment (GA) scores were evaluated when bDMARDs or tsDMARD treatment was initiated or switched, as well as at each 1-year follow-up visit. Quantitative measurements of RA disease activity, such as disease activity scores of 28 joints based on ESR and CRP and the clinical disease activity index, were calculated using the obtained data. ILD was defined as a progressive fibrotic disease of the lung parenchyma and was confirmed by chest radiography or chest computed tomography (CT) by each physician. Information on comorbidities or extra-articular manifestations was obtained from the KOBIO data. In this study, the RA-ILD group was defined as patients with ILD at the initial assessment or during follow-up. AEs during treatment with bDMARDs or tsDMARDs, defined using the Medical Dictionary for Regulatory Activities (v. 20.0), were evaluated. AEs were also assessed after switching from bDMARDs or tsDMARDs, as well as after their discontinuation.

Statistical analysis

Data were presented as mean ± standard deviation or frequency (percentage). Baseline demographic and clinical characteristics were compared between groups (RA-ILD *vs*. RA-non-ILD) using the chi-square test for categorical variables and an independent t-test for continuous variables. Logistic regression analysis was used to evaluate risk factors for AEs and infections. Multivariable models were fitted by including variables with $p<0.2$ from the univariable models. Furthermore, the

Table I. Baseline characteristics of patients with RA with ILD (RA-ILD) and without ILD (RA-non-ILD) in KOBIO registry.

Variable	Total (n=2,266)	RA-ILD (n=169)	RA-non-ILD (n=2,097)	*p*-value
Demographics				
Age	54.5 ± 13.0	64.0 ± 9.5	53.7 ± 13.0	<0.001
Sex				<0.001
Female	1,875 (82.7)	108 (63.9)	1,767 (84.3)	
Male	391 (17.3)	61 (36.1)	330 (15.7)	
BMI,	22.7 ± 3.5	22.9 ± 3.3	22.7 ± 3.5	0.097
Smoking				<0.001
Ex-smoker	211 (9.3)	38 (22.5)	173 (8.3)	
Current smoker	172 (7.6)	19 (11.2)	153 (7.3)	
Never	1,883 (83.1)	112 (66.3)	1,771 (84.5)	
Comorbidities				
Diabetes mellitus	282 (12.4)	43 (25.4)	239 (11.4)	<0.001
Hypertension	679 (30.0)	68 (40.2)	611 (29.1)	0.002
Hyperlipidaemia	465 (20.5)	55 (32.5)	410 (19.6)	<0.001
Cardiovascular disease	115 (5.1)	20 (11.8)	95 (4.5)	<0.001
Cancer	13 (0.6)	1 (0.6)	12 (0.6)	1.000
COPD	32 (1.4)	9 (5.3)	23 (1.1)	<0.001
Asthma	30 (1.3)	6 (3.6)	24 (1.1)	0.021
Disease status				
Disease duration (years)	7.6 ± 7.4	7.7 ± 7.8	7.6 ± 7.3	0.953
RF positivity, n=2,181	1,815 (83.2)	147 (91.3)	1,668 (82.6)	0.004
Anti-CCP Ab positivity, n=1,899	1,632 (85.9)	133 (91.1)	1,499 (85.5)	0.062
Tender joint count	8.9 ± 7.0	9.1 ± 7.4	8.9 ± 6.9	0.805
Swollen joint count	6.8 ± 5.5	7.3 ± 6.2	6.8 ± 5.5	0.330
Patient global assessment, n=2,265	6.9 ± 2.0	6.8 ± 2.0	6.9 ± 2.0	0.832
Physician global assessment	6.5 ± 1.8	6.6 ± 1.7	6.5 ± 1.8	0.426
ESR, mm/hr	49.2 ± 28.1	57.5 ± 29.7	48.6 ± 27.8	<0.001
CRP, mg/dL, n=2,261	2.3 ± 3.4	2.6 ± 3.7	2.3 ± 3.4	0.104
DAS28-ESR, n=2,265	5.6 ± 1.1	5.7 ± 1.1	5.6 ± 1.1	0.111
DAS28-CRP, n=2,260	4.9 ± 1.1	4.9 ± 1.1	4.9 ± 1.1	0.507
SDAI, n=2,260	29.3 ± 12.0	29.9 ± 11.6	29.3 ± 12.0	0.395
CDAI, n=2,265	27.0 ± 11.2	27.3 ± 10.9	27 ± 11.2	0.686
Radiographic erosions, n=1,582	876 (55.4)	53 (48.2)	823 (55.9)	0.116
Function				
RAPID3, n=2,261	15.4 ± 5.6	16 ± 5.5	15.3 ± 5.6	0.185
Medication				
Previous treatments				
Prior use of methotrexate	2143 (94.6)	138 (81.7)	2005 (95.6)	<0.001
Prior use of sulfasalazine	924 (40.8)	69 (40.8)	855 (40.8)	0.989
Prior use of leflunomide	1205 (53.2)	77 (45.6)	1128 (53.8)	0.039
Concomitant treatments				
Methotrexate	1452 (64.1)	79 (46.8)	1373 (65.5)	<0.001
Sulfasalazine	30 (1.3)	8 (4.7)	22 (1.1)	<0.001
Leflunomide	82 (3.6)	9 (5.3)	73 (3.5)	0.217
Corticosteroid, dosage, mean, mg/day (prednisone-equivalent), median (IQR), n=1,941	5 (2.5-7.5)	5 (3.9-7.5)	5 (2.5-7.5)	0.511
Prior use of biologic agents	555 (24.5)	41 (24.3)	514 (24.5)	0.942
Number of prior biologic agents, n=2,263				0.865
0	1708 (75.5)	128 (75.7)	1580 (75.5)	
1	386 (17.1)	27 (16.0)	359 (17.1)	
≥2	169 (7.5)	14 (8.3)	155 (7.4)	
Current bDMARDs or tsDMARDs type				<0.001
TNF inhibitors				
Etanercept	333 (14.7)	25 (14.8)	308 (14.7)	0.973
Infliximab	226 (10)	3 (1.8)	223 (10.7)	<0.001
Adalimumab	396 (17.5)	14 (8.3)	382 (18.2)	0.001
Golimumab	175 (7.7)	9 (5.3)	166 (7.9)	0.225
Rituximab	19 (0.8)	0 (0.0)	19 (0.9)	0.391
Abatacept	311 (13.7)	55 (32.5)	256 (12.2)	<0.001
Tocilizumab	565 (25.0)	47 (27.8)	518 (24.7)	0.369
JAK inhibitors				
Tofacitinib	163 (7.2)	10 (5.9)	153 (7.3)	0.505
Baricitinib	74 (3.3)	6 (3.6)	68 (3.3)	0.829
Upadacitinib	1 (0.0)	0 (0.0)	1 (0.1)	1.000
Death	47 (2.1)	16 (9.5)	31 (1.5)	<0.001

Data presented as mean ± standard deviation or n (%).

ILD: interstitial lung disease: KOBIO: Korean College of Rheumatology Biologics & Targeted therapy; BMI: Body Mass Index; COPD: chronic obstructive pulmonary disease; RF: rheumatoid factor; Anti-CCP Ab: anti-citrullinated protein antibody; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS: Disease Activity Score; VAS: visual analogue scale; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; RAPID3: routine assessment of patient index data 3; IQR: inter-quartile range; bDMARDs: biologic disease-modifying anti-rheumatic drugs; tsDMARDs: target synthetic disease-modifying anti-rheumatic drugs; TNF: tumour necrosis factor; JAK: janus kinase. Biosimilars were included in each originators.

p-values are calculated using chi square test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U-test for continuous variables. Bold values indicate significant *p*-values.

These data were modified by our previous data (8).

plausibility of the interaction and the presence of multicollinearity were also evaluated. All statistical analyses were performed using the SAS statistical software (v. 9.4, SAS Institute). Statistical significance was set at $p<0.05$.

