# Impact of concomitant methotrexate on JAK inhibitors in rheumatoid arthritis-associated interstitial lung disease: a retrospective single-centre study from the KEIO-RA cohort

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## Abstract

### Objective

*Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) complicates disease management due to the limited methotrexate (MTX) use. Janus kinase (JAK) inhibitors are effective as monotherapy, but the impact of concomitant MTX in RA-ILD remains unclear and controversy. We compared the clinical course of patients with RA-ILD receiving JAK inhibitors with or without MTX.*

### Methods

*We analysed consecutive RA-ILD patients treated with JAK inhibitors in the KEIO-RA cohort (2013–2025), a retrospective single-centre longitudinal cohort. Patients were stratified by concomitant MTX use. The primary outcome was JAK inhibitor retention rates for 24 months and secondary outcomes included ILD progression (KL-6, %FVC, and HRCT scores), arthritis activity improvement (CDAI), glucocorticoid dose reduction, and adverse events.*

### Results

*We evaluated 86 treatment courses; 26.7% (n=23) received JAK inhibitors with MTX. The overall 24-month retention rate was 42.3%. Retention rates did not differ between MTX and non-MTX groups (47.9% vs. 41.7%, p=0.43). Among courses on therapy ≥12 months, there was no significant difference between ILD progression between MTX and non-MTX groups, as indicated by KL-6 levels (309.0 to 324.0 U/mL, p=1.00; 525.0 to 507.0 U/mL, p=0.57, respectively), %FVC (96.9% to 96.7%, p=0.56; 80.6% to 82.0%, p=0.88, respectively), and HRCT score (4 to 3, p=0.72; 4 to 4, p=0.81, respectively), as well as arthritis improvement, glucocorticoid dose reduction, and safety. Multivariable analysis identified prior exposure to multiple bDMARDs or JAK inhibitors as an independent predictor of discontinuation.*

### Conclusion

*In RA-ILD, our study found no significant differences in the effectiveness of JAK inhibitors for both ILD and arthritis, retention, and safety, with or without MTX.*

**Key words**

rheumatoid arthritis, interstitial lung disease, Janus kinase inhibitor

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## Introduction

Interstitial lung disease (ILD) is a common and serious extra-articular manifestation of rheumatoid arthritis (RA), affecting approximately 10–20% of patients (1, 2). Uncontrolled arthritis activity is associated with progression of ILD and increased risk of acute exacerbation of RA-ILD (1, 3), which carries a high mortality rate of 30–50% (4, 5). Therefore, achieving remission or low disease activity is essential not only to prevent joint destruction but also to reduce ILD progression risk (1).

However, the presence of ILD complicates RA management and is recognised as a risk factor for difficult-to-treat (D2T) RA (6). RA-ILD patients tend to be older and often have impaired renal function, limiting the use of methotrexate (MTX), a first-line RA therapy (1). This restriction may reduce the effectiveness of biological disease-modifying anti-rheumatic drugs (bDMARDs), particularly tumour necrosis factor (TNF) inhibitors (7), leading to lower retention rates in patients with RA-ILD compared to those without ILD (8). Moreover, TNF inhibitors appear less effective than non-TNF inhibitors in preventing RA-ILD progression, further limiting treatment options (9).

Janus kinase (JAK) inhibitors have been reported as a potential treatment option for D2T RA (10-12), and accumulating evidence also supports their effectiveness in RA-ILD (13). In the general RA population, JAK inhibitors can be effective without concomitant MTX (14, 15), although additional benefits of MTX co-administration have been reported (14, 16 ,17). Although JAK inhibitor monotherapy is recognised as effective for RA and the effectiveness of JAK inhibitors in RA-ILD has been investigated, the specific benefit of adding MTX in patients with RA-ILD remains entirely unknown and theoretically debated because of concerns about MTX-related pulmonary toxicity. We therefore compared the 24-month retention, effectiveness and safety of JAK inhibitors with or without MTX in patients with RA-ILD.

## Materials and methods

### *Patients and data collection*

We retrospectively reviewed all consecutive patients from KEIO-RA-cohort who visited the department of rheumatology at Keio University Hospital between January 2013 and May 2025 and received treatment with JAK inhibitors. The diagnosis of RA was based on the the 2010 classification criteria established by the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) (18). The unit of analysis in this study was the treatment course, defined as the continuous use of a single JAK inhibitor. A single patient could contribute multiple treatment courses. Clinical courses were followed up for 24 months. Ethical approval was obtained from the Keio University School of Medicine Ethics Committee (approval no. 20130506), and the study adhered to the principles of the Declaration of Helsinki. Informed consent was waived in line with Japanese ethical standards.

