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SUPPLEMENTARY MATERIAL

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

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Supplementary Table 1. Key features of the selected studies.

Author, year	Design	Population (n of patients)	Drug	Objectives	Main results
Efficacy of JAKis in RA-ILD					
(1)	Retrospective (conference abstract)	RA-ILD (15)	TOF 10 mg daily	Evolution of symptoms, lung functional data, HRCT	No worsening, but stability of dyspnea and PFTs during a 12-month follow up (4 patients out of 15, 26.6%, improved from PFTs baseline parameters).
(2)	Case series (conference abstract)	RA-ILD (3)	TOF	Clinical and imaging outcomes	Improvement of respiratory symptoms and HRCT during follow up (no data on follow up duration).
(3)	Retrospective	RA (15)	BAR	Detect changes in lung function parameters, serum inflammatory and fibrotic biomarkers	Increase in DLCO and KCO percentage after 6 months of therapy, reduction of KL-6 levels in RA-ILD patients during 6-months follow up.
(4)	Prospective	RA-ILD (47), RA (387)	TOF	Efficacy and safety of TOF	Average stability of PFTs during a 12-month follow up, similar retention rate between groups (RA-ILD vs RA). In RA-ILD group the most common cause of discontinuation was infection (no data on type of infections, 5 patients out of 47, 10.63%).
(5)	Case report	RA-ILD (2)	TOF	Outcome of refractory RA-ILD OP phenotype	OP and RA well controlled, GCs successfully tapered.
(6)	Case series	RA-ILD (3)	TOF	Assess TOF efficacy and safety	No exacerbation of ILD.
(7)	Retrospective	RA-ILD (75)	JAKis (not specified separately), ABA	Assess JAKis vs ABA efficacy in RA-ILD	Both JAKis and ABA proved stability or improvement of RA-ILD based on Borg dyspnea index and PFTs during 18-months follow up.
(8)	Case report	RA-ILD (1)	TOF	Assess TOF efficacy	Stability of respiratory symptoms and PFTs, good safety profile, preventing from frequent infections

					which occurred with previous therapies (TCZ, RTX) (no data on mean duration of follow up).
(9)	Retrospective (conference abstract)	RA-ILD (17)	BAR	Long term retention rate, efficacy and safety of BAR	Good retention rate (59%), safety of drugs, stability of PFTs volumes (no data on mean duration of follow up).
(10)	Retrospective	RA-ILD (43)	JAKis (BAR, FIL, TOF, UPA)	Efficacy and safety of JAKis	Stability of PFTs and HRCT (median follow-up duration 19.1 months), improvement of DLCO in 2 out of 25 patients (of which data were available), 8%, improvement of HRCT in 2 out of 43 patients, 4.65%.
(11)	Case report	RA-ILD (1)	UPA	Assess UPA efficacy	Improvement of PFTs and no signs of ILD worsening
(12)	Retrospective	RA-ILD (71)	JAKis (TOF, BAR), ABA	Assess JAKis vs ABA efficacy in RA-ILD	JAKi is as safe and effective as ABA
(13)	Ongoing RCT	RA-ILD	TOF, MTX	Efficacy of TOF compared to MTX on ILD at 24 weeks	Ongoing
(14)	Ongoing RCT	RA-ILD	TOF	Assess TOF efficacy	Ongoing
Safety and pulmonary adverse events of JAKis					
(15)	RCT	RA (4362)	TOF (5 mg and 10 mg twice daily regimens), TNFis	Assess TOF vs TNFis safety concerning infections	More infections with TOF vs TNFis in RA patients, concerning pneumonia events: - 6.5% in TOF 5 mg twice daily group - 6.9% in TOF 10 mg twice daily group - 5.4% in TNFis group (no distinction between TNFis drugs).
(16)	Post hoc analysis	RA (197)	TOF	Assess TOF efficacy and safety	Good efficacy and safety data in RA patients. Low incidence of ILD (1 out of 197 patients, 0.5%) only with TOF 10 mg twice daily.
(17)	Post marketing surveillance	RA (34223)	TOF	Assess TOF safety	No safety risk in real-world RA setting. 229 lung infections, 207 respiratory adverse events (estimated RR 0.60 per 100 patients/year), of which 9 ILD (4.34%), but 2 patients reported pre-existing ILD.
(18)	Retrospective	RA-associated	BAR, TOF, RTX	Assess pulmonary safety of JAKis vs	No increase in hospitalization rate or death due to respiratory causes in JAKis group compared to RTX