Results

Patient characteristics

Table I shows the baseline characteristics of the patients with RA-ILD (n=169) and without ILD (n=2,097). Patients with ILD were significantly older (mean age, 64.0±9.5 years) than those without ILD (mean age, 53.7±13.0 years; $p<0.001$). A higher proportion of males was observed in the ILD group (36.1%) compared to that of the non-ILD group (15.7%; $p<0.001$). Patients with ILD exhibited a higher prevalence of comorbidities, such as diabetes (25.4% *vs*. 11.4%), hypertension (40.2% *vs*. 29.1%), hyperlipidaemia (32.5% *vs*. 19.6%), cardiovascular disease (11.8% *vs*. 4.5%), chronic obstructive pulmonary disease (COPD) (5.3% *vs*. 1.1%), and asthma (3.6% *vs*. 1.1%) compared to those without ILD (all $p<0.05$). Disease status was comparable between the two groups, with no significant differences in disease duration, tender joint count, or swollen joint count. However, patients with ILD exhibited higher portions of RF positivity (91.3% *vs*. 82.6%, $p=0.004$) and ESR compared to those without ILD (57.5±29.7 mm/hr *vs*. 48.6±27.8 mm/hr, $p<0.001$). Patients with ILD were less likely to receive methotrexate and leflunomide. The two groups had similar functional scores, as measured by the Routine Assessment of Patient Index Data 3. During the study, 47 (2.1%) deaths occurred among the patients with RA, while 16 (9.5%) of those with RA-ILD.

During follow-up, infections were identified in the RA-ILD group. Table II shows the baseline characteristics of patients with RA-ILD who developed infections during treatment and those who did not. Out of 169 patients, 63 (37.3%) developed infections and 106 (62.7%) did not. The groups were comparable in terms of age, sex, body mass index, comorbidities, disease status, and previous treatments. However, the infection group included a higher

Table II. Baseline characteristics of patients with rheumatoid arthritis associated interstitial lung disease (RA-ILD) with and without infection during treatment.

	RA-ILD (n=169)	RA-ILD with Infection (n=63)	RA-ILD without Infection (n=106)	*p*-value
Demographics				
Age, mean (years)	64.0 ± 9.5	63.6 ± 8.9	64.2 ± 9.9	0.417
Sex				0.676
Female	108 (63.9)	39 (61.9)	69 (65.1)	
Male	61 (36.1)	24 (38.1)	37 (34.9)	
BMI, mean	22.9 ± 3.3	22.7 ± 3.5	23.0 ± 3.2	0.548
Smoking				0.034
Ex-smoker	38 (22.5)	21 (33.3)	17 (16.0)	
Current smoker	19 (11.2)	6 (9.5)	13 (12.3)	
Never	112 (66.3)	36 (57.1)	76 (71.7)	
Comorbidities				
Diabetes mellitus	43 (25.4)	19 (30.2)	24 (22.6)	0.278
Hypertension	68 (40.2)	26 (41.3)	42 (39.6)	0.833
Hyperlipidaemia	55 (32.5)	19 (30.2)	36 (34.0)	0.610
Cardiovascular disease	20 (11.8)	7 (11.1)	13 (12.3)	0.823
Cancer	1 (0.6)	0 (0.0)	1 (0.9)	1.000
COPD	9 (5.3)	6 (9.5)	3 (2.8)	0.080
Asthma	6 (3.6)	2 (3.2)	4 (3.8)	1.000
Disease status				
Disease duration (years)	7.7 ± 7.8	7.8 ± 8.2	7.7 ± 7.5	0.955
RF positivity, n=161	147 (91.3)	51 (87.9)	96 (93.2)	0.254
Anti-CCP Ab positivity, n=146	133 (91.1)	51 (91.1)	82 (91.1)	1.000
Tender joint count	9.1 ± 7.4	10.0 ± 8.4	8.6 ± 6.7	0.426
Swollen joint count	7.3 ± 6.2	7.9 ± 7.2	7.0 ± 5.5	0.610
Patient global assessment	6.8 ± 2.0	7.0 ± 1.9	6.7 ± 2.1	0.642
Physician global assessment	6.6 ± 1.7	6.6 ± 1.6	6.7 ± 1.7	0.616
ESR, mm/hr	57.5 ± 29.7	60.7 ± 30.7	55.6 ± 29.0	0.403
CRP, mg/dL	2.6 ± 3.7	2.8 ± 3.2	2.6 ± 4.0	0.828
DAS28-ESR	5.7 ± 1.1	5.8 ± 1.1	5.6 ± 1.1	0.221
DAS28-CRP	4.9 ± 1.1	5.0 ± 1.2	4.9 ± 1.1	0.314
SDAI	29.9 ± 11.6	31.2 ± 12.0	29.1 ± 11.3	0.390
CDAI	27.3 ± 10.9	28.4 ± 11.0	26.5 ± 10.8	0.384
Radiographic erosions, n=110	53 (48.2)	21 (51.2)	32 (46.4)	0.623
Function				
RAPID3	16.0 ± 5.5	16.8 ± 5.4	15.6 ± 5.5	0.162
Medication				
Previous treatments				
Prior use of methotrexate	138 (81.7)	50 (79.4)	88 (83.0)	0.553
Prior use of sulfasalazine	69 (40.8)	28 (44.4)	41 (38.7)	0.461
Prior use of leflunomide	77 (45.6)	29 (46.0)	48 (45.3)	0.925
Concomitant treatments				
Methotrexate	79 (46.8)	32 (50.8)	47 (44.3)	0.416
Sulfasalazine	8 (4.7)	3 (4.8)	5 (4.7)	1.000
Leflunomide	9 (5.3)	2 (3.2)	7 (6.6)	0.487
Corticosteroid, dosage, mean, mg/day (prednisone-equivalent), median (IQR), n=148	5.0 (3.9-7.5)	5.0 (2.5-7.5)	5.0 (4.0-7.5)	0.531
Prior use of biologic agents	41 (24.3)	18 (28.6)	23 (21.7)	0.314
Number of prior biologic agents				0.207
0	128 (75.7)	45 (71.4)	83 (78.3)	
1	27 (16.0)	14 (22.2)	13 (12.3)	
³2	14 (8.3)	4 (6.4)	10 (9.4)	
Current bDMARDs or tsDMARDs type				
TNF inhibitors				
Etanercept	25 (14.8)	12 (19.1)	13 (12.3)	0.494
Infliximab	3 (1.8)	3 (4.8)	0 (0.0)	0.558
Adalimumab	14 (8.3)	5 (7.9)	9 (8.5)	0.862
Golimumab	9 (5.3)	3 (4.8)	6 (5.7)	0.731
Rituximab	0 (0.0)	0 (0.0)	0 (0.0)	-
Abatacept	55 (32.5)	18 (28.9)	37 (34.9)	0.779
Tocilizumab	47 (27.8)	16 (25.4)	31 (29.3)	0.524
JAK inhibitors				
Tofacitinib	10 (5.9)	3 (4.8)	7 (6.6)	0.744
Baricitinib	6 (3.6)	3 (4.8)	3 (2.8)	0.674
Upadacitinib	0 (0.0)	0 (0.0)	0 (0.0)	-
Death	16 (9.5)	10 (15.9)	6 (5.7)	0.028

Data presented as mean ± standard deviation or n (%).

ILD: interstitial lung disease: KOBIO: Korean College of Rheumatology Biologics & Targeted therapy; BMI: Body Mass Index; COPD: chronic obstructive pulmonary disease; RF: rheumatoid factor; Anti-CCP Ab: anti-citrullinated protein antibody; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; DAS: Disease Activity Score; VAS: visual analogue scale; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; RAPID3: routine assessment of patient index data 3; IQR: inter-quartile range; bDMARDs: biologic disease-modifying anti-rheumatic drugs; tsDMARDs: target synthetic disease-modifying anti-rheumatic drugs; TNF: tumour necrosis factor; JAK: janus kinase. Biosimilars were included in each originators.

p-values are calculated using chi square test or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U-test for continuous variables. Bold values indicate significant *p*-values.