### *ILD assessment*

At the initial visit, all patients underwent chest radiography, and high-resolution computed tomography (HRCT) was performed when ILD was clinically suspected. In confirmed ILD cases, pulmonary function tests (PFT) were conducted as part of routine evaluation. ILD assessment on chest HRCT was based on reports by clinical radiologists and reviewed by rheumatologists with more than ten years of clinical experience. ILD patterns were classified according to the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of Idiopathic Interstitial Pneumonias (19). The extent of ILD was evaluated using the HRCT score according to Goh's algorithm, which assesses airspace consolidation, ground-glass attenuation, and fibrosing changes (interlobular septal thickening and/or reticular opacity) across five anatomical levels: 1. origin of the great vessels, 2. main carina, 3. pulmonary venous confluence, 4. midway between the third and fifth sections, 5. immediately above the diaphragm (20). Two trained rheumatologists (KoS and KaS) independently and blindly evaluated the HRCT scans using ImageJ software (National Institutes of Health, USA) (21), follow-

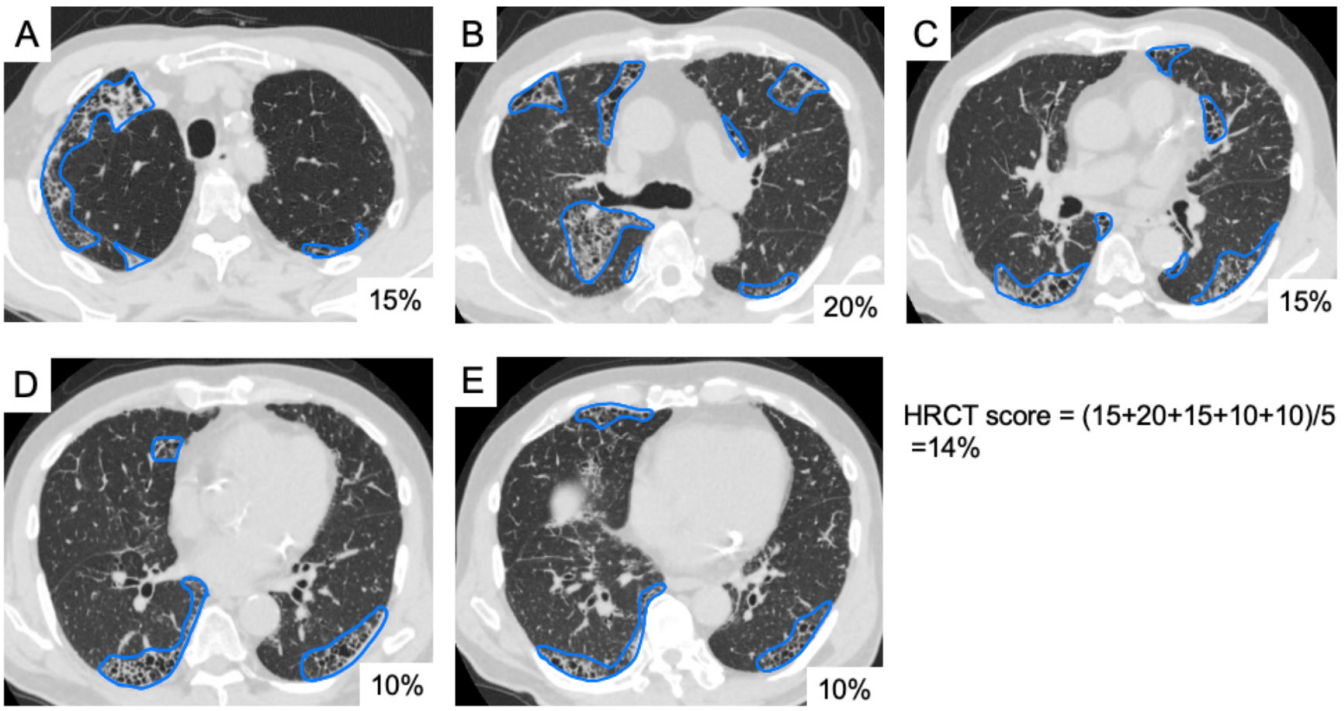


**Fig. 1.** Scoring of HRCT.
The extent of ILD was assessed using the HRCT scoring system based on Goh's algorithm, which evaluates the area of ILD across five anatomical zones: (1) the origin of the great vessels (**A**), (2) the main carina (**B**), (3) the pulmonary venous confluence (**C**), (4) the midpoint between the third and fifth sections (**D**), and (5) the region immediately above the diaphragm (**E**). Each area was manually delineated and quantified using ImageJ software and scored to the nearest five percent. The extent of area was calculated as the mean percentage across the five zones: HRCT score: (15+20+15+10+10)/5 = 14%

ing a previously described method (5). Discrepancies between observers were resolved by consensus. Representative scoring results are presented in Figure 1. Chest HRCT was evaluated annually as part of standard practice.

