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ORIGINAL RESEARCH

Real-world association of biologic and targeted synthetic DMARD use with mortality in rheumatoid arthritis-associated interstitial lung disease: a nationwide cohort study

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ABSTRACT

Objectives To investigate the association between biologic and targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) use and all-cause mortality and cause-specific mortality in patients with rheumatoid arthritis-associated interstitial lung disease (RA-ILD).

Methods We identified patients with incident RA-ILD between 2010 and 2021 using the National Health Insurance database. The index date was the date of RA-ILD diagnosis, and subsequent b/tsDMARD use was treated as time-dependent exposure. Inverse probability of treatment weighting (IPTW) was used to balance measured baseline covariates. All-cause mortality was analysed using time-dependent Cox proportional hazards models and cause-specific mortality using time-dependent Fine–Grey competing-risk models.

Results Among 6292 patients with RA-ILD, 1074 received b/tsDMARD during follow-up and 5218 received conventional synthetic DMARDs only. 1964 deaths occurred. After IPTW, b/tsDMARD use was associated with lower all-cause mortality (HR 0.75, 95% CI 0.62 to 0.89), respiratory-related mortality (subdistribution HR (sHR) 0.72, 95% CI 0.56 to 0.91) and ILD-related mortality nested within respiratory mortality (sHR 0.63, 95% CI 0.43 to 0.88). No statistically significant associations were observed for cardiovascular, cancer-related or infection-related mortality. In class-specific analyses, HRs for all-cause mortality versus non-b/tsDMARDs were 0.61 (95% CI 0.44 to 0.86) for tumour necrosis factor inhibitors, 0.71 (0.53 to 0.9) for abatacept, 0.68 (0.52 to 0.89) for tocilizumab, 0.76 (0.28 to 2.06) for rituximab and 0.61 (0.39 to 0.95) for Janus kinase inhibitors.

Conclusions b/tsDMARD use was associated with lower all-cause mortality and respiratory-related mortality in patients with RA-ILD. Further studies incorporating clinical, pulmonary function and radiological data are needed to confirm these findings.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is associated with substantial mortality, while the mortality implications of biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) use in RA-ILD remain uncertain.

WHAT THIS STUDY ADDS

⇒ b/tsDMARD use was associated with lower all-cause mortality and respiratory-related mortality, including ILD-related deaths, in patients with RA-ILD.

⇒ In separate class-specific comparisons with non-b/tsDMARD treatment, tumour necrosis factor inhibitors, abatacept, tocilizumab and Janus kinase inhibitors were each associated with lower all-cause mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings provide complementary real world evidence regarding b/tsDMARD use in RA-ILD and may inform treatment decision-making, while highlighting the need for further studies incorporating detailed measures of ILD severity, pulmonary function and radiological characteristics.

INTRODUCTION

Interstitial lung disease (ILD) is a serious pulmonary manifestation of rheumatoid arthritis (RA), occurring in approximately 5%–18% of patients,[1 2] and up to 25% when subclinical disease detected by chest CT is included.[3] RA-associated ILD (RA-ILD) is a major cause of mortality in patients with RA; cohort studies have reported 5-year survival rates of 36%–41%[4–6] and approximately 2-fold to 10-fold higher mortality than in patients with RA without ILD.[4 7–9]

Despite the clinical importance of RA-ILD, the management of RA-ILD remains a therapeutic dilemma: RA disease activity and ILD activity are often discordant, and control of

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joint inflammation does not necessarily prevent progression of lung disease.[10] Furthermore, biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) may increase the risk of infections, including pneumonia, raising safety concerns in patients with underlying ILD.[11–13] In addition, although the evidence is inconsistent, tumour necrosis factor (TNF) inhibitors have been suggested to worsen RA-ILD.[14–16] Given these competing risks, clinicians face substantial uncertainty about whether to initiate or maintain b/tsDMARD therapy after a diagnosis of RA-ILD.

The 2023 guidelines from the American College of Rheumatology and the American College of Chest Physicians (ACR/CHEST) conditionally recommend mycophenolate, azathioprine and rituximab as first-line treatment options for RA-ILD, with cyclophosphamide as an additional option and tocilizumab as a subsequent option.[17] The 2025 guidelines from the European Respiratory Society and the European Alliance of Associations for Rheumatology (ERS/EULAR) conditionally favour abatacept, rituximab and Janus kinase (JAK) inhibitors over other immunosuppressive agents, while tocilizumab and conventional immunosuppressive therapies (such as mycophenolate and azathioprine) may be used according to usual clinical practice.[18] However, these recommendations rest largely on low-certainty or very-low-certainty evidence, reflecting the limited availability of high-quality data.

We therefore assessed the real world association between b/tsDMARD use and both all-cause mortality and cause-specific mortality in patients with RA-ILD using data from the National Health Insurance Service (NHIS) linked to the national death registry. We further examined whether these associations differed by treatment-switching status and by b/tsDMARD class.