Table III. Reasons for switching to another agent or discontinuation treatment and adverse events related withdrawal.

Variable	Total (n=2,266)	RA-ILD (n=169)	RA-non-ILD (n=2,097)	*p*-value
Withdrawal	1,036 (45.7)	97 (57.4)	939 (44.8)	0.002
Discontinuation	480 (21.2)	55 (32.5)	425 (20.3)	<0.001
Switching	556 (24.5)	42 (24.9)	514 (24.5)	0.995
Withdrawal reason				
Clinical remission	43 (4.2)	2 (2.1)	41 (4.4)	0.421
Inefficacy	458 (44.3)	34 (35.1)	424 (45.3)	0.072
Adverse events	304 (29.4)	44 (45.4)	260 (27.8)	<0.001
Other reasons	229 (22.2)	17 (17.5)	212 (22.6)	0.311
Unknown	2 (0.1)	0 (0.0)	2 (0.1)	1.000
Adverse events related withdrawal				
Mycobacteria tuberculosis infection	8 (0.8)	0 (0.0)	8 (0.8)	1.000
Atypical mycobacterial infection	7 (0.7)	2 (2.1)	5 (0.5)	0.134
Pneumocystis jiroveci infection	1 (0.1)	0 (0.0)	1 (0.1)	1.000
Herpes zoster infection	5 (0.5)	1 (1.0)	4 (0.4)	0.389
Other infection	51 (4.9)	20 (20.6)	31 (3.3)	<0.001
Malignancy Solid	18 (1.7)	3 (3.1)	15 (1.6)	0.234
Lymphoma	4 (0.4)	0 (0.0)	4 (0.4)	1.000
Malignancy Other	4 (0.4)	2 (2.1)	2 (0.2)	0.046
Acute coronary syndrome	1 (0.1)	0 (0.0)	1 (0.1)	1.000
Congestive heart failure	1 (0.1)	1 (1.0)	0 (0.0)	0.094
Interstitial lung disease progression	6 (0.6)	5 (5.2)	1 (0.1)	<0.001
Pulmonary embolism	1 (0.1)	1 (1.0)	0 (0)	0.094
Hepatitis B reactivation	3 (0.3)	0 (0.0)	3 (0.3)	1.000
Transaminitis only	5 (0.5)	0 (0.0)	5 (0.5)	1.000
Neutropenia	4 (0.4)	0 (0.0)	4 (0.4)	1.000
Conception	6 (0.6)	0 (0.0)	6 (0.6)	1.000
Infusion/injection reaction	108 (10.4)	4 (4.1)	104 (11.1)	0.050
Psoriasis	2 (0.2)	0 (0.0)	2 (0.2)	1.000
Others	115 (11.1)	16 (16.5)	99 (10.6)	0.961

Data presented as n (%). Bold values indicate significant *p*-value <0.05.

proportion of ex-smokers (33.3%) compared to that of the non-infection group (16.0%, p=0.034). Among patients with RA-ILD, the mortality rate was significantly higher in the infection group (n=10) than that in the non-infection group (n=6, p=0.028).

Reasons for treatment withdrawal and AE-related withdrawal

Table III presents the reasons for switching to another agent or discontinuing treatment in patients with RA with and without ILD. The rate of treatment switching was comparable between the ILD and non-ILD groups (24.9% *vs.* 24.5%). However, the rate of discontinuation was significantly higher in the ILD group (32.5%) than that in the non-ILD group (20.3%, p<0.001). In the ILD group, the most common reason for treatment switching or discontinuation was AEs (45.4%), followed by lack of efficacy (35.1%). However, in the non-ILD group, the most common reason for treatment switching or discontinuation was lack of efficacy (45.3%), followed by AEs (27.8%). A small proportion of patients discontinued therapy after achieving clinical remission (ILD group, 2.1%; non-ILD group, 4.4%). The overall AEs leading to treatment discontinuation or switching are shown in Table III. Infections and infusion-related reactions were the most common AEs resulting in treatment withdrawal in the RA-ILD and non-ILD groups, respectively.

A total of 16 (9.5%) and 31 (1.5%) deaths were reported in the RA-ILD and non-ILD groups, respectively (p<0.001). In the ILD group, the causes of death included other infection (excluding atypical mycobacterial and *Pneumocystis jiroveci* infection) (n=5), atypical mycobacterial infection (n=2), malignancy (n=1), congestive heart failure (n=1), ILD aggravation (n=2), and others (n=5). In the non-ILD group, the causes of death included infection (n=3), atypical mycobacterial infection (n=2), *Pneumocystis jirovecii* infection (n=1), malignancy (n=1), lymphoma (n=1),

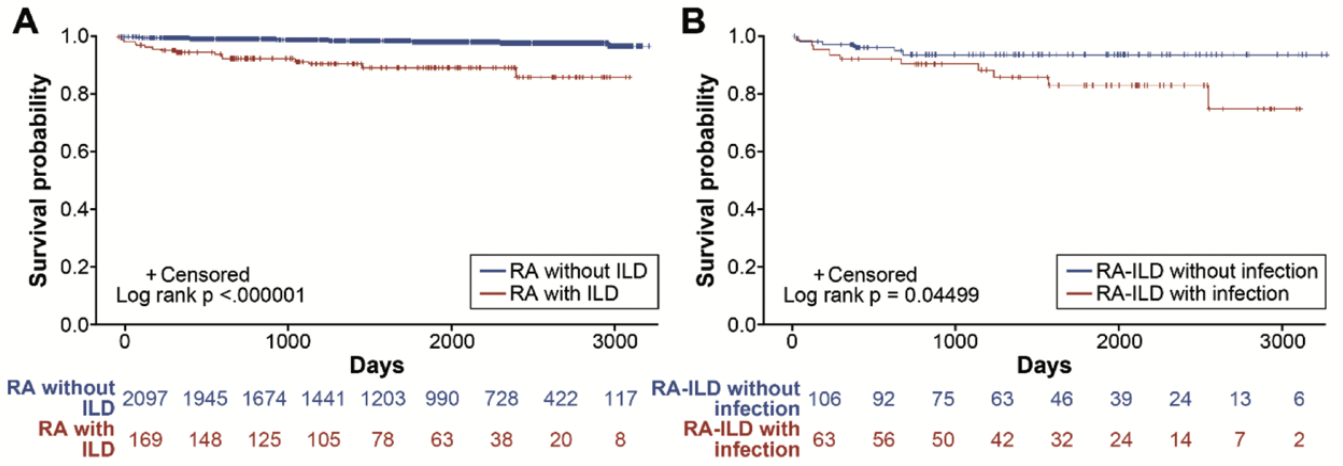

Fig. 1. Kaplan-Meier curves for mortality according to the presence of ILD in the total population of patients with RA (n=2,266) (**A**) and infection in patients with RA-ILD (n=169) (**B**).
ILD: interstitial lung disease; RA: rheumatoid arthritis.

Table IV. Risk factors of any adverse events in total RA and RA-ILD.