*Clinical assessment*

Demographic and clinical data at initiation of JAK inhibitors were obtained from patients' medical records, including age, sex, body mass index, disease duration, smoking history, treatment history, adverse events, and laboratory data. HRCT scores and PFT results within one year before the initiation of JAK inhibitor therapy were also obtained. Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73m$^2$ persisting for more than three months. Adverse events were collected through a retrospective chart review. Our data collection focused on the following outcomes: infections, newly diagnosed malignancies, cardiovascular events, all-cause mortality, and any other adverse events leading to treatment discontinuation. Infections requiring hospitalisation were defined as any infectious event that resulted in a formal hospital admission, verified by review of admission notes and hospital administrative data. Cardiovascular events were defined according to the criteria used in the ORAL Surveillance trial (22), and were identified and verified by the study investigators through a systematic retrospective chart review. RA disease activity was assessed by Clinical Disease Activity Index (CDAI) (23) and the Disease Activity Score in 28 joints using C-reactive protein (DAS28-CRP) (24). These data were collected at the initiation of JAK inhibitors. Additionally, for patients who continued JAK inhibitor treatments for more than 12 months, RA disease activity measures, HRCT scores, PFT results and laboratory data were also collected at 24 months after treatment initiation. Last observation carried forward method was applied to routinely obtained variables, including RA disease activity measures, HRCT scores, and laboratory data, to address missing values, while the analysis of PFT data was limited to courses who underwent PFT follow-up. The primary outcome of this study was the 24-month retention rate of JAK inhibitors. As secondary outcomes, we evaluated 24-month changes in arthritis activity (assessed by CDAI), glucocorticoid dose and ILD progression (evaluated by percent predicted forced vital capacity (%FVC) and HRCT score), and incidence of adverse events. As laboratory markers for ILD and arthritis, we also collected data on Krebs von den Lungen-6 (KL-6) and matrix metalloproteinase-3 (MMP-3) levels. KL-6 is a glycoprotein expressed on alveolar epithelial cells, and its serum concentration reflects alveolar epithelial injury, thereby serving as an indicator of ILD severity (25). MMP-3 is a proteolytic enzyme produced by synovial tissues, serving as a marker of arthritis activity and joint destruction (26).

*Statistical analysis*

Continuous variables are expressed as medians with interquartile ranges (IQRs), while categorical variables are reported as percentages. Comparisons of two groups for continuous and categorical data were conducted using the linear mixed-effects models and gen-

**Table I.** Clinical characteristics of patients at initiation of JAK inhibitors.

| Characteristics | All (n=86) | Non-MTX group (n=63) | MTX group (n=23) | *p*-value |
|---|---|---|---|---|
| Age, median [IQR] (years) | 75.0 [65.0-79.3] | 78.0 [67.0-81.0] | 67.0 [58.0-74.0] | <0.01* |
| Female (n, %) | 76 (88.4) | 57 (90.5) | 19 (82.6) | 0.24 |
| BMI, median [IQR] (kg/m$^2$) | 22.0 [19.4-24.1] | 21.4 [18.9-23.6] | 22.2 [19.5-24.1] | 0.99 |
| Disease duration, median [IQR] (years) | 14.0 [3.5-21.0] | 15.0 [3.5-21.0] | 13.0 [2.5-20.0] | 0.99 |
| Smoking [a] (n, %) | 27 (31.4) | 17 (27.0) | 10 (43.5) | 0.27 |
| Type of ILD (n, %) | | | | |
| NSIP | 34 (39.5) | 25 (39.7) | 9 (39.1) | 0.97 |
| UIP | 49 (57.0) | 36 (57.1) | 13 (56.5) | 0.73 |
| HRCT score, median [IQR] | 4 [2.5-8] | 5.0 [2.0-8.0] | 4.0 [3.0-5.0] | 0.39 |
| Baseline PFT [b], median [IQR] [a] | | | | |
| %FVC (%) | 97.7 [84.2-106.4] | 97.5 [83.7-106.2] | 100.5 [86.4-111.05] | 0.99 |
| %DLco (%) | 62.2 [49.2-67.0] | 63.5 [43.1-67.0] | 61.7 [53.1-65.3] | 0.79 |
| RF positive (n, %) | 79 (91.9) | 58 (92.1) | 21 (91.3) | 0.90 |
| RF titre, median [IQR] | 126.5 [41.3-485.8] | 118 [44.0-500.0] | 213.0 [21.0-468.0] | 0.99 |
| Anti-CCP positive (n, %) | 78 (90.7) | 58 (92.1) | 20 (86.9) | 0.69 |
| Anti-CCP titre, median [IQR] | 102 [18.2-505] | 142.0 [17.7-582.0] | 96.8 [30.5-318.3] | 0.70 |
| D2T RA (n, %) | 64 (74.4) | 48 (76.2) | 16 (69.6) | 0.58 |
| DAS28-CRP | 4.07 [3.0-5.1] | 3.7 [2.9-4.8] | 4.3 [3.8-5.5] | 0.21 |
| CDAI | 15.4 [8.7-24.2] | 13.4 [7.4-23.4] | 19.1 [11.9-25.7] | 0.27 |
| Laboratory test, median [IQR] | | | | |
| CRP (mg/dL) | 0.17 [0.03-1.58] | 0.15 [0.03-1.39] | 0.21 [0.02-2.17] | 0.37 |
| Erythrocyte sedimentation rates (mm/h) | 23 [10-69.5] | 21.0 [8.5-62.0] | 42.0 [10.0-79.0] | 0.24 |
| KL-6 (U/mL) | 479 [285.5-549.5] | 505 [299.0-560.0] | 370 [267.0-485.8] | 0.20 |
| MMP-3 (ng/mL) | 114.3 [51.3-192.6] | 119.9 [50.7-199.8] | 108.6 [55.0-157.1] | 0.43 |
| eGFR (ml/min/1.73m$^2$) | 67.0 [53.0-76.0] | 65.0 [53.0-75.0] | 72.0 [55.0-92.0] | 0.99 |
| eGFR <60 (n, %) | 33 (38.4) | 25 (39.7) | 8 (34.8) | 0.91 |
| Prior treatment history of RA (n, %) | | | | |
| Glucocorticoids | 38 (44.2) | 29 (46.0) | 9 (39.1) | 0.43 |
| csDMARDs | 78 (90.7) | 55 (87.3) | 23 (100.0) | 0.78 |
| Methotrexate | 63 (73.3) | 40 (63.5) | 23 (100.0) | 0.04* |
| b/tsDMARDs | 77 (89.5) | 58 (92.1) | 19 (82.6) | 0.74 |
| TNF inhibitor | 52 (60.5) | 34 (54.0) | 18 (78.3) | 0.16 |
| Abatacept | 36 (41.9) | 33 (52.4) | 3 (13.0) | 0.03* |
| IL-6 inhibitor | 63 (73.3) | 47 (74.6) | 16 (69.6) | 0.69 |
| JAK inhibitor | 28 (32.6) | 24 (38.1) | 4 (17.4) | 0.09 |
| Recent treatment of RA (n, %) | | | | |
| Glucocorticoids | 27 (32.1) | 19 (31.2) | 8 (34.8) | 0.78 |
| Dose of prednisolone, median [IQR] (mg) | 7.5 [5.0-10.0] | 8.0 [6.0-12.0] | 4.5 [1.8-7.3] | 0.19 |
| csDMARDs | 44 (51.2) | 22 (34.9) | 22 (95.7) | <0.01* |
| Methotrexate | 25 (29.1) | 4 (6.4) | 23 (100.0) | <0.01* |
| Dose of methotrexate, median [IQR] (mg/week) | 8 [4-10] | 7 [4.5-9.5] | 8 [4.0-10.0] | 0.97 |
| b/tsDMARDs | | | | |
| TNF inhibitor | 12 (13.9) | 5 (7.9) | 7 (30.4) | <0.01* |
| Abatacept | 9 (10.5) | 7 (11.1) | 2 (8.7) | 0.55 |
| IL-6 inhibitor | 30 (34.9) | 23 (36.5) | 7 (30.4) | 0.53 |
| JAK inhibitor | 24 (27.9) | 21 (33.3) | 3 (13.0) | 0.08 |
| Number of prior b/tsDMARDs, median [IQR] | 3 [2-5] | 3 [2-5] | 2 [2-4] | 0.09 |