METHODS

Study design and data source

We conducted this retrospective cohort study using the nationwide claims database of the NHIS,[19] which provides mandatory health insurance coverage for almost the entire Korean population. The NHIS database contains detailed information on demographics, diagnoses, procedures, prescriptions and healthcare utilisation. Mortality data were obtained by linking the NHIS data with the national death registry maintained by Statistics Korea, which provides nationwide data on deaths, including the date and cause of death coded according to the International Classification of Diseases, Tenth Revision (ICD-10).

Study population

Definition of seropositive RA

Patients with seropositive RA were identified between January 2010 and December 2021. Seropositive RA was defined as the presence of ICD-10 code M05 together with the special-case code V223, which is assigned under the Korean Rare Intractable Disease (RID) registration programme.[20 21] The RID programme requires physician certification against established diagnostic criteria, ensuring diagnostic accuracy. To further enhance validity, the M05 code was required to appear at least twice with intervals of 7–365 days. To minimise the inclusion of ILD caused by other systemic disease, patients with diagnoses of systemic lupus erythematosus (M32), systemic sclerosis (M34), overlap syndrome or mixed connective tissue disease (M35.1), sarcoidosis (D86), dermatomyositis (M33.0, M33.1), polymyositis (M33.2), inflammatory myositis (M60.8, M60.9) or inclusion body myositis (G72.4) were excluded.

Definition of RA-ILD

Among patients with seropositive RA, those with incident RA-ILD were identified between January 2010 and December 2021. RA-ILD was defined as the presence of an ILD-related ICD-10 code in either at least one inpatient claim or in two outpatient claims separated by 7–365 days. The ILD-related ICD-10 codes included J84.1 (other interstitial pulmonary disease with fibrosis), J84.8 (other specified interstitial pulmonary diseases), J84.9 (interstitial pulmonary disease, unspecified) and M05.1 combined with J99.0 (rheumatoid lung disease), consistent with previously published definitions of RA-ILD.[16] To ensure incident cases, patients with RA-ILD diagnoses recorded between 2002 and 2009 were excluded. To improve diagnostic specificity, patients were additionally required to have undergone at least one chest CT during the study period. This requirement restricted the cohort to patients in whom thoracic imaging had been performed and did not, by itself, establish the presence of ILD; the accuracy of the case-ascertainment algorithm was therefore assessed separately. The diagnostic codes used to identify seropositive RA and RA-ILD are summarised in online supplemental table 1. The study population selection is shown in figure 1.

Validation of the RA-ILD identification algorithm

We performed a hospital-based validation to evaluate the validity of the claims-based RA-ILD identification algorithm. All consecutive patients with seropositive RA at our institution who met the same ILD diagnostic code criteria as those used in the nationwide cohort between 2010 and 2021 were identified. RA-ILD was confirmed when both of the following were present: (1) A chest CT report describing findings consistent with ILD, and (2) A corresponding diagnosis of RA-ILD documented in the clinical notes by a pulmonologist or rheumatologist. Chest CT scans were not independently re-interpreted for this analysis; existing radiology reports and clinical documentation were reviewed retrospectively. The positive predictive value (PPV) was calculated as the proportion of confirmed RA-ILD cases among patients identified by the claims-based algorithm, with exact binomial (Clopper-Pearson) 95% CIs.

Exposure definition

The index date was defined as the date of RA-ILD diagnosis. Exposure was defined according to DMARD