	Total RA (n=2,266)				RA-ILD (n=169)			
	Univariable model		Multivariable model		Univariable model		Multivariable model	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
ILD	1.68 (1.14, 2.47)	0.009	1.54 (1.03, 2.31)	0.035				
Elderly (*vs*. <65years)	1.26 (1.00, 1.57)	0.047	1.05 (0.82, 1.34)	0.693	1.92 (0.88, 4.18)	0.102	3.01 (1.25-7.24)	0.014
Male (*vs*. female)	0.87 (0.69, 1.10)	0.238			0.89 (0.41, 1.94)	0.771		
BMI	1.02 (0.99, 1.04)	0.225			1.02 (0.91, 1.14)	0.802		
Current smoking (*vs*. non-smoking)	0.89 (0.70, 1.13)	0.326			1.85 (0.78, 4.41)	0.164	2.54 (0.94-6.85)	0.065
Disease duration	1.02 (1.01, 1.03)	0.006	1.02 (1.00, 1.03)	0.029	1.00 (0.95, 1.05)	0.863		
Biologics								
Abatacept (*vs*. TNFi)	0.94 (0.71, 1.24)	0.662	0.81 (0.61, 1.07)	0.138	0.99 (0.39, 2.48)	0.975		
Tocilizumab (*vs*. TNFi)	1.19 (0.94, 1.50)	0.143	1.10 (0.87, 1.39)	0.430	1.34 (0.49, 3.69)	0.570		
JAK inhibitors (*vs*. TNFi)	0.56 (0.42, 0.75)	<0.001	0.52 (0.39, 0.70)	<0.001	1.19 (0.29, 4.94)	0.809		
Rituximab (*vs*. TNFi)	1.48 (0.49, 4.50)	0.488	1.27 (0.41, 3.94)	0.678	-			
Patient global assessment	0.99 (0.95, 1.04)	0.676			0.97 (0.81, 1.17)	0.761		
Physician global assessment	0.95 (0.90, 1.00)	0.034	0.95 (0.90, 1.01)	0.101	0.86 (0.68, 1.08)	0.199	0.86 (0.66-1.13)	0.289
DAS28-ESR	1.02 (0.94, 1.11)	0.603			0.98 (0.70, 1.37)	0.906		
DAS28-CRP	1.00 (0.92, 1.08)	0.958			1.01 (0.72, 1.42)	0.953		
SDAI	1.00 (0.99, 1.00)	0.218			1.00 (0.97, 1.03)	0.988		
CDAI	1.00 (0.99, 1.00)	0.192	0.99 (0.98, 1.00)	0.178	0.99 (0.96, 1.03)	0.629		
RAPID3	1.01 (1.00, 1.03)	0.136	1.02 (1.00, 1.03)	0.133	1.03 (0.97, 1.11)	0.338		
Diabetes mellitus	1.19 (0.90, 1.59)	0.220			0.55 (0.24, 1.23)	0.144	0.48 (0.19-1.2)	0.116
Hypertension	1.42 (1.15, 1.74)	0.001	1.26 (1.00, 1.57)	0.046	0.52 (0.25, 1.12)	0.094	0.47 (0.2-1.11)	0.084
Hyperlipidaemia	1.31 (1.04, 1.66)	0.023	1.13 (0.88, 1.44)	0.346	1.20 (0.53-2.72)	0.663		
Cardiovascular diseases	1.50 (0.95, 2.36)	0.081	1.21 (0.76, 1.95)	0.424	0.41 (0.15-1.13)	0.084	0.33 (0.1-1.05)	0.060
COPD	1.78 (0.73, 4.34)	0.206			2.08 (0.25-17.21)	0.498		
Asthma	3.72 (1.12, 12.29)	0.031	2.94 (0.88, 9.84)	0.081	-	-		
RF positivity	1.12 (0.88, 1.43)	0.360			0.62 (0.13, 2.93)	0.550		
Anti-CCP Ab positivity	0.99 (0.74, 1.31)	0.917			0.65 (0.14, 3.11)	0.592		
Prior use of methotrexate	1.01 (0.68, 1.51)	0.945			0.37 (0.11, 1.30)	0.121	0.38 (0.1-1.41)	0.148
Prior use of sulfasalazine	0.92 (0.76, 1.10)	0.342			1.34 (0.61, 2.93)	0.464		
Prior use of leflunomide	1.11 (0.93, 1.33)	0.251			1.08 (0.51, 2.29)	0.850		
Prior use of csDMARDs	0.98 (0.56, 1.70)	0.941			0.42 (0.05, 3.47)	0.424		
Prior use of biologic agents	1.19 (0.96, 1.48)	0.109	1.14 (0.90, 1.43)	0.283	0.86 (0.37, 2.04)	0.737		
Concomitant methotrexate	0.76 (0.63, 0.92)	0.005	0.82 (0.67, 1.00)	0.050	1.33 (0.62, 2.84)	0.467		
Concomitant sulfasalazine	0.81 (0.38, 1.75)	0.599			0.74 (0.14, 3.86)	0.725		
Concomitant leflunomide	1.05 (0.64, 1.71)	0.849			0.48 (0.11, 2.03)	0.319		
Concomitant corticosteroid	1.12 (0.87, 1.45)	0.371			1.28 (0.43, 3.79)	0.653		
Dose of corticosteroid	1.02 (0.99, 1.05)	0.227			1.02 (0.92, 1.14)	0.670		

bDMARDs: biologic disease-modifying anti-rheumatic drugs; tsDMARDs: target synthetic disease-modifying anti-rheumatic drugs; ILD: interstitial lung disease; OR: odds ratio; CI: confidence interval; BMI: Body Mass Index; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; RAPID3: routine assessment of patient index data 3; RF: rheumatoid factor; Anti-CCP Ab: anti-citrullinated protein antibody; csDMARDs: conventional-synthetic disease-modifying anti-rheumatic drugs.
Bold values indicate significant *p*-values.

acute coronary syndrome (n=1), others (n=11), and unknown causes (n=10) (Supplementary Table S1). Figure 1A shows the Kaplan-Meier curve for mortality according to the presence of ILD in all patients with RA (n=2,266). The curve for patients with RA-ILD was consistently lower than that for those without ILD, indicating a lower survival probability in the group with ILD. This suggested that the presence of ILD is associated with a higher risk of mortality in patients with RA ($p<0.001$). Figure 1B shows the mortality curve of patients with RA-ILD who developed infections (n=63) during the follow-up period. The difference in the survival curve between the two groups was statistically significant, suggesting that infections in the RA-ILD group were associated with a higher mortality risk ($p=0.045$).

Risk factors for overall AEs in patients with RA and RA-ILD treated with bDMARDs or tsDMARDs

To identify the risk factors associated with overall AEs in patients with RA and RA-ILD treated with biologics or tsDMARDs, univariable and multivariable analyses were conducted separately for the entire RA and RA-ILD patient populations (Table IV). In the whole RA population, ILD (odds ratio [OR] =1.68, $p=0.009$), older age (OR=1.26, $p=0.047$), longer disease duration (OR=1.02, $p=0.006$), JAK inhibitors (OR=0.56, $p<0.001$), lower physician global assessment (OR 0.95, $p=0.034$), hypertension (OR=1.42, $p=0.001$), hyperlipidaemia (OR=1.31, $p=0.023$), asthma (OR=3.72, $p=0.031$), and concomitant methotrexate (OR=0.76, $p=0.005$) were associated with overall AEs. In the multivariable analysis, ILD (OR=1.54, $p=0.035$), long disease duration (OR=1.02, $p=0.029$), JAK inhibitors (OR=0.52, $p<0.001$), hypertension (OR=1.26, $p=0.046$), and concomitant methotrexate (OR=0.82, $p=0.050$) were associated with overall AEs in the whole RA patient population. In the RA-ILD population, older age (OR=1.92, $p=0.102$), current smoking (OR=1.85, $p=0.164$), lower physician global assessment (OR=0.86, $p=0.199$), diabetes mellitus (OR=0.55, $p=0.144$), hypertension (OR=0.52, $p=0.094$), cardiovascular disease (OR=0.41, p 0.084), and prior use of methotrexate (OR=0.37, $p=0.121$) were associated with overall AEs. Among these, only older age (OR=3.01, $p=0.014$) was found to be

Table V. Risk factors of infection in total RA and RA-ILD.