CCP: cyclic citrullinated peptide; b/tsDMARDs: biological or targeted synthetic disease modifying anti-rheumatic drugs; BMI: body mass index; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs; D2T RA: difficult-to-treat rheumatoid arthritis; DAS28: Disease Activity Score in 28 joints; %DLco: percent predicted diffusing capacity of the lung for carbon monoxide; %FVC: percent predicted forced vital capacity; HRCT: high-resolution computed tomography; ILD: interstitial lung disease; IQR: interquartile range; KL-6: Krebs von den Lungen-6; MMP-3: matrix metalloproteinase-3; NSIP: non-specific interstitial pneumonia; PFT: pulmonary function test; RF: rheumatoid factor; TNF: tumour necrosing factor; UIP: usual interstitial pneumonia. [a] Smoking included past or current habit. [b] PFT was conducted in 44 cases; within 12 months before initiation of JAKi. * $p$<0.0.5

eralised linear mixed-effects models, respectively, with patient-level random effects to account for clustering within individuals. Survival analysis was carried out using Kaplan-Meier curves and the mixed-effect Cox's proportional hazards models. Mixed-effects logistic regression models were used to identify factors associated with discontinuation of JAK inhibitors, and linear mixed-effects models were used to examine factors associated with pulmonary outcomes. Variables that were clinically important were used as covariates. All statistical analyses were performed using JMP v. 18 (SAS Institute Inc., Cary, NC, USA) or R v. 4.4.2 (R Development Core Team, Vienna, Austria). Figures were generated with GraphPad Prism v. 10.4.1 (GraphPad Software Inc., USA).

*Baseline patient characteristics*

In the KEIO-RA cohort, 273 patients received JAK inhibitor treatment.

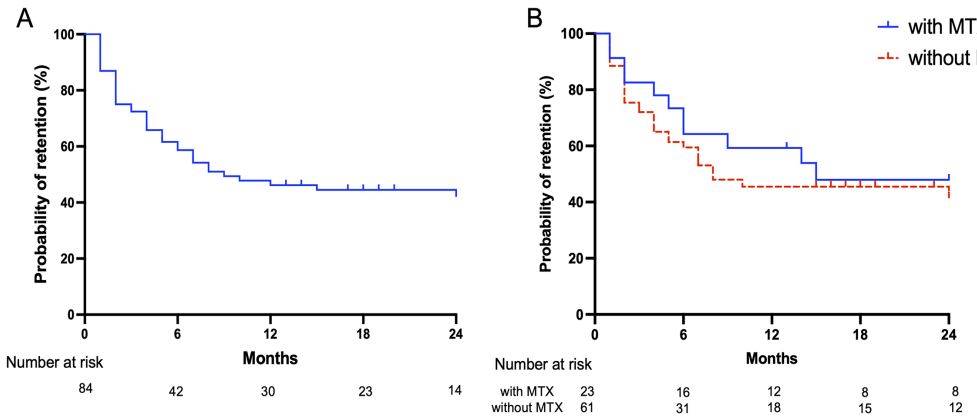


**Fig. 2.** Kaplan-Meier analyses for the 24-month retention rates of JAK inhibitors in patients with RA-ILD.
Kaplan-Meier curves show the 24-month retention rates for JAK inhibitors (**A**).
Patients were also stratified into two groups: those treated with MTX and those without (**B**).
MTX: methotrexate.