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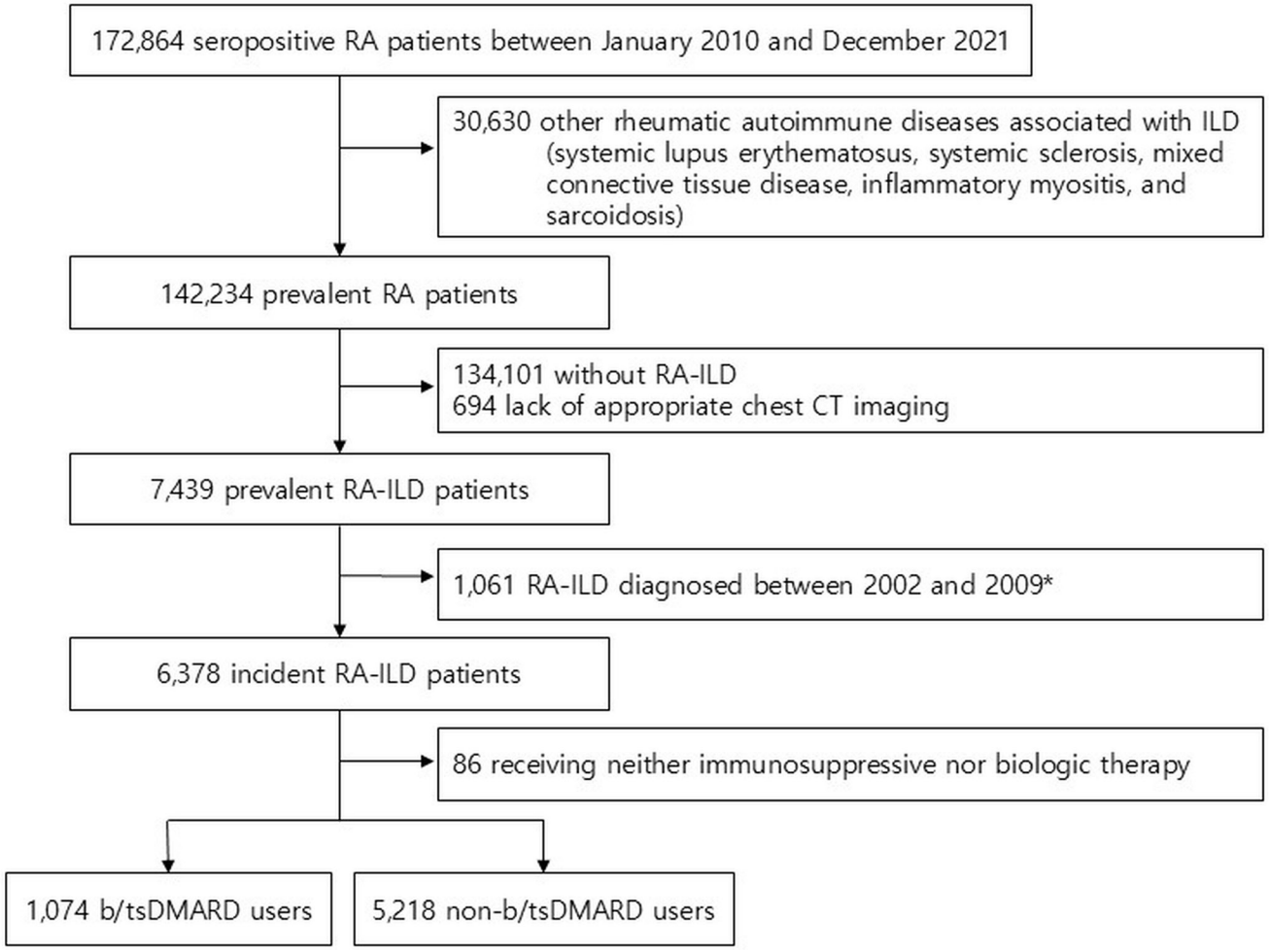


Figure 1 Flow chart of patient selection. *To identify incident RA-ILD cases between 2010 and 2021, patients who met the operational definition of RA-ILD between 2002 and 2009 were excluded. b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; ILD, interstitial lung disease; RA, rheumatoid arthritis; RA-ILD, rheumatoid arthritis-associated interstitial lung disease.

treatment after the RA-ILD diagnosis, regardless of prior b/tsDMARDs use. For descriptive comparisons and propensity score weighting, patients were classified into two treatment groups: the b/tsDMARD group that included patients with any b/tsDMARD exposure during follow-up and the non-b/tsDMARD group that comprised patients treated with conventional synthetic DMARDs (csDMARDs) without subsequent b/tsDMARD exposure. Patients who did not receive any DMARD after RA-ILD diagnosis were excluded. b/tsDMARDs included TNF inhibitors, abatacept, tocilizumab, rituximab and JAK inhibitors.

Covariates

Potential confounders included age, sex, time from RA-ILD diagnosis to first DMARD prescription, socioeconomic status, Charlson Comorbidity Index (CCI) and maximum glucocorticoid dose. Socioeconomic status was classified into tertiles by insurance premium level (Q1–Q3). The maximum glucocorticoid dose was defined as the maximum daily prednisolone-equivalent dose during the 6 months before the index date and was categorised as <10 mg/day, 10–30 mg/day and >30 mg/day. CCI and maximum glucocorticoid dose were assessed during 6 months before the index date; age, sex and socioeconomic status were assessed at the index date.

Outcomes

The primary outcome was all-cause mortality. Deaths were identified through linkage with the national death registry. Secondary outcomes included mortality related to respiratory disease, ILD, cardiovascular disease, cancer and infection. ILD-related mortality was included within respiratory-related mortality and was not treated as a mutually exclusive category. Cause-specific mortality was classified according to ICD-10 codes, as detailed in online supplemental table 1. Participants were followed from the date of RA-ILD diagnosis until death or for a maximum of 5 years, whichever occurred first.

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Subgroup analyses

Two subgroup analyses of all-cause mortality were performed according to b/tsDMARD treatment patterns. First, patients in the b/tsDMARD group were classified into single users or switchers. Single users were defined as patients who received only one class of b/tsDMARD during follow-up, whereas switchers were defined as those who received at least two b/tsDMARD classes. Each subgroup was separately compared with the non-b/tsDMARD group. Second, class-specific analyses were performed for TNF inhibitors, abatacept, tocilizumab, rituximab and JAK inhibitors. Class-specific analyses were restricted to single users to minimise the potential influence of treatment switching. Each b/tsDMARD class was separately compared with the non-b/tsDMARD group, and no direct comparisons between b/tsDMARD classes were performed.