	Total RA (n=2,266)				RA-ILD (n=169)			
	Univariable model		Multivariable model		Univariable model		Multivariable model	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
ILD	1.97 (1.42, 2.74)	<0.001	1.87 (1.31-2.66)	0.001				
Elderly (*vs*. <65years)	1.18 (0.94, 1.48)	0.153	0.95 (0.74-1.22)	0.687	1.20 (0.64, 2.24)	0.566		
Male (*vs*. female)	1.07 (0.84, 1.38)	0.580			1.15 (0.60, 2.19)	0.676		
BMI	1.00 (0.97, 1.03)	0.898			0.97 (0.88, 1.07)	0.562		
Current smoking (*vs*. non-smoking)	1.28 (1.00, 1.64)	0.047	1.15 (0.89-1.48)	0.295	1.90 (0.99, 3.65)	0.054	2.11 (1.06-4.21)	0.035
Disease duration	1.00 (0.99, 1.02)	0.832			1.00 (0.96, 1.04)	0.937		
Biologics								
Abatacept (*vs*. TNFi)	0.71 (0.53, 0.96)	0.026	0.58 (0.42-0.80)	0.001	0.59 (0.27, 1.30)	0.193	0.58 (0.25-1.33)	0.196
Tocilizumab (*vs*. TNFi)	0.79 (0.62, 1.00)	0.046	0.75 (0.59-0.95)	0.019	0.63 (0.28, 1.42)	0.265		
JAK inhibitors (*vs*. TNFi)	0.52 (0.36, 0.75)	<0.001	0.50 (0.35-0.73)	<0.001	0.73 (0.23, 2.31)	0.593		
Rituximab (*vs*. TNFi)	0.49 (0.14, 1.71)	0.265	0.52 (0.15-1.80)	0.302				
Patient global assessment	1.01 (0.96, 1.06)	0.726			1.07 (0.92, 1.26)	0.362		
Physician global assessment	1.02 (0.97, 1.07)	0.523			0.99 (0.82, 1.19)	0.905		
DAS28-ESR	1.05 (0.96, 1.14)	0.286			1.20 (0.91, 1.60)	0.200		
DAS28-CRP	1.04 (0.95, 1.13)	0.414			1.16 (0.87, 1.54)	0.318		
SDAI	1.00 (0.99, 1.01)	0.730			1.02 (0.99, 1.04)	0.255		
CDAI	1.00 (0.99, 1.01)	0.835			1.02 (0.99, 1.05)	0.274		
RAPID3	1.01 (0.99, 1.02)	0.441			1.04 (0.98, 1.11)	0.163	1.05 (0.99-1.12)	0.106
Diabetes mellitus	1.31 (0.99, 1.72)	0.060	1.08 (0.80-1.45)	0.630	1.48 (0.73, 2.99)	0.279		
Hypertension	1.42 (1.16, 1.74)	0.001	1.29 (1.03-1.62)	0.030	1.07 (0.57, 2.02)	0.833		
Hyperlipidaemia	1.39 (1.11-1.75)	0.005	1.26 (0.99-1.60)	0.064	0.84 (0.43-1.64)	0.610		
Cardiovascular diseases	1.72 (1.16-2.56)	0.007	1.30 (0.86-1.98)	0.217	0.89 (0.34, 2.38)	0.823		
COPD	2.17 (1.07-4.42)	0.033	1.72 (0.81-3.62)	0.156	3.61 (0.87-14.99)	0.077	3.01 (0.68-13.34)	0.147
Asthma	1.35 (0.61-2.96)	0.459			0.84 (0.15, 4.7)	0.839		
RF positivity	0.98 (0.75, 1.27)	0.853			0.53 (0.18, 1.60)	0.260		
Anti-CCP Ab positivity	1.16 (0.85, 1.58)	0.356			1.00 (0.31, 3.21)	0.994		
Prior use of methotrexate	0.70 (0.47, 1.04)	0.077	0.82 (0.52, 1.29)	0.396	0.79 (0.36, 1.74)	0.553		
Prior use of sulfasalazine	1.20 (0.99, 1.45)	0.071	1.11 (0.89, 1.37)	0.355	1.27 (0.67, 2.39)	0.461		
Prior use of leflunomide	1.10 (0.91, 1.34)	0.323			1.03 (0.55, 1.93)	0.925		
Prior use of csDMARDs	1.02 (0.57, 1.84)	0.938			0.37 (0.10, 1.38)	0.139	0.36 (0.09-1.47)	0.153
Prior use of biologic agents	1.09 (0.87, 1.36)	0.456			1.44 (0.71, 2.95)	0.315		
Concomitant methotrexate	0.72 (0.59, 0.88)	0.001	0.79 (0.63, 1.00)	0.045	1.30 (0.69, 2.42)	0.417		
Concomitant sulfasalazine	0.95 (0.41, 2.23)	0.910			1.01 (0.23, 4.38)	0.989		
Concomitant leflunomide	1.15 (0.70, 1.90)	0.576			0.46 (0.09, 2.31)	0.348		
Concomitant corticosteroid	1.04 (0.79, 1.36)	0.809			0.61 (0.25, 1.54)	0.298		
Dose of corticosteroid	1.03 (1.00, 1.06)	0.023	1.02 (1.00, 1.05)	0.106	0.99 (0.91, 1.07)	0.767		

bDMARDs: biologic disease-modifying anti-rheumatic drugs; tsDMARDs: target synthetic disease-modifying anti-rheumatic drugs; ILD: interstitial lung disease; OR: odds ratio; CI: confidence interval; BMI: Body Mass Index; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index; RAPID3: routine assessment of patient index data 3; RF: rheumatoid factor; Anti-CCP Ab: anti-citrullinated protein antibody; csDMARDs: conventional-synthetic disease-modifying anti-rheumatic drugs.
Bold values indicate significant *p*-values.

associated with overall AEs in the multivariable analysis.

Risk factors associated with infections in patients with RA and RA-ILD treated with bDMARDs or tsDMARDs

Univariable and multivariable analyses were performed separately for all patients with RA and those with RA-ILD treated with biologics or tsDMARDs (Table V). In the whole RA population, ILD (OR=1.97, $p<0.001$), current smoking status (OR=1.28, $p=0.047$), abatacept (OR=0.71, $p=0.026$), tocilizumab (OR = 0.79, $p=0.046$), JAK inhibitors (OR= 0.52, $p<0.001$), hypertension (OR=1.42, $p=0.001$), hyperlipidaemia (OR=1.39, $p=0.005$), cardiovascular diseases (OR=1.72, $p=0.007$), COPD (OR=2.17, $p=0.033$), concomitant methotrexate (OR=0.72, $p=0.001$), and dose of corticosteroid (OR=1.03, $p=0.023$) were associated with infections. In the multivariable analysis, ILD (OR=1.87, $p=0.001$), abatacept (OR=0.58, $p=0.001$), tocilizumab (OR=0.75, $p=0.019$), JAK inhibitors (OR=0.50, $p<0.001$), hypertension (OR=1.29, $p=0.03$), and concomitant methotrexate (OR=0.79, $p=0.045$) were associated with infections in all patients with RA. In the ILD group, current smoking status (OR=1.90, $p=0.054$), abatacept (OR=0.59, $p=0.193$), routine assessment of patient index data 3 (OR=1.04, $p=0.163$), COPD (OR=3.61, $p=0.077$), and prior use of csDMARDs (OR=0.37, $p=0.139$) were associated with infections. Among these, only a current smoking status was associated with infections (OR=2.11, $p=0.035$) in the multivariable analysis.

Discussion

The present follow-up observational study, based on a national registry, aimed to investigate the influence of co-existing ILD on the maintenance of bDMARDs or tsDMARDs in patients with RA. The specific focus of the study was on AEs that lead to medication withdrawal. The overall withdrawal rate of bDMARDs or tsDMARDs owing to AEs in all RA populations included in the KOBIO registry was 13.4%, which is similar to that reported in previous studies (16). Reported rates vary across different factors, including the specific medication used, patient characteristics, and treatment duration, ranging from a few percent to as high as 40% (17-20).

