JANUS KINASE INHIBITORS IN RHEUMATOID ARTHRITIS-ASSOCIATED INTERSTITIAL LUNG DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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OBJECTIVE

The treatment of rheumatoid arthritis-associated interstitial lung disease (RA-ILD) remains challenging due to the scarcity of proven effective therapeutic options. This study aimed to investigate the effectiveness and safety of Janus kinase inhibitors (JAKi) in RA-ILD.

METHODS

We systematically reviewed the literature to identify studies evaluating the efficacy and safety of JAK inhibitors in RA-ILD. A meta-analysis was performed using the random-effects model

RESULTS

The literature search identified seven observational studies assessing the safety and efficacy of JAKi in RA-ILD and three studies analyzing the risk of developing de novo ILD in RA patients treated with JAKi.

The studies included a total of 183 RA-ILD patients treated with different JAKi: tofacitinib in 106 cases, baricitinib in 60 cases, upadacitinib in 3 cases, and filgotinib in 3 cases. In 11 cases, the specific JAKi used was not specified. At the start of JAKi treatment, pulmonary function test data were available for only 56.3% (103/183) of patients with RA-ILD. The mean %pFVC was 92.11% (range: 79.83% to 107.8%) and the mean %pDLCO was 60.60% (range: 59.72% to 70.9%). None of the studies specified the mean decline in these parameters from the diagnosis of ILD to the initiation of JAKi treatment. Therefore, it cannot be assumed that all cases corresponded to progressive RA-ILD. The radiological ILD pattern was available for 143 patients, with 40.5% (58/143) classified as UIP or probable UIP.

Among 183 patients with RA-ILD, the pooled analysis demonstrated an increase of 2.07% in %pFVC (95% CI: 0.57–3.58; p = 0.007) and 3.12% in %pDLCO (95% CI: 2.11–4.12; p <0.001). Thoracic HRCT scans showed improvement in 11% of patients (95% CI: 0.01–0.29). The pooled proportion of patients experiencing worsening of pre-existing ILD was 5% (95% CI: 0.01–0.11).

Adverse events were reported in 14% of cases (95% CI: 0.08–0.21), with the frequency of clinically significant infections ranging from 4.5% to 25%.

The risk of developing de novo ILD in patients receiving JAKi was low, with an incidence rate of 0.20 per 1,000 person-years (95% CI: 0.14–0.25). Comparisons with abatacept and rituximab suggested similar efficacy and safety profiles.

CONCLUSION

JAK inhibitors are well tolerated and provide a viable alternative to rituximab and abatacept for RA-ILD, with comparable efficacy, safety, and treatment persistence. They primarily stabilize or modestly improve pulmonary outcomes, with low risks of ILD progression, exacerbations, and infections, expanding therapeutic options for these patients.

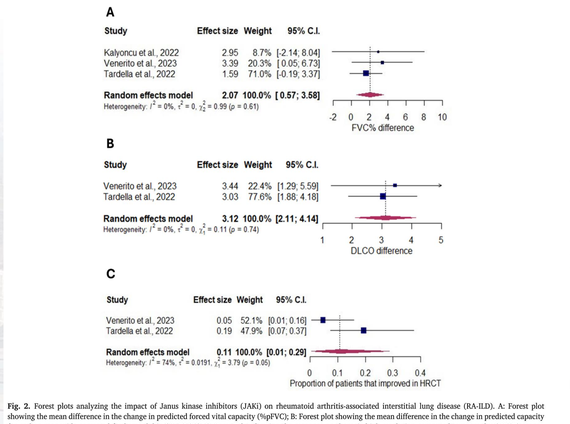

Fig. 2. Forest plots analyzing the impact of Janus kinase inhibitors (JAKi) on rheumatoid arthritis-associated interstitial lung disease (RA-ILD). A: Forest plot showing the mean difference in the change in predicted forced vital capacity (%pFVC); B: Forest plot showing the mean difference in the change in predicted capacity for carbon monoxide corrected for hemoglobin (%pDLCO); C: Forest plot showing the response on thoracic high-resolution computed tomography (HRCT) scans.