Sensitivity analyses

Three sensitivity analyses were performed to assess potential residual confounding related to very high-dose glucocorticoid exposure, concomitant immunosuppressive agents and prior b/tsDMARD exposure. First, patients who received methylprednisolone ≥125 mg/day on at least one occasion during the 6 months before RA-ILD diagnosis were excluded. This threshold was selected because conventional pulse therapy (≥250 mg/day) was administered to only 1.3% of the cohort. In contrast, 5.4% of patients received ≥125 mg/day, allowing a sufficient number of patients with extreme glucocorticoid exposure to be identified. Second, patients who received methotrexate or tacrolimus, the concomitant immunosuppressive agents that differed between the treatment groups at baseline (online supplemental table 2), were excluded. Third, the analysis was restricted to patients without prior b/tsDMARD exposure before RA-ILD diagnosis to minimise the influence of prior treatment history.

Statistical analyses

Data are presented as mean±SD for continuous variables and as number (percentage) for categorical variables. Propensity scores for b/tsDMARD exposure were estimated using the covariates described above, and normalised inverse probability of treatment weighting (IPTW) was applied to balance measured covariates between the treatment groups. Covariate balance before and after IPTW was assessed using standardised mean differences (SMDs), with an absolute SMD <0.1 considered indicative of acceptable balance.

For all-cause mortality, unweighted and IPTW-weighted time-dependent Cox proportional hazards models were used to estimate HRs and 95% CIs. Cause-specific mortality was analysed using unweighted and IPTW-weighted time-dependent Fine–Grey subdistribution hazard models, in which deaths from causes other than the outcome of interest were treated as competing events. The corresponding estimates for cause-specific mortality were expressed as subdistribution HRs (sHRs) with 95% CIs. Robust variance estimation was used for the IPTW-weighted models, and p values were obtained from the corresponding Wald tests. Results were reported as the number of events, incidence rates (IRs) per 1000 person-years, and HRs or sHRs with 95% CIs, as appropriate.

For each of the subgroup, class-specific and sensitivity analyses, propensity scores and IPTW were re-estimated for the corresponding comparison or restricted cohort, and the IPTW-weighted time-dependent Cox proportional hazards analysis for all-cause mortality was repeated.

A Simon–Makuch survival curve was generated to visually depict all-cause survival according to time-dependent b/tsDMARD exposure status. A conventional Kaplan–Meier curve was not used because treatment status varied over time during follow-up.

As a quantitative bias analysis for potential unmeasured confounding, E-values were calculated on the risk-ratio scale, using approximate risk ratios (RRs) derived from the IPTW-weighted effect estimates, for both the point estimates and the corresponding 95% CI limit closest to the null. The E-values represent the minimum strength of association that an unmeasured confounder would need to have with both b/tsDMARD exposure and mortality, conditional on the measured covariates, to fully explain the observed association. For 95% CIs that included the null value (RR=1.00), the E-value for the CI limit closest to the null was set to 1.00.

Statistical analyses were conducted using SAS Enterprise Guide V.7.1 (SAS Institute, Cary, North Carolina, USA) and R V.4.5.2 (R Foundation for Statistical Computing). A two-sided value of p<0.05 was considered statistically significant.

RESULTS

Study population and baseline characteristics

A total of 6292 patients with RA-ILD were included in the final analysis after the inclusion and exclusion criteria were applied (figure 1). In a hospital-based validation applying the identical algorithm at our institution, 84 of 90 consecutive patients were confirmed to have RA-ILD, yielding a PPV of 93.3% (95% CI 86.1% to 97.5%); the 6 discordant patients had alternative pulmonary diagnoses or findings on chest CT, including emphysema, atelectasis, bronchiectasis, ground-glass opacity in the paravertebral region and eosinophilic pneumonia. Of the 6292 patients, 1074 patients received b/tsDMARDs during follow-up and 5218 received csDMARDs only. Baseline clinical characteristics of the study population before and after IPTW are summarised in table 1. Before weighting, the b/tsDMARD group comprised patients who were younger, were more likely to be female, had a longer interval from RA-ILD diagnosis to the first DMARD prescription, and had a higher maximum glucocorticoid dose than those in the non-b/tsDMARD group.

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Table 1 Baseline characteristics of patients with RA-ILD before and after IPTW