Consistent with the anticipated findings based on multiple pieces of evidence, patients with RA-ILD experienced significantly higher rates of overall AEs. Nearly half of these patients had to switch or discontinue bDMARDs or tsDMARDs due to the occurrence of such AEs (21).

Interestingly, in the analysis of the factors influencing the occurrence of AEs in the overall RA patient population, we observed that RA-related ILD was the most influential factor in increasing the incidence rate of overall AEs. In contrast, the combination of methotrexate with bDMARDs or tsDMARDs was observed to reduce the occurrence of overall AEs in our study. This is contrary to the general belief that this combination therapy may increase the risk of specific AEs, such as hepatotoxicity or gastrointestinal symptoms (22). The interpretation of our findings suggested that methotrexate can contribute to reducing immune-related AEs associated with bDMARDs or tsDMARDs by enhancing its immunosuppressive effects (23, 24). In addition, when combined with specific bDMARDs or tsDMARDs, methotrexate may exhibit a synergistic effect, enhancing its efficacy while maintaining a favourable safety profile. These findings are supported by a limited number of studies that align with our results (25).

We also observed that the frequency of overall AEs, including infections, was low in patients treated with abatacept, tocilizumab, and JAK inhibitors. In contrast to our findings, a recent large observational cohort study revealed that JAK inhibitors are associated with a higher incidence of AEs, leading to medication discontinuation (26). However, given that the majority of JAK inhibitor users in our study were patients treated with tofacitinib, and both our study and other studies had relatively small sample sizes for JAK inhibitors, further analysis of JAK inhibitors should be conducted (26). Despite the general understanding that non-anti-TNF biological agents are superior in terms of efficacy and safety for patients with RA-ILD, it is intriguing that no significant differences were observed in the occurrence of overall AEs among the agents administered in patients with RA-ILD included in the KOBIO registry (27-29). Based on the consistent findings of previous studies highlighting the superiority of non-anti-TNF biologics in patients with RA-ILD (27-29), it is highly probable that our registry primarily consisted of patients with RA-ILD who were predominantly treated with these agents, resulting in a lack of differences among the various agents in terms of their outcomes. In patients with RA-ILD, old age was identified as a factor influencing the occurrence of overall AEs associated with the use of bDMARDs or tsDMARDs.

Numerous warnings have been issued regarding the potential risks of using bDMARDs or tsDMARDs in older patients with RA-ILD for a long time (30). Age-related physiological changes and comorbidities in older patients may contribute to the higher risk of AEs (31). Additionally, impaired lung function can affect drug clearance, leading to a prolonged presence of drugs in the body and an increased likelihood of AEs. This heightened vulnerability can result in the exacerbation of respiratory symptoms, deterioration of lung function, or development of new pulmonary complications (32). These concerns were substantiated in the present study, which revealed that infection is the primary cause of bDMARDs or tsDMARD withdrawal owing to AEs in patients with RA-ILD. Disease progression of ILD was identified as a subsequent cause. Infection-related withdrawal of bDMARDs or tsDMARDs was observed in less than 3% of the overall RA patient population; however, it exceeded to 20% among patients with RA-ILD, consistent with findings from multiple studies (33, 34).

Undoubtedly, patients receiving treatment with bDMARDs or tsDMARDs are at an increased risk of infections (35, 36). The findings of this study highlighted the significant effect of ILD on infection rates and underscore its influence on infection susceptibility. Efforts by rheumatologists and patients are crucial to prevent infections in patients with RA-ILD, and a fundamental step is to identify and minimise the risk factors for infection. In our study, we observed that among various factors, a current smoking status emerged as the most influential factor that increased the risk of infection in patients with RA-ILD. Smoking is widely acknowledged as a prominent risk factor for the development of RA, particularly increasing the risk of ILD (37). In addition, it creates an environment prone to infection by causing ciliary dysfunction, increased mucus production, and structural lung damage, while impairing immune cell function, leading to compromised immune responses and heightened susceptibility to infections (38, 39). These detrimental changes are more pronounced in individuals with ILD than in those without ILD (40). Recent reports have also highlighted the potential of smoking to facilitate the proliferation of harmful bacteria and decrease the abundance of beneficial bacteria, leading to an imbalance in the respiratory microbiota and an elevated risk of infections (41).

As bDMARDs and tsDMARDs in RA represent a double-edged sword with significant efficacy and potential AEs, a considerable number of studies have focused on the increased risk of infections associated with immunosuppressive therapy. Consistent with the findings of this study, many reports have demonstrated an elevated risk of infections in patients with RA-ILD, particularly among those who smoke (42, 43). Other studies have also revealed associations between increased infection risk in patients with RA-ILD and factors, such as older age, disease duration, disease activity, type of bDMARDs or tsDMARDs, and a history of treatment failure (43-47). However, our study did not yield significant results for these factors with several potential explanations. First, considering that most research findings indicate that a prednisolone dose of ≥10 mg increases the risk of infection, we aimed to minimise glucocorticoid doses in patients receiving bDMARDs or tsDMARDs (48). Most patients in our study used prednisone at a dose of approximately 5 mg, which was not associated with an increased risk of infection. Second, our study predominantly included biolog-

ics-naive patients. While previous studies reported a potential increase in the frequency of AEs among patients who experienced two or more treatment failures with bDMARDs or tsDMARDs, our study did not yield significant results in this regard (47). Further long-term registry studies are warranted to draw definitive conclusions regarding the relationship between the number of treatment failures and the occurrence of AEs.

Unfortunately, infections in patients with RA-ILD are significantly associated with increased mortality rates. The similarity in respiratory symptoms between infections and underlying pulmonary diseases can lead to delayed recognition and treatment of infections, resulting in worse outcomes and higher mortality rates. Our findings are consistent with those of previous studies that identified respiratory diseases (such as pneumonia or ILD progression), malignancies, and cardiovascular diseases as the main causes of mortality in patients with RA (49, 50). Despite numerous reports on the impact of ILD patterns and pulmonary function test results, such as forced vital capacity or diffusing capacity of the lung for carbon monoxide, on mortality rates in studies including patients with RA-ILD, our analysis did not include an assessment of ILD severity (51). Although the presence of ILD was confirmed in the KOBIO registry, the lack of high-resolution computed tomography features and pulmonary function test data during data collection limited our ability to assess the relationship between ILD severity/patterns, ILD duration, and mortality rates or AEs. Additionally, the antifibrotic agents nintedanib and pirfenidone, known for their effectiveness in ILD, are still limitedly used in South Korea due to stringent reimbursement criteria for secondary ILD, resulting in no patients receiving these medications in our study. We were unable to ascertain the use of prophylactic antibiotics, which could influence the occurrence of infections. The primary limitation of our study is the significant lack of detailed information related to ILD.

This study had several other limitations. Specific bDMARDs were infrequently used, and there was limited usage of JAK inhibitors, with the majority of patients receiving tofacitinib. Due to the data collection period ending in December 2021, there were few patients treated with recently approved and utilised baricitinib and upadacitinib. Furthermore, none of the patients with RA-ILD in our study received rituximab. Rituximab is widely known to benefit patients with RA-ILD by delaying ILD progression and ensuring treatment efficacy and safety (52). However, this is primarily due to the requirement for hospitalisation during rituximab treatment in South Korea, which limited the number of patients receiving this medication in the KOBIO registry, primarily consisting of an outpatient population. Additionally, as our study had an observational design, inherent limitations exist including a higher rate of loss to follow-up compared with that of clinical trials. Despite these limitations, our study has notable strengths as a subsequent analysis using national registry data, allowing for a comparison of the effects of bDMARDs and tsDMARDs on RA-ILD. This study provides a comprehensive analysis of AEs and infections, which are crucial factors in treatment decisions and outcomes for patients with RA, particularly those with concurrent ILD. To the best of our knowledge, this national registry analysis focusing on AEs and infections in patients with RA-ILD is the first of its kind. The findings may contribute to the effective management of RA and ILD through close monitoring, cautious medication selection, and personalised treatment strategies.