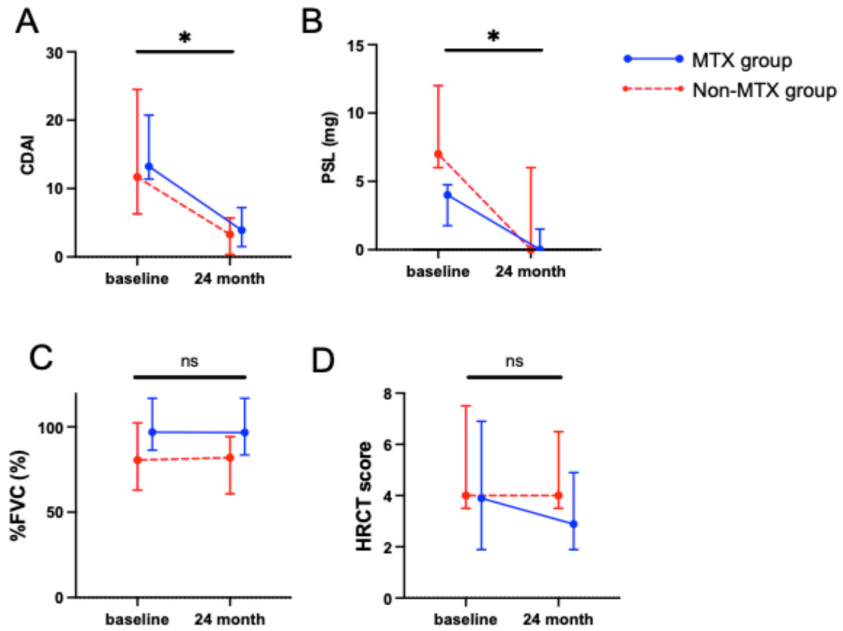


**Fig. 3.** Changes in treatment-related variables after 24 months of JAK inhibitor therapy.
Graphs depict the following variables at baseline and after 24 months of treatment with JAK inhibitors with or without MTX: CDAI (**A**), PSL dose (**B**), %FVC (**C**), and HRCT score (**D**). The change in %FVC was assessed in patients who underwent pulmonary function tests both before and after initiation of JAK inhibitors (n=8). *$p$<0.05.
CDAI: Clinical Disease Activity Index, %FVC: percent predicted forced vital capacity, HRCT: high-resolution computed tomography, ns: not significant.

Among them, 58 patients were complicated with RA-ILD with 86 treatment courses (tofacitinib: n=14, baricitinib: n=25, peficitinib: n=11, upadacitinib: n=22, and filgotinib: n=14). Among these, 23 courses (26.7%) were treated with JAK inhibitors plus MTX (MTX group), while 63 (73.3%) were treated without MTX (non-MTX group). Their clinical characteristics at JAK inhibitor initiation are summarised in Table I. The median age was 75 years, and 88.4% were female. Most cases were positive for rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) antibody (RF, 91.9%; anti-CCP, 90.7%). Of note, 74.4% of courses have been treated with more than two modes of bDMARDs or JAK inhibitors, classified as D2T RA. Baseline characteristics, including disease duration, sex, seropositivity, D2T RA, arthritis activity, ILD subtype, and pulmonary function, were comparable between MTX and non-MTX groups. However, at treatment initiation, non-MTX group were older (78 *vs.* 67 years, $p$<0.01), more frequently treated with prior abatacept (52.4% *vs.* 13%, $p$=0.03) or JAK inhibitors (33.3% *vs.* 13.0%, $p$=0.08), and less frequently with MTX (6.4% *vs.* 100%, $p$<0.01) and TNF inhibitors (54.0% *vs.* 78.3%, $p$<0.01) compared to those of MTX group.

*Comparison of retention rates among MTX and non-MTX groups*

The overall retention rates were 58.7% at 6 months, 46.2% at 12 months, and 42.3% at 24 months (Fig. 2A). At 24 months, retention rates were comparable between MTX and non-MTX groups (47.9% [95% confidence interval 30.3–75.7] *vs.* 41.7% [28.4–57.3], $p$=0.43) (Fig. 2B). We also analysed the 24-month retention rate of JAK inhibitors, stratified into three groups: baricitinib, tofacitinib, and others, which demonstrated comparable retention rates (37.8% [18.3–71.8] *vs.* 35.7% [17.7–72.1] *vs.* 46.5% [33.0–65.4], $p$=0.8) (Supplementary Fig. S1).

