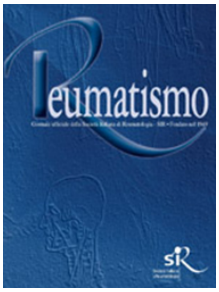

Reumatismo - The Italian Journal of Rheumatology

https://www.reumatismo.org/reuma

eISSN 2240-2683

Please cite this article as:

Maranini B, Foti R, Taha M, et al. **Janus kinase inhibitors in rheumatoid arthritis-associated interstitial lung disease: where do we stand and what may be the future?** *Reumatismo* doi: 10.4081/reumatismo.2025.1754

Submitted: 13-06-2024
Accepted: 25-08-2024

Janus kinase inhibitors in rheumatoid arthritis-associated interstitial lung disease: where do we stand and what may be the future?

Beatrice Maranini, Roberta Foti, Moustapha Taha, Veronica Venturelli, Andrea Lo Monaco, Marcello Govoni

Rheumatology Unit, Department of Medical Sciences, University of Ferrara, Italy

Correspondence: Beatrice Maranini, Rheumatology Unit, Department of Medical Sciences, University of Ferrara, Via Aldo Moro 8, 44124, Cona (FE), Italy.
E-mail: beatrice.maranini@edu.unife.it

Key words: JAK inhibitors, interstitial lung disease, ILD, rheumatoid arthritis, RA.

Contributions: BM, conceptualization, writing - original draft preparation; BM, RF, MT, VV, ALM, MG, methodology, data curation, writing- review and editing; BM, RF, MT, VV, ALM, investigation; MG, supervision. All authors have read and agreed to the published version of the manuscript.

Conflict of interest: the authors declare that they have no conflict of interest.

Ethics approval and consent to participate: not applicable.

Informed consent: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: the authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Funding: this research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

Summary
Objective. Interstitial lung disease (ILD) is rare, but it is one of the most frequent extra-articular manifestations and a relevant cause of morbidity and mortality in rheumatoid arthritis (RA). Over the past few years, Janus kinase inhibitors (JAKis) have been reported to have promising efficacy in the treatment of active RA, but recent concerns have been raised about their safety profile, namely malignancy and cardiovascular disease, limiting their use to certain patient categories.
Methods. The objective of this narrative review is to summarize the current evidence of the efficacy and safety of JAKis in RA-ILD management, investigating a possible emerging role for this drug class in such subset of patients.
Results. Current studies focusing on JAKis in RA-ILD are scarce, but they globally report an overall stabilization of respiratory symptoms, functional data, and radiographic extension of ILD. In some cohorts, JAKis determined even an encouraging improvement in lung disease, and few reports presented good tolerability of JAKis in combination with antifibrotics. Concerning the safety profile, no significant increased risk of pulmonary infection has been reported.
Conclusions. Thus far, evidence regarding the role of JAKis in the treatment of RA-ILD remains relatively limited, and additional prospective studies are needed to better understand the place of JAKis, if any, in preventing/stabilizing ILD in RA patients.

Introduction

Rheumatoid arthritis (RA) is a systemic immune-mediated inflammatory disease, which primarily manifests as a symmetric erosive polyarthritis. Extra-articular manifestations may occur, with lung involvement being one of the most common, including rheumatoid nodules, parenchymal disease, pleuritis, bronchiectasia, and, less frequently pulmonary vascular disease [vasculitis and pulmonary hypertension (PAH)] (1).

Among pulmonary complications, interstitial lung disease (ILD) is one of the most frequent (2). Although cardiac disease is the first cause of RA-related mortality, pulmonary disease is also a considerable contributor, responsible for ∼10-20% of all-cause deaths (3). People affected by RA have a three- to four-fold increased risk of ILD compared with the general population (4).

The prevalence of ILD among patients with RA has shown great variability in prior studies, ranging from 1 to 58% depending on the methodology and definitions used (*e.g.*, clinically significant or asymptomatic pre-clinical ILD, radiographic-only signs) (5-7).

ILD is more frequently observed in elderly people, especially over 70 years of age, as well as in male and seropositive RA (3, 8-10), along with a history of or current smoking, high RA disease activity (*e.g.*, Clinical Disease Activity Index >10), and family history of RA-ILD (11).

Patients with RA-ILD commonly report nonspecific respiratory symptoms, such as dry cough and exertional dyspnea (12). Optimal screening, diagnostic, and treatment approaches for RA-associated pulmonary disease are still lacking, and so far, there are only a few international guidelines concerning the treatment of RA-ILD. The only available evidence derives from observational studies, and up to date, no clinical trial has been completed on this topic. The British Thoracic Society in 2008 first proposed guidelines for RA-ILD (13). In them, the first-line treatment of RA-ILD involved the use of prednisone 0.5 mg/kg/day, subsequently tapered, and possibly combined with disease-modifying antirheumatic drugs (DMARDs), such as cyclosporine, azathioprine, and cyclophosphamide. Nevertheless, the latter DMARDs do not provide effective management of the articular symptoms, when compared with other drugs, such as methotrexate (MTX) or biological DMARDs (bDMARDs). Similar therapeutic indications derive from the more recent ACR 2023 ILD Clinical Practice Guidelines (14), concerning more the treatment of ILD than that of RA-ILD, which should consider also articular symptoms. The Spanish Guidelines of 2022, contemplate the use of MTX on an individual basis, and of rituximab or abatacept considering both articular or pulmonary involvement (15). However, currently, no guidelines mention any preferable agent to effectively manage both pulmonary and articular diseases together.