		ILD or bronchiectasis (47)		RTX in patients with concurrent ILD or bronchiectasis	group during follow up (mean duration of follow-up for patients receiving JAKis: 1.1 years, SD = 0.62, and for patients receiving RTX: 2.14 years, SD = 1).
(19)	Systematic review and meta-analysis	Autoimmune diseases, among which RA (29758)	BAR, FIL, TOF, UPA vs placebo, MTX, ADA	Assess JAKis safety concerning pulmonary adverse events	JAKis increase the risk of non-opportunistic respiratory infections compared with placebo. Low risk of serious pulmonary adverse events.
(20)	Post marketing report (conference abstract)	RA (1288)	BAR	Assess BAR safety	Low incidence of pneumonia (8 out of 1288 patients, 0.62%) and ILD (2 out of 1288 patients, 0.15%).
(21)	Post-marketing interim analysis (conference abstract)	RA (3929)	TOF	Assess TOF safety	Serious infections within the range reported in post-marketing surveillance of biologic treatments. Low incidence of pneumonia (33 out of 3929 patients, 0.83%).
(22)	Retrospective (conference abstract)	RA (32)	BAR, TOF	Assess BAR and TOF safety	BAR and TOF effective and safe in RA management. Low incidence of ILD (1 out of 32 patients, 3.12%, in BAR cohort).
JAKis prescription in RA-ILD, retention rate and incident rates of ILD during treatment					
(23)	Retrospective registry study	RA-ILD (85175)	DMARDs	Prevalence of DMARD prescription in RA-ILD patients	Patients with ILD are less frequently prescribed MTX, more frequently GCs and bDMARDs, especially ABA, RTX, TCZ and also JAKis, but not TNFis. Incident ILD was 0.13%–0.21% per year and remained stable over time. No association between ILD and JAKis therapy.
(24)	Retrospective	RA (28559)	ADA, ABA, RTX, TCZ, TOF	Incidence rates of ILD in RA patients undergoing b/tsDMARDs treatment	Lower incidence of ILD with TOF, compared to other bDMARDs.

(25)	Systematic review	-	All DMARDs	Impact of all DMARDs on RA-ILD	No evidence of MTX and LEF worsening ILD. RTX and ABA show more ILD stabilization (and sometimes improvement) compared to TNFis. Scarce data for tsDMARDs.
(26)	Post hoc analysis	RA (7061)	TOF (5 mg and 10 mg twice daily regimens)	Incidence rates of ILD in TOF 5 mg or 10 mg twice daily vs placebo	Incidence rates of 0.18 per 100 patients-years in TOF group, and ILD events were associated with known risk factors for ILD in RA.
(27)	Registry study	RA-ILD (159), RA (477)	b/tsDMARDs	Long term retention rate and safety of b/tsDMARDs	Lower b/tsDMARDs retention rate in RA-ILD group compared to RA group.
(28)	Retrospective	RA (3770)	BAR	Incidence rates of ILD	Low incidence of ILD (21 out of 3770 patients, 0.55%).
(29)	Post marketing report	RA (4731)	BAR	Assess BAR efficacy and safety	Low incidence of ILD (13 out of 4731 patients, 0,27%).
(30)	Retrospective	RA (150225)	csDMARDs, b/tsDMARDS	Incidence rates of ILD	Lower incidence of ILD with TOF, compared to other bDMARDs.

ABA, abatacept; ADA, adalimumab; BAR, baricitinib; DLCO, diffusing capacity of the ung for carbon monoxid; DMARDs, disease-modifying antirheumatic drugs; bDMARDs, biologic disease-modifying antirheumatic drugs, tsDMARDs, targeted synthetics disease-modifying antirheumatic drugs; FIL, filgotinib; GCs, glucocorticoids; HRCT, high resolution chest tomography; ILD, interstitial lung disease; JAKis, Janus kinase inhibitors; KCO, carbon monoxide transfer coefficient; LEF, leflunomide; MTX, methotrexate; PFTs, pulmonary function tests; RA, rheumatoid arthritis; RCT, randomized controlled trial; RD, risk difference; RR, risk ratio; RTX, rituximab; SD, standard deviation; TCZ, tocilizumab; TNFis, tumor necrosis factor inhibitors; TOF, tofacitinib; UPA, upadacitinib.

References

1. 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.
2. Charaja HJM, Luza ME, Leon DP. Interstitial lung disease improvement in patients with rheumatoid arthritis and tofacitinib. J Clin Rheumatol 2019; 25: S48.
3. 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.
4. 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.

5. 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.
6. 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.
7. 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.
8. 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.
9. 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.
10. V 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.
11. 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.
12. 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.
13. 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..
14. 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.
15. 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.
16. 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.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.

22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.
29. 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.
30. 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.

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.

ILD incidence rates during JAKi treatment	
Mean duration of follow up	
No data (*n* of articles)	4 [1-4]
24 weeks (*n* of articles)	1 [5]
1.6 years (*n* of articles)	1 [6]
Comparison	
No data on JAKi molecule (*n* of articles)	1 [1]
TOF (5 or 10 mg twice daily) vs placebo (*n* of articles)	1 [2]
TOF (no data on dose), ADA, ABA, RTX, TCZ (*n* of articles)	2 [4, 6]
BAR (2 and 4 mg twice daily) (*n* of articles)	1 [5]
BAR (from 2 to 8 mg daily) (*n* of articles)	1 [3]
Outcome	
No association between ILD and JAKis therapy (*n* of articles)	4 [1-3, 5]
Lower incidence of ILD with JAKis compared to other drugs (*n* of articles)	2 [4, 6]

ABA, abatacept; ADA, adalimumab; BAR, baricitinib; CER, certolizumab; ETA, etanercept; GOL, golimumab; HCQ, hydroxychloroquine; ILD, interstitial lung disease; INF, infliximab; JAKis, Janus kinase inhibitors; LEF, leflunomide; MTX, methotrexate; RA, rheumatoid arthritis; RTX, rituximab; SD, standard deviation; SSZ, sulfasalazine; UIP, usual interstitial pneumonia; UPA, upadacitinib; TNFi, tumor necrosis factor inhibitors; TCZ, tocilizumab; TOF, tofacitinib.

References

1. 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.
2. 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.
3. 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.
4. 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.

5. 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.
6. 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.