*Secondary outcomes*

For the analysis of 24-month changes in arthritis activity and ILD progression, we evaluated 30 treatment courses in patients who were able to continue JAK inhibitor treatment for at least 12 months. Among 30 treatment courses, 12 courses (40%) were treated with JAK inhibitors plus MTX. Detailed characteristics of these 30 courses are provided in Supplementary Table S1. The median interval between HRCT assessments was 18 months [15-25]. Re-

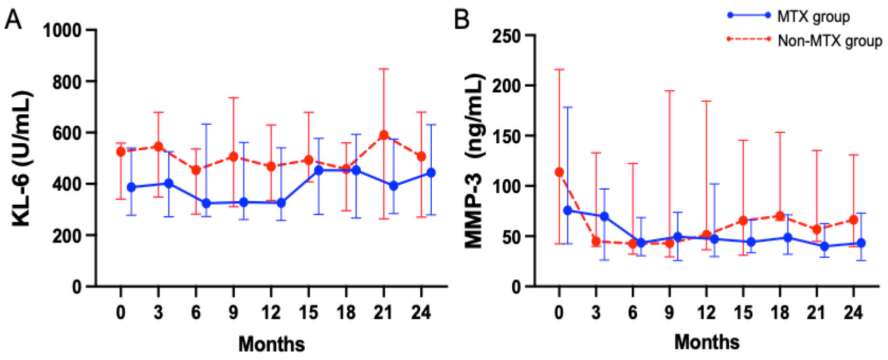


**Fig. 4.** Changes in KL-6 and MMP-3 levels during 24 months after JAK inhibitor initiation.
Graphs show the time course of KL-6 (**A**) and MMP-3 levels (**B**) during 24 months after JAK inhibitor initiation. Bars are interquartile range.
KL-6: Krebs von den Lungen-6, MMP-3: matrix metalloproteinase-3.

garding arthritis activity, CDAI showed significant improvement in both MTX (13.2 [11.3–20.7] to 3.8 [1.3–7.1], $p<0.001$) and non-MTX (11.7 [6.3–24.5] to 3.3 [0.3–5.7], $p<0.001$) groups (Fig. 3A). Prednisolone dose decreased in both MTX (4 mg [1.8–4.8] to 0 mg [0–1.5], $p=0.04$) and non-MTX (7 mg [6–12] to 0 mg [0–6], $p=0.02$) groups (Fig. 3B). Furthermore, ILD remained stable in both MTX and non-MTX groups, as indicated by no significant changes in %FVC (96.9% [86.4–116.7] to 96.7% [83.7–116.7], $p=0.56$; 80.6% [62.9–102.3] to 82.0% [60.8–94.3], $p=0.88$, respectively), and HRCT score (4 [2–7] to 3 [2–5], $p=0.72$; 4 [3.5–7.5] to 4 [3.5–6.5], $p=0.81$, respectively) (Fig. 3C-D). Changes in %FVC and HRCT scores over 24 months were comparable between the MTX and non-MTX groups (-2.0% [-4.6 – -0.1] *vs.* -2.7% [-8.9–1.7], $p=0.78$; and 0 [-2–0] *vs.* 0 [0–0], $p=0.99$, respectively), and linear mixed-effects models showed concomitant MTX use was not associated with these changes (Suppl. Table S2).

*Changes in KL-6 and MMP-3 levels after JAK inhibitors initiation*

As laboratory markers for ILD and arthritis, changes in KL-6 and MMP-3 levels after JAK inhibitor initiation are shown in Figure 4. In both MTX and non-MTX groups, KL-6 levels remained stable (Fig. 4A), and MMP-3 levels improved after initiation of JAK inhibitor therapy. No statistically significant differences were observed between the two groups.

*Safety*

Regarding the reasons for discontinuation of JAK inhibitor, the most common was lack of effectiveness (29/44; 65.9%), followed by adverse events (13/44; 29.5%), with infections being the most frequent among them (Table II). The distribution of discontinuation reasons was generally comparable between groups, although ineffectiveness was more frequently observed in MTX group compared to non-MTX group (90.9% *vs.* 57.6%, $p=0.07$). The incidence of adverse events, including cardiovascular events, infections requiring hospitalisation, and varicella-zoster infection, was comparable between MTX and non-MTX groups, although non-MTX group showed a higher tendency toward adverse events (Table II). There was no treatment-related deaths during JAK inhibitor therapy. Two patients experienced acute exacerbation of ILD (AE-ILD) during two treatment courses, and was controlled with high-dose glucocorticoids and cyclophosphamide. Both treatment courses were in the non-MTX group without any concomitant therapy, were JAK inhibitor-naive, and their baseline ILD patterns were classified as NSIP. AE-ILD developed within four months of JAK inhibitor initiation, with one course treated with baricitinib showing a rapid improvement in arthritis activity from moderate to low at the time of AE-ILD onset (CDAI: 15.7 → 5.4), while another course treated with filgotinib experienced an arthritis relapse at the time of AE-ILD after having achieved remission with JAK inhibitor initiation (CDAI: 22 → 0 → 3.1).

*Factors associated with the discontinuation of JAK inhibitors*

To examine the factors associated with the discontinuation of JAK inhibitors, we conducted a mixed-effects logistic regression analysis including age, sex, number of previously used bDMARDs or JAK inhibitors, CDAI, current glucocorticoid and methotrexate use, previous JAK inhibitors use, and HRCT score. The analysis revealed that high number of previously used bDMARDs or JAK inhibitors was associated with discontinuation of JAK inhibitors, while other factors were not (Table III).