To date, targeted synthetics DMARDs (tsDMARDs), Janus kinase inhibitors (JAKis), namely baricitinib, tofacitinib, filgotinib, upadacitinib and peficitinib (only in Japan) have been licensed for RA management (16, 17). Despite the rapid onset of action on the articular disease with prompt clinical benefit, concerns about the side-effects emerged (*e.g.*, cytopenia, increased risk of infections, remarkably reactivation of herpes zoster, hypercholesterolemia, increased rates of thromboembolic events, risk of malignancies and cardiovascular events) along with a paucity of long-term safety data, especially for the most recently available JAKis. Such adverse effects led on September 2021, the US Food and Drug Administration (FDA) issuing a Drug Safety Communication regarding the use of tofacitinib and two other JAKis, upadacitinib and baricitinib, both approved for RA treatment by the FDA and the European Medicines Agency (EMA) (18). On January 2023, the EMA Pharmacovigilance Risk Assessment Committee recommended JAKis employment only if no suitable treatment alternatives are available in patients aged 65 years or above, those at increased risk of major cardiovascular events, such as heart attack or stroke, those who smoke or have been a smoker for a long time in the past, and those at increased risk of malignancies (19).

Whether or not JAKis are safe or may even slow or reverse RA-ILD is not yet known, but few data support JAK inhibition in preventing or treating such conditions. The aim of this narrative review is to elucidate the impact of JAK inhibition on patients with RA-ILD.

Methods

A broad search of the literature up to 29th February 2024 was conducted on different electronic platforms: PubMed, Embase, Scopus, and Cochrane Library. JAKi, baricitinib, filgotinib, tofacitinib, upadacitinib, ILD, RA, and their respective MESH terms were used as keywords. Records were imported into a bibliographic management software (EndNote) and articles appearing in more than one database were considered only once.

Articles were organized by topic and synthesized, covering three content categories: i) efficacy of JAKis in RA-ILD; ii) safety and pulmonary side effects of JAKis; iii) JAKis prescription in RA-ILD, drug retention rate and incident rates of ILD during treatment.

Data from selected papers were extracted. Figure 1 summarizes the methodology of the screening process: 30 articles were critically reviewed and included, and search strategies were adopted complying with recommendations for narrative reviews (20).

In *Supplementary Table 1* we summarize the key findings of the main articles examined and in Figure 2, the main JAK/signal transducer and activator of transcription activation and downstream signaling pathways in ILD.

Efficacy of Janus kinase inhibitors in rheumatoid arthritis associated with interstitial lung disease

Despite the widespread employment of JAKis in recent years for the management of RA, to date only a few observational studies and case series reported data on ILD courses in patients using these drugs.

All JAKis licensed in RA were represented in our literature search.

Significant stabilization of respiratory symptoms (in terms of dyspnea and dry cough) (21, 22), fibrosis extent at high-resolution computed tomography (HRCT) (23-27), and pulmonary function tests (PFTs) were recorded (21, 24, 26, 28, 29). Some patients even experienced improvement of PFTs (24, 26, 30), and of HRCT scan repeated during follow-up monitoring (with a reduction in size and density of ground glass findings, nodules and/or abnormal interstitial areas) (24, 31, 32).

Few papers reported occasionally PFTs and HRCT worsening at re-assessment (21, 24, 25), but only two records reported the ILD pattern in patients experiencing radiological worsening during follow-up: in the first one (patients treated with baricitinib and tofacitinib), a worsened HRCT occurred in two patients with usual interstitial pneumonia (UIP) and two presenting nonspecific interstitial pneumonia pattern (24); in the other paper (patients treated with tofacitinib only), ILD worsening appeared in a UIP pattern patient (21). No other study provided data on lung radiological features in patients who experienced ILD worsening while taking JAKis, which is a relevant limit, since different RA-ILD patterns may present different responses to therapy.

Another not trivial aspect concerns the definition of ILD worsening/improvement in the selected papers, which is defined only in a few publications. In one study, the "worsened" group included patients with pulmonary fibrosis' progression ≥15%, the "improved" group encompassed patients with pulmonary fibrosis' reduction ≥15% and the "stable" group patients showing progression or reduction of fibrosis <15% at HRCT revaluation (25). In another study, at PFTs, FVC was defined as "stable" if lung function improvement or deterioration was less than 20%, "improved" with ≥ 20% increase; "worsened" for >20% deterioration. Concerning diffusing capacity of the lung for carbon monoxid (DLCO), an improvement or deterioration of 15% classified patients as ILD improving or worsening, respectively (24). The lack of standardized definitions of worsening or improving ILD in the majority of current publications makes it difficult to extrapolate robust conclusions.