Conclusions

The present study utilised the KOBIO registry to identify significant risk factors associated with AEs and infections in patients with RA and RA-ILD receiving bDMARDs or tsDMARDs. Patients with RA-ILD exhibited a higher rate of withdrawal from b/tsDMARDs because of AEs and infections than those without ILD. Older age was identified as a risk factor for AEs in the RA-ILD group, whereas a current smoking status was identified as a risk factor for infections. These findings highlighted the need for careful monitoring and personalised treatment strategies for patients with RA-ILD to minimise the occurrence of AEs and infections and improve treatment outcomes.

Acknowledgment

We thank the KOBIO study team for aiding with the data management and preparation.

References

1. FAZELI MS, KHAYCHUK V, WITTSTOCK K *et al*.: Rheumatoid arthritis-associated interstitial lung disease: epidemiology, risk/prognostic factors, and treatment landscape. *Clin Exp Rheumatol* 2021; 39: 1108-18. https://doi.org/10.55563/clinexprheumatol/h9tc57
2. ROUBILLE C, HARAOUI B: Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. *Semin Arthritis Rheum* 2014; 43: 613-26. https://doi.org/10.1016/j.semarthrit.2013.09.005
3. MARCOUX V, LOK S, MONDAL P *et al*.: Treatment of rheumatoid arthritis-associated interstitial lung disease in a multi-center registry cohort. *J Thorac Dis* 2023; 15: 2517-27. https://doi.org/ 10.21037/jtd-22-1820
4. ROCHA-MUÑOZ AD, PONCE-GUARNEROS M, GAMEZ-NAVA JI *et al*.: Anti-cyclic citrullinated peptide antibodies and severity of interstitial lung disease in women with rheumatoid arthritis. *J Immunol Res* 2015; 2015: 151626. https://doi.org/10.1155/2015/151626
5. SPARKS JA, HE X, HUANG J *et al*.: Rheumatoid arthritis disease activity predicting incident clinically apparent rheumatoid arthritis-associated interstitial lung disease: a prospective cohort study. *Arthritis Rheumatol* 2019; 71: 1472-82. https://doi.org/10.1002/art.40904
6. AKIYAMA M, KANEKO Y: Pathogenesis, clinical features, and treatment strategy for rheumatoid arthritis-associated interstitial lung disease. *Autoimmun Rev* 2022; 21: 103056. https://doi.org/10.1016/j.autrev.2022.103056
7. ALBRECHT K, STRANGFELD A, MARSCHALL U, CALLHOFF J: Interstitial lung disease in rheumatoid arthritis: incidence, prevalence and related drug prescriptions between 2007 and 2020. *RMD Open* 2023; 9: e002777. https://doi.org/10.1136/rmdopen-2022-002777
8. KELLY CA, NISAR M, ARTHANARI S *et al*.: Rheumatoid arthritis related interstitial lung disease - improving outcomes over 25 years: a large multicentre UK study. *Rheumatology* (Oxford) 2021; 60:1882-90. https://doi.org/10.1093/rheumatology/keaa577
9. GARAFFONI C, ADINOLFI A, BORTOLUZZI A *et al*.: Novel insights into the management of rheumatoid arthritis: one year in review 2023. *Clin Exp Rheumatol* 2023; 41: 2129-41. https://doi.org/10.55563/clinexprheumatol/nat8nl
10. LEE SK, SHIN K, JUNG JY, SUH CH, KIM JW, KIM HA: Retention rate and safety of biologic and targeted synthetic DMARDs in