## Discussion

In this study, we comprehensively evaluated the retention rates, effectiveness, and safety profiles of JAK inhibitors with or without concomitant MTX in RA-ILD, a subgroup historically D2T due to limited therapeutic options and higher rates of treatment discontinuation. Our results found no significant differences in the effectiveness and tolerability of JAK inhibitors with or without MTX. Our results provide real-world evidence that may guide the use of JAK inhibitors in RA-ILD, particularly when MTX is limited or contraindicated.

Maintaining disease control in RA is essential not only for arthritis but also for preventing ILD progression; however, treatment remains challenging due to its D2T nature and the limited use of MTX (1). Therefore, several studies have focused on the utility of non-TNF inhibitor monotherapy, such as rituximab, abatacept or anti-IL-6 inhibitors, for the treatment of RA-ILD (3, 27). JAK inhibitors have shown effectiveness as monotherapy (14, 15) and their safety in RA-ILD has also been reported. A meta-analysis by Narváez *et al*. showed a low risk of developing de novo ILD or experiencing ILD progression in RA patients treated with JAK inhibitors (13), and a nation-wide study by Triboulet *et al*. reported overall ILD stability following JAK inhibitor initiation (28). However, studies evaluating JAK inhibitors with or without MTX in RA-ILD remain limited (29). Furthermore, previous real-world studies have mainly focused on pulmonary out-

**Table II.** Reasons for discontinuation, and adverse events occurred during treatment with JAK inhibitors.

| | All (n=86) | Non-MTX group (n=63) | MTX group (n=23) | *p*-value |
|---|---|---|---|---|
| Duration of treatment continuation, median [IQR] (months) | 6.0 [2.0-20.0] | 5.0 [2.0-17.0] | 13.0 [4.0-24.0] | 0.10 |
| Discontinuation (n, %) | 44 (51.2) | 33 (52.4) | 11 (47.8) | 0.72 |
| Reasons for discontinuation (n, % among discontinued cases) | | | | |
| Ineffectiveness | 29/44 (65.9) | 19/33 (57.6) | 10/11 (90.9) | 0.09 |
| Adverse events | 13/44 (29.5) | 12/33 (36.4) | 1/11 (9.1) | 0.16 |
| Infection | 5/44 (11.4) | 4/33 (12.1) | 1/11 (9.1) | 0.93 |
| Worsening of ILD | 2/44 (4.6) | 2/33 (6.1) | 0/11 (0.0) | 0.77 |
| Adverse events (n, % among all cases) | | | | |
| Cancer | 2 (2.3) | 2 (3.2) | 0 (0) | 0.45 |
| Cardiovascular events | 2 (2.3) | 2 (3.2) | 0 (0) | 0.24 |
| Deep vein thrombosis | 0 (0.0) | 0 (0.0) | 0 (0) | 1.00 |
| Infection which requires hospitalisation | 5 (5.8) | 4 (6.4) | 1 (4.4) | 0.68 |
| Pneumonia | 3 (3.5) | 3 (4.8) | 0 (0) | 0.78 |
| Varicella zoster virus infection | 6 (7.0) | 5 (7.9) | 1 (4.4) | 0.85 |
| Death | 0 (0) | 0 (0) | 0 (0) | 1.00 |

ILD: interstitial lung disease; IQR: interquartile range.

**Table III.** Multiple logistic regression analysis for JAK inhibitor discontinuation.

| | Univariate analysis OR [95% CI] | *p*-value | Multivariate analysis OR [95% CI] | *p*-value |
|---|---|---|---|---|
| Female | 1.66 [0.42-7.21] | 0.46 | 2.19 [0.49-11.98] | 0.32 |
| Age | 1.00 [0.96-1.05] | 0.86 | 1.02 [0.98-1.08] | 0.49 |
| Number of previously used b/tsDMARDs | 1.31 [1.06-1.65] | 0.01* | 1.39 [1.01-1.97] | 0.04* |
| Previous JAK inhibitors use | 1.43 [0.53-3.60] | 0.44 | 0.62 [0.14-2.56] | 0.51 |
| CDAI | 1.03 [0.99-1.09] | 0.10 | 1.04 [0.99-1.09] | 0.16 |
| Glucocorticoid use | 1.14 [0.47-3.54] | 0.59 | 1.18 [0.35-3.93] | 0.79 |
| MTX use | 0.83 [0.29-2.25] | 0.71 | 0.63 [0.17-2.27] | 0.48 |
| HRCT score | 0.96 [0.87-1.03] | 0.30 | 0.99 [0.89-1.08] | 0.86 |

b/tsDMARDs: biological or targeted synthetic disease-modifying anti-rheumatic drugs; HRCT: high-resolution computed tomography; MTX: methotrexate; OR: odds ratio. * $p<0.05$.

comes in RA-ILD patients treated with JAK inhibitors, often without comprehensive assessment of arthritis activity or drug retention rates (8, 13, 28, 30, 31). Given that uncontrolled arthritis contributes to ILD progression (32) and that RA-ILD is frequently refractory to standard treatments (6), it is imperative to evaluate both joint and lung disease parameters, as well as long-term treatment adherence, to optimise patient management. To our knowledge, this is the first study in RA-ILD to compare JAK inhibitors with or without concomitant MTX, evaluating both arthritis and ILD outcomes. Our study demonstrated comparable effectiveness of JAK inhibitors with or without MTX for both arthritis and ILD, highlighting their potential as a therapeutic option.