Peculiarly, lung improvement may be observed even in patients with no known diagnosis of ILD. One retrospective study analyzed the effectiveness of baricitinib therapy (4 mg daily, in combination or not with other DMARDs) in 15 RA patients, among which 4 RA-ILD patients (27%), demonstrating a significant increase in DLCO and diffusion coefficient percentages at 6-months follow up compared to

baseline values not only in RA-ILD patients, but also in RA patients without ILD history (30). On a speculative basis, based on these findings, we could assume that JAKis may ameliorate lung homeostasis and function even in asymptomatic patients and subclinical RA-ILD, but further studies are needed to better clarify this assumption.

Only one study effectively investigated the difference between monotherapy and combination therapy in RA-ILD management, showing no improvement nor deterioration at both HRCT and PFTs between MTX plus JAKi combination therapy and patients taking JAK inhibitor monotherapy (24).

Only two studies investigated JAKis effects in comparison with other drugs (abatacept) in RA-ILD treatment (25, 27), observing similar rates of functional improvement, in the absence of imaging worsening.

To our knowledge, no evidence on coadministration of antifibrotics (nintedanib and pirfenidone) and JAKis in RA-ILD currently exists. Antifibrotic drugs could offer a valid therapeutic chance in progressive RA-ILD as adjunctive therapy to DMARDs (33). However, they could lead to additional side effects (*e.g.*, liver toxicity and diarrhea), potentially reducing adherence to DMARDs and even JAKis, a not trivial aspect. In fact, joint disease activity control is not a negligible point since, as reported, worst clinimetric indexes may correlate with worst ILD outcomes: Citera *et al.* demonstrated that for every 1-unit increase in Disease Activity Score-28 with Erythrocyte Sedimentation Rate (DAS28-ESR), patients were 1.3 times more likely to experience an ILD event (34).

According to the emerging need for well-designed, randomized controlled trials (RCTs) of JAKis in RA-ILD patients, currently two prospective interventional trials of tofacitinib have been launched and are presently recruiting: PULMORA (effects of tofacitinib *vs*. MTX on RA-ILD; ClinicalTrials.gov identifier: NCT004311567) and RAILDTo (Tofacitinib in the treatment of RA -related ILD; ClinicalTrials.gov identifier: NCT005246293) (35, 36).

Safety and pulmonary side effects of Janus kinase inhibitors

Abatacept and other bDMARDs, such as rituximab and tocilizumab, have demonstrated reasonable efficacy in slowing RA-ILD progression (37-39), but rituximab and tocilizumab present a higher infectious risk compared with abatacept; in particular the risk associated with rituximab raises concerns about its use in ILD patients (40).

Little is known about the pulmonary safety of JAKis in RA-ILD (34, 41-50), since observational studies and RCTs lack enrollment of patients with pre-existing ILD. Rates of serious infections are higher in patients with ILD *vs.* those without ILD (34, 51). This aspect requires careful management, but emerging data emphasize the advantage of managing RA-ILD employing JAKis in the event of infectious complications due to their short half-life (28).

Comprehensively, the literature has not demonstrated any significant concern regarding the respiratory safety of JAKis. No particular concern about pneumonia emerged (41, 44, 45, 47, 48), even in the Indian population, which accounts for 23% of the global burden of pneumonia (52). Only one systematic review and meta-analysis reported an increased risk of non-opportunistic respiratory infections among JAKis compared with placebo (41).

In the ORAL Surveillance trial (44), pneumonia occurred in 6.5% of the tofacitinib group 5 mg twice daily, 6.9% in the tofacitinib group 10 mg twice daily, 5.4% in the tumor necrosis factor inhibitors (TNFis) group (with no difference among TNFis drugs), without statistical significance.

Another key aspect is the risk of lung cancer in ILD patients. A higher risk of lung cancer has been observed in connective tissue disease-associated interstitial lung disease (CTD-ILD) compared to non-CTD-ILD, with an overall incidence of lung cancer of 165.7 and 161.8 per 10,000 person-years in CTD-ILD and ILD-only, respectively (53).