patients with RA-associated interstitial lung disease: a KOBIO Registry study. *BioDrugs* 2023; 37: 247-57. https://doi.org/10.1007/s40259-023-00578-6
11. CUBERO CC, CARMONA EC, CASASEMPERE PV: Systematic review of the impact of drugs on diffuse interstitial lung disease associated with rheumatoid arthritis. *Rheumatol Clin* (Engl Ed) 2020: S1699-258X(20)30111-X. https://doi.org/10.1016/j.reuma.2020.04.015
12. LIANG M, MATTESON EL, ABRIL A, DISTLER JHW: The role of antifibrotics in the treatment of rheumatoid arthritis-associated interstitial lung disease. *Ther Adv Musculoskelet Dis* 2022; 14:1759720X221074457. https://doi.org/10.1177/1759720X221074457
13. KIM J, KOH JH, CHOI SJ *et al*.: KOBIO, the first web-based Korean Biologics Registry operated with a unified platform among distinct disease entities. *J Rheum Dis* 2021; 28: 176-82. https://doi.org/10.4078/jrd.2021.28.4.176
14. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62: 2569-81. https://doi.org/10.1002/art.27584
15. 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. https://doi.org/10.1002/art.1780310302
16. SOUTO A, MANEIRO JR, GÓMEZ-REINO JJ: Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. *Rheumatology* (Oxford) 2016; 55: 523-34. https://doi.org/10.1093/rheumatology/kev374
17. LI KJ, CHANG CL, HSIN CY, TANG CH: Switching and discontinuation pattern of biologic disease-modifying antirheumatic drugs and tofacitinib for patients with rheumatoid arthritis in Taiwan. *Front Pharmacol* 2021; 12: 628548. https://doi.org/10.3389/fphar.2021.628548
18. RAMIRO S, LANDEWÉ R, VAN DER HEIJDE D, HARRISON D, COLLIER D, MICHAUD K: Discontinuation rates of biologics in patients with rheumatoid arthritis: are TNF inhibitors different from non-TNF inhibitors? *RMD Open* 2015; 1: e000155. https://doi.org/10.1136/rmdopen-2015-000155
19. EBINA K, HASHIMOTO M, YAMAMOTO W *et al*.: Drug tolerability and reasons for discontinuation of seven biologics in 4466 treatment courses of rheumatoid arthritis-the ANSWER cohort study. *Arthritis Res Ther* 2019; 21: 91. https://doi.org/10.1186/s13075-019-1880-4
20. STRAND V, MILLER P, WILLIAMS SA, SAUNDERS K, GRANT S, KREMER J: Discontinuation of biologic therapy in rheumatoid arthritis: analysis from the Corrona RA Registry. *Rheumatol Ther* 2017; 4: 489-502. https://doi.org/10.1007/s40744-017-0078-y
21. CURTIS JR, SARSOUR K, NAPALKOV P, COSTA LA, SCHULMAN KL: Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor α agents, a retrospective cohort study. *Arthritis Res Ther* 2015; 17: 319. https://doi.org/10.1186/s13075-015-0835-7
22. ONDA K, HONMA T, MASUYAMA K: Methotrexate-related adverse events and impact of concomitant treatment with folic acid and tumor necrosis factor-alpha inhibitors: an assessment using the FDA adverse event reporting system. *Front Pharmacol* 2023; 14: 1030832. https://doi.org/10.3389/fphar.2023.1030832
23. SCHAEVERBEKE T, TRUCHETET ME, KOSTINE M, BARNETCHE T, BANNWARTH B, RICHEZ C: Immunogenicity of biologic agents in rheumatoid arthritis patients: lessons for clinical practice. *Rheumatology* (Oxford) 2016; 55: 210-20. https://doi.org/10.1093/rheumatology/kev277
24. DANG QM, WATANABE R, SHIOMI M *et al*.: Rheumatic immune-related adverse events due to immune checkpoint inhibitors-A 2023 update. *Int J Mol Sci* 2023; 24: 5643. https://doi.org/10.3390/ijms24065643
25. TERABE K, TAKAHASHI N, ASAI S *et al*.: Reasons and risk factors for discontinuation of treatment with any biological disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a long-term observational study. *Mod Rheumatol* 2022; roac090. https://doi.org/10.1093/mr/roac090
26. LAUPER K, IUDICI M, MONGIN D *et al*.: Effectiveness of TNF-inhibitors, abatacept, IL6-inhibitors and JAK-inhibitors in 31 846 patients with rheumatoid arthritis in 19 registers from the 'JAK-pot' collaboration. *Ann Rheum Dis* 2022; 81: 1358-66. https://doi.org/10.1136/annrheumdis-2022-222586
27. GOMIDES APM, DE ALBUQUERQUE CP, SANTOS ABV *et al*.: Real-life data of survival and reasons for discontinuation of biological disease-modifying drugs 'in' rheumatoid arthritis. *Int J Clin Pharm* 2021; 43: 737-42. https://doi.org/10.1007/s11096-020-01171-5
28. MENA-VÁZQUEZ N, GODOY-NAVARRETE FJ, MANRIQUE-ARIJA S *et al*.: Non-anti-TNF biologic agents are associated with slower worsening of interstitial lung disease secondary to rheumatoid arthritis. *Clin Rheumatol* 2021; 40: 133-42. https://doi.org/10.1007/s11096-020-01171-5
29. FERNÁNDEZ-DÍAZ C, ATIENZA-MATEO B, CASTAÑEDA S *et al*.: Abatacept in monotherapy vs combined in interstitial lung disease of rheumatoid arthritis-multicentre study of 263 Caucasian patients. *Rheumatology* (Oxford) 2021; 61: 299-308. https://doi.org/10.1093/rheumatology/keab317.
30. MUROTA A, KANEKO Y, YAMAOKA K, TAKEUCHI T: Safety of biologic agents in elderly patients with rheumatoid arthritis. *J Rheumatol* 2016; 43: 1984-8. https://doi.org/10.3899/jrheum.160012
31. NOVELLA-NAVARRO M, BALSA A: Difficult-to-treat rheumatoid arthritis in older adults: implications of ageing for managing patients. *Drugs Aging* 2022; 39: 841-49. https://doi.org/10.1007/s40266-022-00976-5
32. KHAN MS, ROBERTS MS: Challenges and innovations of drug delivery in older age. *Adv Drug Deliv Rev* 2018; 135: 3-38. https://doi.org/10.1016/j.addr.2018.09.003
33. RICHTER A, LISTING J, SCHNEIDER M *et al*.: Impact of treatment with biologic DMARDs on the risk of sepsis or mortality after serious infection in patients with rheumatoid arthritis. *Ann Rheum Dis* 2016; 75: 1667-73. https://doi.org/10.1136/annrheumdis-2015-207838
34. MENA-VÁZQUEZ N, ROJAS-GIMENEZ M, ROMERO-BARCO CM *et al*.: Predictors of progression and mortality in patients with prevalent rheumatoid arthritis and interstitial lung disease: a prospective cohort study. *J Clin Med* 2021; 10: 874. https://doi.org/10.3390/jcm10040874
35. SINGH JA, CAMERON C, NOORBALOOCHI S *et al*.: Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet* 2015; 386: 258-65. https://doi.org/10.1016/S0140-6736(14)61704-9
36. ARAUJO AGS, BORBA HHL, TONIN FS *et al*.: Safety of biologics approved for the treatment of rheumatoid arthritis and other autoimmune diseases: a disproportionality analysis from the FDA Adverse Event Reporting System (FAERS). *BioDrugs* 2018; 32: 377-90. https://doi.org/10.1007/s40259-018-0285-2
37. CHEN N, DIAO CY, GAO J, ZHAO DB: Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Semin Arthritis Rheum* 2022; 55: 152004. https://doi.org/10.1016/j.semarthrit.2022.152004
38. LUGG ST, SCOTT A, PAREKH D, NAIDU B, THICKETT DR: Cigarette smoke exposure and alveolar macrophages: mechanisms for lung disease. *Thorax* 2022; 77: 94-101. https://doi.org/10.1136/thoraxjnl-2020-216296
39. JIANG C, CHEN Q, XIE M: Smoking increases the risk of infectious diseases: a narrative review. *Tob Induc Dis* 2020; 18: 60. https://doi.org/10.18332/tid/123845
40. MARGARITOPOULOS GA, VASARMIDI E, JACOB J, WELLS AU, ANTONIOU KM: Smoking and interstitial lung diseases. *Eur Respir Rev* 2015; 24: 428-35. https://doi.org/10.1183/16000617.0050-2015
41. HUANG C, SHI G: Smoking and microbiome in oral, airway, gut and some systemic diseases. *J Transl Med* 2019; 17: 225. https://doi.org/10.1186/s12967-019-1971-7
42. JOSEPH RM, MOVAHEDI M, DIXON WG, SYMMONS DP: Risks of smoking and benefits of smoking cessation on hospitalisations for cardiovascular events and respiratory infection in patients with rheumatoid arthritis: a retrospective cohort study using the Clinical Practice Research Datalink. *RMD Open* 2017; 3: e000506. https://doi.org/10.1136/rmdopen-2017-000506
43. SINGH JA: Infections with biologics in rheumatoid arthritis and related conditions: a scoping review of serious or hospitalised infections in observational studies. *Curr Rheumatol Rep* 2016; 18: 61. https://doi.org/10.1007/s11926-016-0609-5
44. CANTINI F, NICCOLI L, NANNINI C *et al*.: Tailored first-line biologic therapy in patients with rheumatoid arthritis, spondyloarthritis, and psoriatic arthritis. *Semin Arthritis Rheum* 2016; 45: 519-32. https://doi.org/10.1016/j.semarthrit.2015.10.001

45. JOHNSTON SS, TURPCU A, SHI N, FOWLER R, CHU BC, ALEXANDER K: Risk of infections in rheumatoid arthritis patients switching from anti-TNF agents to rituximab, abatacept, or another anti-TNF agent, a retrospective administrative claims analysis. *Semin Arthritis Rheum* 2013; 43: 39-47. https://doi.org/10.1016/j.semarthrit.2012.12.024
46. CECCONI M, RANZA R, TITTON DC *et al*.: Incidence of infectious adverse events in patients with rheumatoid arthritis and spondyloarthritis on biologic drugs-data from the Brazilian registry for biologics monitoring. *J Clin Rheumatol* 2020; 26:73-8. https://doi.org/10.1097/rhu.0000000000000935
47. CANTINI F, NICCOLI L, NANNINI C *et al*.: Second-line biologic therapy optimization in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *Semin Arthritis Rheum* 2017; 47: 183-92. https://doi.org/10.1016/j.semarthrit.2017.03.008
48. ZAMORA-LEGOFF JA, KRAUSE ML, CROWSON CS, RYU JH, MATTESON EL: Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. *Clin Rheumatol* 2016; 35: 2585-89. https://doi.org/10.1007/s10067-016-3357-z
49. LEE YK, AHN GY, LEE J *et al*.: Excess mortality persists in patients with rheumatoid arthritis. *Int J Rheum Dis* 2021; 24: 364-72. https://doi.org/10.1111/1756-185x.14058
50. LEE EE, SHIN A, LEE J *et al*.: All-cause and cause-specific mortality of patients with rheumatoid arthritis in Korea: A nation-wide population-based study. *Joint Bone Spine* 2022; 89: 105269. https://doi.org/10.1016/j.jbspin.2021.105269
51. QIU M, JIANG J, NIAN X *et al*.: Factors associated with mortality in rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis. *Respir Res* 2021; 22: 264. https://doi.org/10.1186/s12931-021-01856-z
52. FUI A, BERGANTINI L, SELVI E *et al*.: Rituximab therapy in interstitial lung disease associated with rheumatoid arthritis. *Intern Med J* 2020; 50: 330-36. https://doi.org/10.1111/imj.14306