Assessment of study quality—uncontrolled observational studies using the Newcastle-Ottawa scale.

Study (Reference)	Intervention	Comparator	Selection	Comparability	Outcome	Total
Venerito et al [13]	Tofacitinib, Baricitinib, Upadacitinib, Filgotinib	No	3	0	3	6
Kalyoncu et al [14]	Tofacitinib	RA patients without ILD treated with tofacitinib	3	1	3	7
Cronin et al [15]	Tofacitinib	Rituximab	4	2	3	9
Tsujii et al [16]	Tofacitinib and Baricitinib	Abatacept	4	2	3	9
Mochizuki et al [17]	JAKi (NS)	Abatacept	4	2	3	9
Tardella et al [18]	Tofacitinib and Baricitinib	Abatacept	4	2	3	9
d'Alessandro et al [19]	Baricitinib	No	3	0	3	6

Main characteristics of included studies that assessed the risk of incident interstitial lung disease in patients with rheumatoid arthritis treated with Janus kinase inhibitors.

Article	Design	Number of treated patients	Type of JAKi	Risk of developing ILD
Baker et al. [25]	Retrospective	1565	Tofacitinib	Crude IR per 1.000 person-years: 1.47 (95 % CI: 0.54–3.27). In this retrospective cohort of patients with RA, those treated with tofacitinib had the lowest incidence of ILD compared with patients treated with bDMARD: adalimumab (13.326 patients) IR: 3.43; abatacept (5676 patients) IR: 4.46; rituximab (5444 patients) IR: 6.15; and tocilizumab (2548 patients) IR: 5.05. In an adjusted model, there was a 69 % reduced risk of ILD in patients treated with tofacitinib compared with those treated with adalimumab.
Citera et al [40]	Retrospective	7061	Tofacitinib	IR: 0.18 per 100 patient-years (95 % CI: 0.13–0.24) Median time to ILD event: 1144 days
Salvarani et al. [41]	Retrospective	3770	Baricitinib	IR: 0.17 per 100 patient-years of exposure The time to onset, calculated from the initiation of baricitinib treatment to the onset of the ILD, ranged from 60 to 1740 days

Abbreviations: IR = incidence rate; ILD = interstitial lung disease.

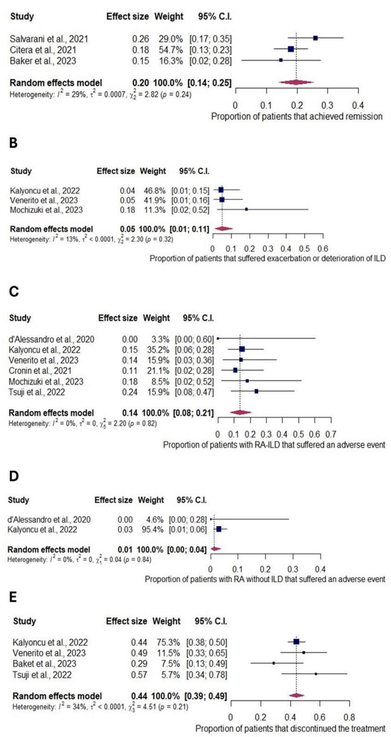

Fig. 3. Forest plots analyzing the safety of Janus kinase inhibitors (JAKi) in rheumatoid arthritis-associated interstitial lung disease (RA-ILD). A: Forest plot illustrating the risk of incident ILD in patients with RA treated with JAKi. B: Forest plot depicting the risk of worsening pre-existing ILD. C and D: Forest plots comparing the risk of adverse events in patients with RA-ILD (C) and in RA patients without ILD, who served as controls (D). E: Forest plot showing the risk of JAKi discontinuation.

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