In the ORAL Surveillance trial, tofacitinib was associated with a higher risk of malignancy, and in a post-hoc analysis, the most frequently reported malignancy was lung cancer (54), an aspect which advises

caution in JAKis utilization. The risk appeared higher with tofacitinib 10 mg twice daily *vs.* TNFi but not with the authorized 5 mg two times daily dose (54).
In our literature search, only three papers reported data on lung neoplasia in RA general population, but not in ILD-RA patients (41, 46, 48).
One study of a 3-year post-marketing experience with tofacitinib reported cases of lung neoplasia (0.18%) during follow-up (46). Contrariwise, no significant risk of lung neoplasm was observed in the meta-analysis of Khoo *et al.* (41).
Additionally, we found no study addressing PAH in RA-ILD patients treated with JAKis. This is a critical point since PAH could be secondary to ILD and may be associated with worse ILD outcomes; thus, both conditions should deserve awareness by clinicians.
A recent pharmacovigilance analysis investigated the risk of PAH associated with protein kinase inhibitors, but the analysis focussed on dasatinib, bosutinib, ponatinib, ruxolitinib and nilotinib, disregarding JAKis licensed in rheumatology practice (55). This study raises potential warnings in PAH induction by the protein kinases family (55).
Of importance, most of the marketed JAKis are eliminated *via* the cytochrome P450 enzymatic complex (56). This can lead to drug-to-drug interactions that need to be taken into consideration, especially when concomitant nintedanib use occurs (57). In contrast to other JAKis, baricitinib is mainly cleared by renal elimination through glomerular filtration and active secretion *via* transporters (58), bypassing cytochrome P450 concerns.

Janus kinase inhibitors prescription in rheumatoid arthritis associated with interstitial lung disease, drug retention rate, and incident rates of interstitial lung disease during treatment
In this section, we have evaluated JAKis prescription and retention rates in RA-ILD patients (8, 59, 60); moreover, we have evaluated the incident rate of ILD during JAKi treatment (8, 34, 42, 61-63).
For this purpose, all RA-licensed JAKis except filgotinib are represented in our literature search.
The association between RA-ILD and the use of csDMARDs, bDMARDs and tsDMARDs remains unclear and which b/tsDMARD is safer also remains elusive (64-66). No robust data exist on tsDMARDs prescription in RA-ILD (8, 59), and presumably one of the problems is older age since it is enumerated among the risk factors for ILD.
A recent post-hoc analysis of Citera *et al.* (34), concerning tofacitinib, showed that out of a cohort of 7061 patients, 0.6% presented an ILD event, a percentage stable over time and associated with known risk factors for ILD in RA (*e.g.*, age ≥65 years, smoking habit and DAS28-ESR score). The rate of ILD events showed no dose-dependent association and it was not influenced by monotherapy or combination therapy. Similar data were shown for baricitinib, documenting a low risk of developing ILD during treatment (42). Notably, few studies proved a lower risk of ILD under tofacitinib compared to other drugs during follow-up observation (61, 63). Noteworthy, no study in our literature search proved an increased risk of ILD under JAKi treatment in RA.
Drug retention rate, evaluated as the time until definitive treatment interruption, is one of the most important criteria for judging treatment effectiveness and safety. In a study by Kalyoncu *et al.* (21), RA patients with and without ILD did not differ in terms of retention rate of tofacitinib (p=0.21). A good persistence rate even with baricitinib was observed in a small retrospective search (23).
Supplementary Table 2 summarizes the main findings of the retrieved articles.

Conclusions
ILD significantly impacts therapeutic options, quality of life, morbidity, and mortality of RA patients. Thus, RA-ILD treatment is a challenging issue, and yet little evidence is available. To the best of our knowledge, there are no studies addressing the efficacy and safety issues of JAKi treatment in RA-ILD patients. Monotherapy administration and short half-life in patients with recurrent infections are

important aspects to consider as potentially advantageous in the RA-ILD population. At the same time, worries about adverse events must be solved.
The current work sought to collect presently available data in this research field, suggesting a relevant unmet area of research, to ensure a better management of RA-ILD patients.

References

1. Wang D, Zhang J, Lau J, Wang S, Taneja V, Matteson EL, et al. Mechanisms of lung disease development in rheumatoid arthritis. Nat Rev Rheumatol 2019; 15: 581-96.
2. Yunt ZX, Solomon JJ. Lung disease in rheumatoid arthritis. Rheum Dis Clin North Am 2015; 41: 225-36.
3. Olson AL, Swigris JJ, Sprunger DB, Fischer A, Fernandez-Perez ER, Solomon J, et al. Rheumatoid arthritis-interstitial lung disease-associated mortality. Am J Respir Crit Care Med 2011; 183: 372-8.
4. Hyldgaard C, Hilberg O, Pedersen AB, Ulrichsen SP, Løkke A, Bendstrup E, et al. A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis 2017; 76: 1700-6.
5. Norton S, Koduri G, Nikiphorou E, Dixey J, Williams P, Young A. A study of baseline prevalence and cumulative incidence of comorbidity and extra-articular manifestations in RA and their impact on outcome. Rheumatology 2013; 52: 99-110.
6. Kim D, Cho SK, Choi CB, Choe JY, Chung WT, Hong SJ, et al. Impact of interstitial lung disease on mortality of patients with rheumatoid arthritis. Rheumatol Int 2017; 37: 1735-45.
7. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010; 62: 1583-91.
8. 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.
9. Esposito AJ, Chu SG, Madan R, Doyle TJ, Dellaripa PF. Thoracic manifestations of rheumatoid arthritis. Clin Chest Med 2019; 40: 545-60.
10. Shaw M, Collins BF, Ho LA, Raghu G. Rheumatoid arthritis-associated lung disease. Eur Respir Rev 2015; 24: 1-16.
11. Sparks JA, He X, Huang J, Fletcher EA, Zaccardelli A, Friedlander HM, 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.
12. Wang T, Zheng XJ, Liang BM, Liang ZA. Clinical features of rheumatoid arthritis-associated interstitial lung disease. Sci Rep 2015; 5: 14897.
13. Bradley B, Branley HM, Egan JJ, Greaves MS, Hansell DM, Harrison NK, et al. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax 2008; 63: v1-58.
14. ACR. 2023 Interstitial Lung disease guidelines. Available from: https://rheumatology.org/interstitial-lung-disease-guideline.
15. Narváez J, Díaz Del Campo Fontecha P, Brito García N, Bonilla G, Aburto M, Castellví I, et al. SER-SEPAR recommendations for the management of rheumatoid arthritis-related interstitial lung disease. Part 2: treatment. Reumatol Clin 2022; 18: 501-12.
16. McLornan DP, Pope JE, Gotlib J, Harrison CN. Current and future status of JAK inhibitors. Lancet 2021; 398: 803-16.
17. Kaneko Y. Efficacy and safety of peficitinib in rheumatoid arthritis. Mod Rheumatol 2020; 30: 773-8.