	Before IPTW			After IPTW		
	b/tsDMARD (n=1074)	Non-b/tsDMARD (n=5218)		b/tsDMARD (n=1791)	Non-b/tsDMARD (n=4501)	
	N (%) or mean SD	N (%) or mean SD	SMD	N (%) or mean SD	N (%) or mean SD	SMD
Age	64.4±10.1	69.6±9.8	−0.52	67.3±12.9	68.2±10.3	−0.08
Sex						
Male	427 (39.8)	2368 (45.4)	−0.11	764 (42.6)	2020 (44.9)	−0.05
Female	647 (60.2)	2850 (54.6)		1027 (57.4)	2481 (55.1)	0.05
Time to first DMARD prescription*	2.2±2.5	0.2±0.7	1.12	1.3±1.8	1.2±1.5	0.07
Socioeconomic status						
Q1 (lower quartile)	263 (24.5)	1322 (25.3)	−0.02	432 (24.1)	1138 (25.3)	−0.03
Q2 (median)	288 (26.8)	1384 (26.5)	0.01	499 (27.9)	1201 (26.7)	0.03
Q3 (upper quartile)	523 (48.7)	2512 (48.1)	0.01	860 (48.0)	2162 (48.0)	0.00
CCI†	2.6±1.7	2.9±1.9	−0.18	2.7±1.8	2.9±1.7	−0.08
Maximum GC dose†						
<10 mg	493 (45.9)	2728 (52.3)	−0.13	865 (48.3)	2221 (49.4)	−0.02
10–30 mg	235 (21.9)	1077 (20.6)	0.03	360 (20.1)	931 (20.7)	−0.01
>30 mg	346 (32.2)	1413 (27.1)	0.11	566 (31.6)	1349 (30.0)	0.03

Values after IPTW represent the weighted pseudo-population resulting from IPTW and should not be interpreted as the actual number of patients.

*Defined as the interval from RA-ILD diagnosis to the first prescription of a DMARD.
†Variables were assessed in the 6 months before the index date (defined as the date of RA-ILD diagnosis); all other variables were assessed at the index date.
b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; CCI, Charlson Comorbidity Index; GC, glucocorticoid; IPTW, inverse probability of treatment weighting; RA-ILD, rheumatoid arthritis-associated interstitial lung disease ; SMD, standardised mean difference.

After IPTW, the measured covariates were well balanced between the groups, with all absolute SMDs <0.1.

All-cause mortality

During follow-up, 1964 deaths occurred. The IR of all-cause mortality was 33.44 per 1000 person-years in the b/tsDMARD group and 87.33 per 1000 person-years in the non-b/tsDMARD group. In the unweighted time-dependent Cox proportional hazards model, b/tsDMARD use was associated with lower all-cause mortality (HR 0.76, 95% CI 0.62 to 0.92; p=0.007). The association remained after IPTW (HR 0.75, 95% CI 0.62 to 0.89; p<0.001) (table 2). The Simon–Makuch plot, shown in figure 2, depicts all-cause survival according to time-dependent b/tsDMARD exposure status.

Cause-specific mortality

Respiratory disease was the most common cause-specific mortality category, accounting for 775 deaths (39.5%), including 417 ILD-related deaths (21.2% of all deaths). In IPTW-weighted time-dependent Fine–Grey competing-risk analyses, b/tsDMARD use was associated with lower respiratory-related mortality (sHR 0.72, 95% CI 0.56 to 0.91; p=0.008), with a similar association observed for ILD-related mortality, which was nested within the respiratory-related mortality category (sHR 0.63, 95% CI 0.43 to 0.88; p=0.011). No statistically significant associations were observed for cardiovascular, cancer-related or infection-related mortality (table 2).

All-cause mortality by b/tsDMARD switching status

Propensity scores and IPTWs were estimated separately for the single-user and switcher comparisons in subgroup analyses according to b/tsDMARD treatment patterns. After weighting, the measured baseline covariates were well balanced in both comparisons (all absolute SMDs <0.1). b/tsDMARD use was associated with lower all-cause mortality among both single users (HR 0.72, 95% CI 0.61 to 0.85; p<0.001) and switchers (HR 0.76, 95% CI 0.63 to 0.93; p=0.006), with each subgroup separately compared with the non-b/tsDMARD group (table 3). The maximum absolute SMDs before and after IPTW for each comparison are presented in online supplemental table 3.

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Table 2 Association between b/tsDMARD use and all-cause mortality and cause-specific mortality using IPTW-weighted time-dependent Cox proportional hazards models

	n	Events	Incidence rate*	Before IPTW†		After IPTW‡	
				HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality							
b/tsDMARD	1074	166	33.44	0.76 (0.62 to 0.92)	0.007	0.75 (0.62 to 0.89)	0.001
Non-b/tsDMARD	5218	1798	87.33	Ref.		Ref.	
Cause-specific mortality							
Respiratory-related mortality							
b/tsDMARD	1074	54	10.30	0.71 (0.51 to 0.92)	0.021	0.72 (0.56 to 0.91)	0.008
Non-b/tsDMARD	5218	721	30.20	Ref.		Ref.	
ILD-related mortality§							
b/tsDMARD	1074	32	6.03	0.65 (0.43 to 0.89)	0.019	0.63 (0.43 to 0.88)	0.011
Non-b/tsDMARD	5218	385	15.46	Ref.		Ref.	
Cardiovascular mortality							
b/tsDMARD	1074	19	3.57	0.92 (0.46 to 1.75)	0.803	0.87 (0.52 to 1.50)	0.597
Non-b/tsDMARD	5218	191	7.48	Ref.		Ref.	
Cancer-related mortality							
b/tsDMARD	1074	21	3.95	0.70 (0.47 to 1.12)	0.106	0.72 (0.44 to 1.65)	0.336
Non-b/tsDMARD	5218	285	11.30	Ref.		Ref.	
Infection-related mortality							
b/tsDMARD	1074	11	2.06	0.94 (0.57 to 1.84)	0.542	0.83 (0.41 to 1.69)	0.613
Non-b/tsDMARD	5218	101	3.92	Ref.		Ref.	