The pathophysiological basis for why JAK inhibitors may inhibit ILD progression even when concomitant MTX is withheld remains unclear. Recently, Nguyen *et al*. reported that lung myofibroblasts express leukaemia inhibitory factor and its receptor, forming an autocrine loop that drives a fibrogenic effector response, with downstream signaling mediated via JAK-STAT pathway (33). Furthermore, Wang *et al*. reported that JAK-STAT pathway is upregulated in the lungs of patients with RA-ILD (34). These findings support the potential effectiveness of JAK inhibitors in suppressing ILD progression, a concept that has also been explored in mouse models of RA-ILD (35).

Previous studies indicate that the 6-month retention rate of JAK inhibitors ranges from 64% to 80% in D2T RA (36, 37), and approximately 90% in RA-ILD (8, 29-31). In our study, the overall retention rate of JAK inhibitors was 58.7% at 6 months and 46.2% at 12 months, which was lower than that reported in previous RA-ILD studies. This discrepancy may be attributed to differences in patient backgrounds. For example, 73.8% of patients in the study by Lee *et al*., 23.8% in the study by Tsujii *et al*., and 28.6% in the study by Cronin *et al*. were b/tsDMARDs-naive (8, 29-31). In contrast, only 10.5% of patients in our study were b/tsDMARD-naive, while 74.4% of patients were D2T RA. Furthermore, the median number of previous b/tsDMARDs was 0 [0–1] in the study by Lee *et al*. (8) and 1 [0–2] in the study by Cronin *et al*. (31), while 3 [2-5] in our study, indicating the D2T nature of the patients included in this study.

In managing RA-ILD, balancing efficacy and safety is particularly critical due to the complex clinical profiles of affected patients. This population tends to be older and frequently requires concomitant glucocorticoid therapy, factors which, along with ILD itself, increase vulnerability to serious infections such as Pneumocystis pneumonia (38, 39). Moreover, JAK inhibitors carry an elevated risk of varicella zoster virus reactivation compared to other bDMARDs (40), and concerns regarding major adverse cardiovascular events have also been raised (22). A systematic review of randomised controlled trials reported that patients receiving JAK inhibitors with MTX had higher rates of adverse events leading to discontinuation compared to those receiving JAK inhibitor monotherapy (41), but whether this also

holds true in the RA-ILD population remain unsolved. Our study found that the overall prevalence and types of adverse events were consistent with previous reports, including infection and worsening of ILD (13). Furthermore, no significant differences were observed between MTX and non-MTX groups, although a trend toward higher adverse events was noted in non-MTX group, potentially attributable to the older age of this population. These findings support the notion that JAK inhibitors are generally tolerable in the RA-ILD population despite their inherent risks. Additionally, our study suggests that concomitant MTX use with JAK inhibitors may be a safe treatment option for patients with RA-ILD when necessary and not contraindicated. Nevertheless, given the heightened susceptibility to infections and cardiovascular complications in this group, cautious patient selection and vigilant monitoring remain essential when employing JAK inhibitors.

Our study has several limitations. First, its single-centre retrospective design led to the small sample size which may have introduced selection bias, and hampered us from conducting comparative analysis for each JAK inhibitor. Furthermore, the baseline characteristics of the MTX and non-MTX groups were not fully comparable, including differences in age and previous treatment strategy, and there may have been a selection bias toward assigning more severe RA-ILD cases to the non-MTX group, as suggested by their older age and the higher doses of glucocorticoids dose. This limits the interpretation of between-group differences, while we performed multivariate analyses to account for potential confounders. Second, the 6-minute walk test was not routinely performed; however, recent guidelines prioritise PFT and CT scans over this test for ILD evaluation (42), supporting our approach. Third, PFT data among courses who continued JAK inhibitor therapy were limited to a small number, introducing potential selection bias and limiting the statistical power to draw definitive conclusions. Fourth, our analysis of long-term outcomes was restricted to the 30 patients who remained on therapy for at least 12 months. This small sample size limits statistical power and introduces a survivorship bias, as who discontinued treatment early due to a lack of effectiveness are inherently excluded. Fifth, while JAK inhibitors show promise as a treatment option, long-term data on their safety and sustained efficacy in this high-risk group remain limited, as our study includes small sample size and observation period was restricted to 24 months, which is relatively short for comprehensively capturing the natural history and progression of RA-ILD. Importantly, the study lacked sufficient statistical power to detect meaningful differences in rare, serious adverse events, such as AE-ILD, necessitating further investigation in larger cohorts. Sixth, inclusion of patients with prior JAK inhibitor exposure creates heterogeneity that may bias retention and safety outcomes. Although our multivariate analysis did not identify prior JAK inhibitor use as a significant independent risk factor for discontinuation, this finding should be interpreted with caution given the limited sample size.

In conclusion, this real-world study found no significant differences in the effectiveness and tolerability of JAK inhibitors with or without MTX in patients with RA-ILD. These findings highlight the potential of JAK inhibitors as a treatment option for this challenging population, but the study lacked sufficient power to detect important differences in rare, serious adverse events such as AE-ILD. Larger prospective studies with longer follow-up are needed to clarify their risk-benefit balance and guide personalised treatment strategies.

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