18. FDA. FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death.
19. EMA. EMA's Safety Committee (PRAC). Janus Kinase Inhibitors—PRAC Recommendation. 2022. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/janus-kinase-inhibitors-jaki.
20. Gasparyan AY, Ayvazyan L, Blackmore H, Kitas GD. Writing a narrative biomedical review: considerations for authors, peer reviewers, and editors. Rheumatol Int 2011; 31: 1409-17.
21. Kalyoncu U, Bilgin E, Erden A, Satis H, Tufan A, Tekgoz E, et al. Efficacy and safety of tofacitinib in rheumatoid arthritis-associated interstitial lung disease: tReasure real-life data. Clin Exp Rheumatol 2022; 40: 2071-7.
22. Saldarriaga-Rivera LM, López-Villegas VJ. Janus kinase inhibitors as a therapeutic option in rheumatoid arthritis and associated interstitial lung disease. Report of four cases. Rev Colomb Reumatol 2019; 26: 137-9.
23. Valero Jaimes JA, De Diego Sola A, Alcorta Lorenzo N, Egües Dubuc CA, Belzunegui Otano JM, Uriarte Isacelaya E, et al. Experience in the current practice with baricitinib in patients with rheumatoid arthritis and intersticial lung disease of the donostia university hospital. Ann Rheum Dis 2022; 81: 1289.
24. Venerito V, Manfredi A, Carletto A, Gentileschi S, Atzeni F, Guiducci S, et al. Evolution of rheumatoid-arthritis-associated interstitial lung disease in patients treated with JAK inhibitors: a retrospective exploratory study. J Clin Med 2023; 12: 957.
25. Tardella M, Di Carlo M, Carotti M, Ceccarelli L, Giovagnoni A, Salaffi F. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. Inflammopharmacology 2022; 30: 705-12.
26. Bejarano MV, Tamborenea MN, Goñi M, Saldarriaga L, Pisoni C, Salinas RG, et al. Interstitial lung disease in patients with rheumatoid arthritis treatedwith tofacitinib. J Clin Rheumatol 2020; 78: 12-S3.
27. Tsujii A, Isoda K, Yoshimura M, Nakabayashi A, Kim DS, Tamada T, et al. Janus kinase inhibitors vs. abatacept about safety and efficacy for patients with rheumatoid arthritis-associated interstitial lung disease: a retrospective nested case-control study. BMC Rheumatol 2024; 8: 4.
28. Vacchi C, Manfredi A, Cassone G, Cerri S, Della Casa G, Andrisani D, et al. Tofacitinib for the treatment of severe interstitial lung disease related to rheumatoid arthritis. Case Rep Med 2021; 2021: 6652845.
29. Nishii Y, Okamoto M, Zaizen Y, Kojima T, Nouno T, Naitou-Nishida Y, et al. Successful treatment of a patient with drug-refractory rheumatoid arthritis-associated interstitial lung disease with upadacitinib: a case report. Medicina 2023; 59: 1960.
30. D'Alessandro M, Perillo F, Metella Refini R, Bergantini L, Bellisai F, Selvi E, et al. Efficacy of baricitinib in treating rheumatoid arthritis: modulatory effects on fibrotic and inflammatory biomarkers in a real-life setting. Int Immunopharmacol 2020; 86: 106748.
31. Charaja HJM, Luza ME, Leon DP. Interstitial lung disease improvement in patients with rheumatoid arthritis and tofacitinib. J Clin Rheumatol 2019; 25: S48.
32. Kodera T, Tsutsumi T, Oka Y, Takeda T, Shirota Y, Kameoka J. Two cases of rheumatoid arthritis complicated by organising pneumonia successfully treated with tofacitinib therapy. Mod Rheumatol Case Rep 2021; 5: 218-25.
33. Jeong E, Hong H, Lee YA, Kim KS. Potential rheumatoid arthritis-associated interstitial lung disease treatment and computational approach for future drug development. Int J Mol Sci 2024; 25: 2682.
34. Citera G, Mysler E, Madariaga H, Cardiel MH, Castañeda O, Fischer A, et al. Incidence rates of interstitial lung disease events in tofacitinib-treated rheumatoid arthritis patients: post hoc analysis from 21 clinical trials. J Clin Rheumatol 2021; 27: e482-e90.