*Incidence rate was calculated as cases per 1000 person-years.
†Before IPTW, all-cause mortality was analysed using an unweighted time-dependent Cox proportional hazards model, whereas cause-specific mortality was analysed using Fine–Grey subdistribution hazard models, with deaths from other causes treated as competing events.
‡After IPTW, all-cause mortality was analysed using an IPTW-weighted time-dependent Cox proportional hazards model, whereas cause-specific mortality was analysed using IPTW-weighted Fine–Grey subdistribution hazard models. IPTW was estimated using the covariates presented in table 1. For cause-specific mortality, HRs represent subdistribution HRs (sHRs).
§ILD-related mortality was nested within respiratory-related mortality and was not treated as a mutually exclusive outcome.
b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; ILD, interstitial lung disease; IPTW, inverse probability of treatment weighting; n, number; Ref., reference.

Mortality by b/tsDMARD class

Class-specific analyses were restricted to single users of b/tsDMARDs, and each class was separately compared with the non-b/tsDMARD group. TNF inhibitors (HR 0.61, 95% CI 0.44 to 0.86; p=0.004), abatacept (HR 0.71, 95% CI 0.53 to 0.97; p=0.030), tocilizumab (HR 0.68, 95% CI 0.52 to 0.89; p=0.005) and JAK inhibitors (HR 0.61, 95% CI 0.39 to 0.95; p=0.028) were each associated with lower all-cause mortality compared with the non-b/tsDMARD group. No statistically significant association was observed for rituximab (HR 0.76, 95% CI 0.28 to 2.06; p=0.590), although the number of rituximab single users was small (n=28) (table 4). No direct comparisons between individual b/tsDMARD classes were performed. After IPTW, measured baseline covariates were well balanced in all class-specific comparisons, with all maximum absolute SMDs <0.1 (online supplemental table 3).

Sensitivity and quantitative bias analyses

Sensitivity analyses yielded findings consistent with the primary analysis. The association between b/tsDMARD use and lower all-cause mortality remained after excluding patients who received methylprednisolone ≥125 mg/day during the 6 months before RA-ILD diagnosis (HR 0.73, 95% CI 0.60 to 0.88, p=001), excluding patients who received methotrexate or tacrolimus (HR 0.69, 95% CI 0.57 to 0.84, p<0.001), and excluding patients with prior b/tsDMARD exposure (HR 0.77, 95% CI 0.62 to 0.94, p=0.016) (online supplemental table 4).

In the quantitative bias analysis, the E-values for the IPTW-weighted associations with all-cause, respiratory-related and ILD-related mortality were 1.75, 1.82 and 2.09, respectively. The corresponding E-values for the 95% CI limits closest to the null were 1.38, 1.34 and 1.42, respectively (online supplemental table 5).

DISCUSSION

Although b/tsDMARDs are central to the management of RA, uncertainty about their effects on RA-ILD has led to therapeutic hesitation in clinical practice. In this nationwide cohort study, b/tsDMARD use was associated

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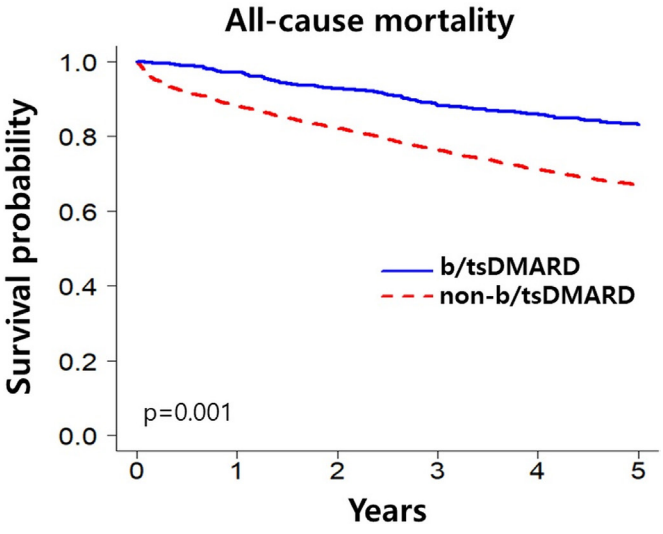


Figure 2 Simon–Makuch survival curve for all-cause mortality according to time-dependent b/tsDMARD exposure. Simon–Makuch curves were generated using normalised inverse probability of treatment weights (IPTWs). Treatment status was modelled as a time-dependent exposure, and the value of p was estimated using an IPTW-weighted time-dependent Cox proportional hazards model with robust variance estimation. Numbers at risk are not shown because exposure status varied over time and the curves are based on IPTW-weighted rather than observed risk sets. b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug.

with lower all-cause mortality in patients with RA-ILD. Lower respiratory-related mortality, including ILD-related mortality, was also observed among b/tsDMARD users. The association with lower all-cause mortality was consistent among both single users and switchers. In class-specific analyses, TNF inhibitors, abatacept, tocilizumab and JAK inhibitors were each associated with lower all-cause mortality compared with the non-b/tsDMARD group, whereas the estimate for rituximab was imprecise owing to the small number of patients and events. Because each class was compared with the non-b/tsDMARD group rather than with one another, these findings should not be interpreted as evidence of comparative effectiveness or safety across classes.