35. ClinicalTrials.gov. Effects of tofacitinib vs methotrexate on rheumatoid arthritis interstitial lung disease (PULMORA). ClinicalTrials.gov. Identifier: NCT04311567. Available from: https://clinicaltrials.gov/ct2/show/NCT04311567.
36. ClinicalTrials.gov. Tofacitinib in the treatment of rheumatoid arthritis-related interstitial lung disease. (RAILDTo). ClinicalTrials.gov Identifier: NCT05246293. Available from: https://clinicaltrials.gov/ct2/show/NCT05246293.
37. Tardella M, Di Carlo M, Carotti M, Giovagnoni A, Salaffi F. Abatacept in rheumatoid arthritis-associated interstitial lung disease: short-term outcomes and predictors of progression. Clin Rheumatol 2021; 40: 4861-7.
38. Barbero MAN, Font CV, Alcala MC, Urgelles JF, Bobillo JR, Nuñez DF, et al. Rituximab improves interstitial lung disease in rheumatoid arthritis patients. Eur Respir J 2017; 50: PA893.
39. Manfredi A, Cassone G, Furini F, Gremese E, Venerito V, Atzeni F, et al. Tocilizumab therapy in rheumatoid arthritis with interstitial lung disease: a multicentre retrospective study. Intern Med J 2020; 50: 1085-90.
40. He C, Li W, Xie Q, Yin G. Rituximab in the treatment of interstitial lung diseases related to anti-melanoma differentiation-associated gene 5 dermatomyositis: a systematic review. Front Immunol 2021; 12: 820163.
41. Khoo JK, Barnes H, Key S, Glaspole IN, Östör AJ. Pulmonary adverse events of small molecule JAK inhibitors in autoimmune disease: systematic review and meta-analysis. Rheumatology 2020; 59: 2217-25.
42. Salvarani C, Sebastiani M, Dieude P, Garcia M, Deberdt W, Rogai V, et al. Baricitinib and the risk of incident interstitial lung disease: a descriptive clinical case report from clinical trials. Rheumatol Ther 2021; 8: 1435-41.
43. Mimori T, Harigai M, Atsumi T, Kuwana M, Takei S, Tamura N, et al. Post-marketing surveillance of tofacitinib in Japanese patients with rheumatoid arthritis: an interim report of safety data. Arthritis Rheumatol 2017; 69: 431.
44. Balanescu AR, Citera G, Pascual-Ramos V, Bhatt DL, Connell CA, Gold D, et al. Infections in patients with rheumatoid arthritis receiving tofacitinib versus tumour necrosis factor inhibitors: results from the open-label, randomised controlled ORAL Surveillance trial. Ann Rheum Dis 2022; 81: 1491-503.
45. Chopra A, Shobha V, Chandrashekara S, Veeravalli SCM, Sharma R, Rao UR, et al. Tofacitinib in the treatment of Indian patients with rheumatoid arthritis: a post hoc analysis of efficacy and safety in phase 3 and long-term extension studies over 7 years. Int J Rheum Dis 2020; 23: 882-97.
46. Cohen S, Curtis JR, DeMasi R, Chen Y, Fan H, Soonasra A, et al. Worldwide, 3-year, post-marketing surveillance experience with tofacitinib in rheumatoid arthritis. Rheumatol Ther 2018; 5: 283-91.
47. Montero P, Milara J, Roger I, Cortijo J. Role of JAK/STAT in interstitial lung diseases; molecular and cellular mechanisms. Int J Mol Sci 2021; 22: 6211.
48. Cronin O, McKnight O, Keir L, Ralston SH, Hirani N, Harris H. A retrospective comparison of respiratory events with JAK inhibitors or rituximab for rheumatoid arthritis in patients with pulmonary disease. Rheumatol Int 2021; 41: 921-8.
49. Matsuno H, Atsumi T, Takei S, Tamura N, Harigai M, Fujii T, et al. Safety of baricitinib under clinical settings in patients with rheumatoid arthritis, using data from all-case post-marketing surveillance and spontaneous reports. Arthritis Rheumatol 2019; 71: 4197-8.
50. Moreno Herrera A, Garcia Marin J, Fages M, Martinez-Echevarria Gil-Delgado Z, Luna Reina RM. Effectiveness and safety of baricitinib and tofacitinib in rheumatoid arthritis in clinical practice. Eur J Hospital Pharm 2022; 29: A76.
51. Azadeh N, Limper AH, Carmona EM, Ryu JH. The role of infection in interstitial lung diseases: a review. Chest 2017; 152: 842-52.