A key finding was the association between b/tsDMARD use and lower respiratory-related mortality, including ILD-related mortality. Given that RA-ILD is a leading cause of death in RA,[22 23] this observation is clinically relevant. Earlier observational data from the British Society for Rheumatology Biologics Register showed no significant difference in mortality between TNF inhibitors and csDMARDs, suggesting that TNF inhibitors were not associated with excess mortality despite concerns regarding ILD worsening.[24] A subsequent analysis from the German Rheumatoide Arthritis: Observation of Biologic Therapy (RABBIT) registry comparing TNF inhibitors with non-TNF bDMARDs and JAK inhibitors suggested differences in mortality according to treatment class, although the findings varied according to the analytical approach.[25] More recently, a 2025 US veterans cohort study using a new-user design with propensity-score matching demonstrated no significant differences in mortality or respiratory-related outcomes between TNF and non-TNF b/tsDMARDs.[26] Our study compared each individual b/tsDMARD class separately with the non-b/tsDMARD group. TNF inhibitors, abatacept, tocilizumab and JAK inhibitors were each associated with lower all-cause mortality. Rituximab was not significantly associated with mortality, but the small number of rituximab users (n=28) precluded us from making conclusions regarding this DMARD. These findings are consistent with the possibility that the observed association with b/tsDMARD use is not restricted to a single treatment class. However, the present analysis cannot determine whether mortality differs between individual b/tsDMARD classes. Current

Table 3 Association between b/tsDMARD use and all-cause mortality among single users and switchers

	N	Event	Incidence rate*	Before IPTW†		After IPTW‡	
				HR (95% CI)	P value	HR (95% CI)	P value
Single users							
b/tsDMARD	823	132	34.89	0.78 (0.66 to 0.93)	0.004	0.72 (0.61 to 0.85)	<0.001
Non-b/tsDMARD	5218	1798	87.33	Ref.		Ref.	
Switchers							
b/tsDMARD	251	34	28.81	0.73 (0.54 to 0.95)	0.031	0.76 (0.63 to 0.93)	0.006
Non-b/tsDMARD	5218	1798	87.33	Ref.		Ref.	

Single users were defined as patients who received only one class of b/tsDMARD during follow-up, whereas switchers were defined as patients who received two or more classes of b/tsDMARDs.
*Incidence rate was calculated as cases per 1000 person-years.
†Before IPTW, all-cause mortality was analysed using an unweighted time-dependent Cox proportional hazards model.
‡After IPTW, all-cause mortality was analysed using an IPTW-weighted time-dependent Cox proportional hazards model. IPTW was estimated using the covariates presented in table 1.
b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; IPTW, inverse probability of treatment weighting; n, number; Ref, reference.

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Table 4 Association between individual b/tsDMARD classes and all-cause mortality among single users

	N	Event	Incidence rate*	Before IPTW†		After IPTW‡	
				HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality							
TNF inhibitor	232	35	32.62	0.65 (0.46 to 0.92)	0.015	0.61 (0.44 to 0.86)	0.004
Abatacept	260	49	41.60	0.75 (0.55 to 0.98)	0.049	0.71 (0.53 to 0.97)	0.030
Tocilizumab	153	22	30.83	0.75 (0.57 to 0.96)	0.031	0.68 (0.52 to 0.89)	0.005
Rituximab	28	5	38.73	0.80 (0.33 to 1.94)	0.628	0.76 (0.28 to 2.06)	0.590
JAK inhibitor	150	21	30.43	0.65 (0.42 to 1.00)	0.052	0.61 (0.39 to 0.95)	0.028
Non-b/tsDMARD	5218	1798	87.33	Ref.		Ref.	

Single users were defined as patients who received only one class of b/tsDMARD during follow-up without switching to another b/tsDMARD class. Each b/tsDMARD class was analysed separately and compared with the non-b/tsDMARD group; no direct comparisons between b/tsDMARD classes were performed.
*Incidence rate was calculated as cases per 1000 person-years.
†Before IPTW, all-cause mortality was analysed using an unweighted time-dependent Cox proportional hazards model.
‡After IPTW, all-cause mortality was analysed using an IPTW-weighted time-dependent Cox proportional hazards model. IPTW was estimated using the covariates presented in table 1.
b/tsDMARD, biologic or targeted synthetic disease-modifying antirheumatic drug; IPTW, inverse probability of treatment weighting; JAK, Janus kinase; n, number; Ref, reference; TNF, tumour necrosis factor.

guidelines, including the 2023 ACR/CHEST[17] and 2025 ERS/EULAR[18] guidelines, do not preferentially support the use of TNF inhibitors in RA-ILD. Accordingly, these exploratory class-specific findings should be regarded as complementary real world evidence rather than evidence supporting class equivalence or preferential use of a particular b/tsDMARD. Dedicated active-comparator studies and, when feasible, randomised trials are needed to address comparative outcomes between individual b/tsDMARDs.

Evidence on the use of JAK inhibitors in RA-ILD remains limited. Recent meta-analyses suggest that JAK inhibitors may be associated with stabilisation[27] or improvement in pulmonary outcomes, with a safety profile comparable to that of abatacept and rituximab.[28] A recent study comparing JAK inhibitors with TNF inhibitors reported a higher risk of mortality, driven mainly by cardiovascular events, although this association was attenuated and no longer statistically significant in sensitivity analyses adjusted for follow-up duration; an increased risk nonetheless persisted among patients older than 65 years.[29] In the present study, JAK inhibitor use was associated with lower all-cause mortality compared with non-b/tsDMARDs; however, our analysis was not designed to compare JAK inhibitors directly with TNF inhibitors or other b/tsDMARD classes. The 2025 ERS/EULAR guideline includes JAK inhibitors as a potential treatment option in selected patients.[18] Thus, our findings add to emerging observational evidence regarding JAK inhibitor use in RA-ILD but should not be interpreted as establishing comparative cardiovascular, malignancy or mortality safety relative to other b/tsDMARDs.

Several mechanisms may potentially explain the observed association between b/tsDMARD use and lower mortality. Effective control of systemic inflammation could reduce articular and extra-articular disease burden and may influence the course of RA-ILD. However, neither medication through improved disease control nor subsequent glucocorticoid reduction was directly evaluated in this study, and these mechanisms therefore remain speculative. Emerging experimental evidence also suggests that JAK-dependent cytokine signalling may contribute to fibrotic pathways. In particular, inhibition of the JAK2/STAT3 pathway has been proposed to attenuate transforming growth factor beta (TGF-β)-mediated fibroblast activation.[30–32] Whether such mechanisms contribute to the mortality associations observed in our cohort cannot be determined from claims data.

Importantly, there is a lack of randomised controlled trial evidence to guide the use of immunomodulatory therapies in RA-ILD. Consequently, recent guidelines, including the 2023 ACR/CHEST and 2025 ERS/EULAR guidelines, rest largely on low-certainty or very-low-certainty evidence, resulting in predominantly conditional recommendations. In this context, large real world studies may provide complementary evidence regarding clinical outcomes that are difficult to evaluate in randomised trials. Nevertheless, observational findings should be interpreted in light of potential treatment-selection bias and residual confounding.

This study has several limitations. First, as an observational study using administrative claims data, residual confounding cannot be fully excluded. Information on smoking status, pulmonary function, radiological patterns and extent of ILD (eg, usual interstitial pneumonia vs non-specific interstitial pneumonia) and quantitative RA disease activity was unavailable; patients with less advanced or more clinically treatable ILD might therefore have been more likely to receive b/tsDMARDs, which could have contributed to the observed association with lower mortality. IPTW balanced the measured covariates (including age and sex) but cannot account

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for such unmeasured characteristics. Glucocorticoid exposure was also assessed only during the 6 months before RA-ILD diagnosis, and longitudinal use during follow-up—which may reflect both disease activity and treatment response and is itself associated with infection and mortality—was not accounted for. The observed E-values suggest that unmeasured confounding would be required to fully explain the observed associations. In addition, RA-ILD was identified using a claims-based algorithm; although hospital-based validation showed a PPV of 93.3%, some misclassification of cases cannot be excluded. Second, cause-specific mortality analyses for individual b/tsDMARD classes were not feasible owing to the limited number of events, and the small number of infection-related deaths in the b/tsDMARD group in particular may have limited power; the absence of statistical significance should therefore not be interpreted as evidence of comparable safety. Lastly, few patients received rituximab, resulting in wide CIs and limiting inference for this class.

Despite these limitations, this study has several strengths. It drew on a nationwide database linked to a national death registry, allowing comprehensive ascertainment of mortality in a large population with RA-ILD. By analysing cause-specific mortality, the study provided additional information regarding the mortality categories underlying the overall association, particularly respiratory-related and ILD-related deaths. Furthermore, previous Asian studies on mortality outcomes have been limited to single-centre cohorts of approximately 200–300 patients with RA-ILD. By contrast, our study evaluated more than 6000 patients with RA-ILD in a nationwide population. The large sample size also enabled analyses based on treatment patterns and individual b/tsDMARD classes, although these secondary analyses should be interpreted cautiously and do not represent direct comparisons between b/tsDMARD classes.

In conclusion, b/tsDMARD use was associated with lower all-cause mortality and respiratory-related mortality in patients with RA-ILD, with similar associations among single users and switchers and in several class-specific comparisons with non-b/tsDMARD treatment. Further studies incorporating detailed clinical, pulmonary function and radiological data are needed to confirm these findings.

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