52. Farooqui H, Jit M, Heymann DL, Zodpey S. Burden of severe pneumonia, pneumococcal pneumonia and pneumonia deaths in Indian states: modelling based estimates. PLoS One 2015; 10: e0129191.
53. Choi WI, Lee DY, Choi HG, Lee CW. Lung cancer development and mortality in interstitial lung disease with and without connective tissue diseases: a five-year Nationwide population-based study. Respir Res 2019; 20: 117.
54. Curtis JR, Yamaoka K, Chen YH, Bhatt DL, Gunay LM, Sugiyama N, et al. Malignancy risk with tofacitinib versus TNF inhibitors in rheumatoid arthritis: results from the open-label, randomised controlled ORAL Surveillance trial. Ann Rheum Dis 2023; 82: 331-43.
55. Cornet L, Khouri C, Roustit M, Guignabert C, Chaumais MC, Humbert M, et al. Pulmonary arterial hypertension associated with protein kinase inhibitors: a pharmacovigilance-pharmacodynamic study. Eur Respir J 2019; 53: 1802472.
56. Ogura T, Taniguchi H, Azuma A, Inoue Y, Kondoh Y, Hasegawa Y, et al. Safety and pharmacokinetics of nintedanib and pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2015; 45: 1382-92.
57. Veeravalli V, Dash RP, Thomas JA, Babu RJ, Madgula LMV, Srinivas NR. Critical assessment of pharmacokinetic drug-drug interaction potential of tofacitinib, baricitinib and upadacitinib, the three approved janus kinase inhibitors for rheumatoid arthritis treatment. Drug Saf 2020; 43: 711-25.
58. Alim K, Bruyère A, Lescoat A, Jouan E, Lecureur V, Le Vée M, et al. Interactions of janus kinase inhibitors with drug transporters and consequences for pharmacokinetics and toxicity. Expert Opin Drug Metab Toxicol 2021; 17: 259-71.
59. Carrasco Cubero C, Chamizo Carmona E, Vela Casasempere P. Systematic review of the impact of drugs on diffuse interstitial lung disease associated with rheumatoid arthritis. Reumatol Clin 2020; S1699-258X(20)30111-X.
60. 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.
61. Xie F, Annapureddy N, Chen L, Lobo JL, Oates JC, Shah A, et al. Rheumatoid arthritis and the risk for interstitial lung disease: a comparison of risk associated with biologic and conventional DMARDs. Arthritis Rheumatol 2017; 69: 137.
62. Takagi M, Atsumi T, Matsuno H, Tamura N, Fujii T, Okamoto N, et al. Safety and effectiveness of baricitinib for rheumatoid arthritis in Japanese clinical practice: 24-week results of all-case post-marketing surveillance. Mod Rheumatol 2023; 33: 647-56.
63. Baker MC, Liu Y, Lu R, Lin J, Melehani J, Robinson WH. Incidence of interstitial lung disease in patients with rheumatoid arthritis treated with biologic and targeted synthetic disease-modifying antirheumatic drugs. JAMA Netw Open 2023; 6: e233640.

Online supplementary material:
Supplementary Table 1. Key features of the selected studies.
Supplementary Table 2. Key features of the selected studies concerning Janus kinase inhibitor (JAKi) prescription in rheumatoid arthritis associated with interstitial lung disease (ILD), JAKis retention rate, and incident rates of ILD during JAKi treatment.

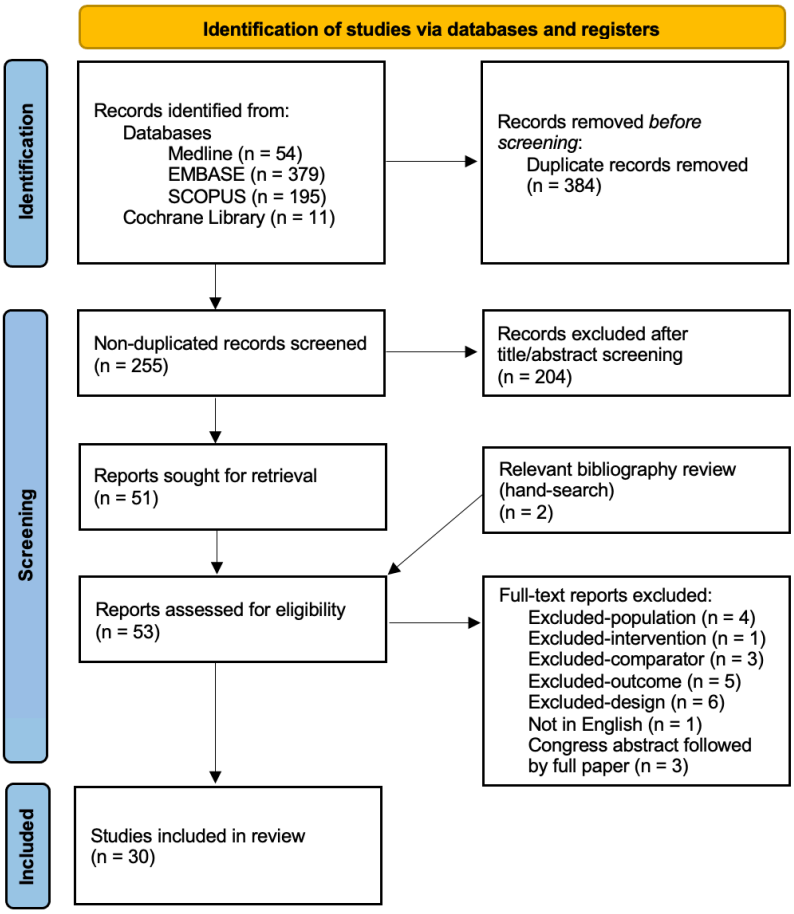

Figure 1. Flow diagram describing the inclusion decision of papers for this review.

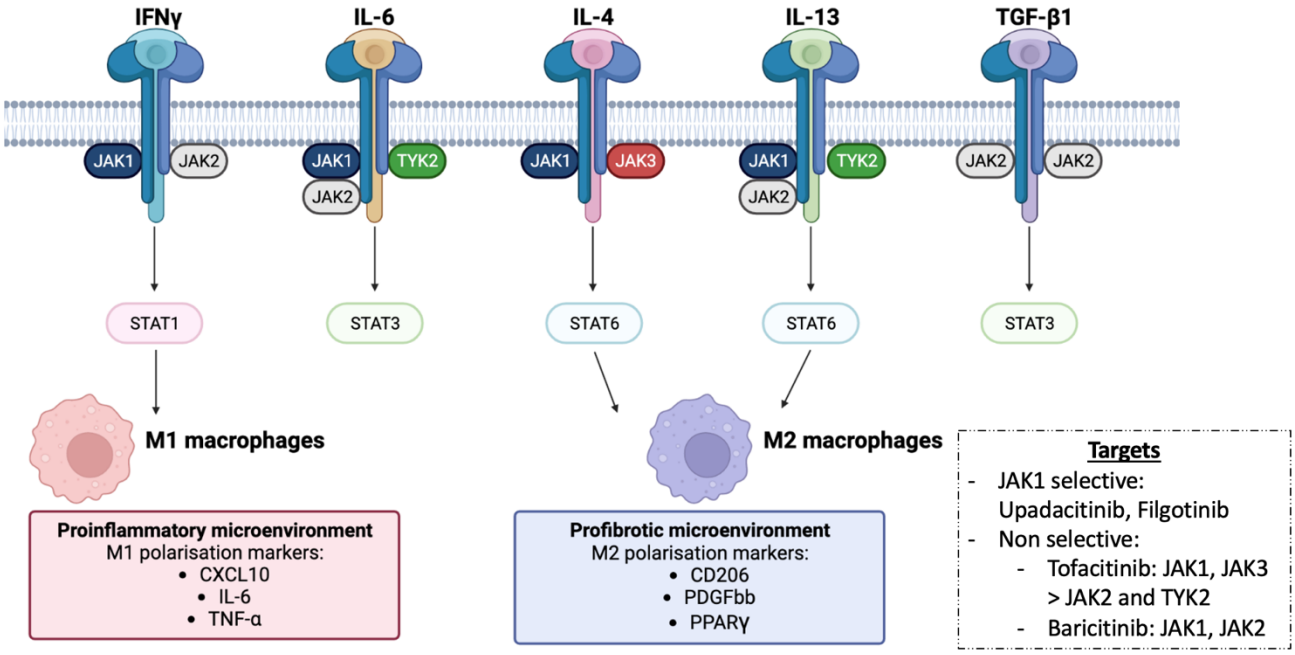

Figure 2. Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathways in ILDs, leading to pro-inflammatory and pro-fibrotic microenvironments. JAK/STAT pathways employs second messengers to transfer extracellular information to the nucleus in order to catalyze gene expression and cellular responses. JAK are four intracellular tyrosine kinases (JAK1, JAK2, JAK3, TYK2). The biological effects of interleukin (IL)-4, IL-6, IL-13, other proinflammatory mediators, such as tumor necrosis factor-α (TNFα) and interferon-γ, and growth factor, namely Transforming growth factor β are mediated through JAK/STAT pathways, many of which have pivotal functions in lung homeostasis. Here are the different JAKs and STATs modulating both pro-inflammatory M1 macrophages and profibrotic M2 macrophages in ILDs. The image was created with BioRender (accessed on 17 March 2024). CD206, cluster of differentiation 206; CXCL10, CXC motif chemokine 10; IFN-γ, interferon-γ; IL, interleukin; JAK, Janus tyrosine kinase; PPAR-γ, platelet-derived growth factor-BB human; STAT, signal transducers and activators of transcription; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor.