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ORIGINAL RESEARCH

Evaluation of rheumatoid arthritis-associated interstitial lung disease in patients treated with JAK inhibitors: a MAJIK-SFR cohort study

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ABSTRACT

Objective To examine the course of interstitial lung disease associated with rheumatoid arthritis (RA-ILD) in France on treatment with Janus kinase inhibitors (JAKis) using the MAJIK-SFR registry.

Methods Prospective national multicentre observational study identifying patients with RA-ILD from the MAJIK-SFR registry. Pulmonary assessment data were collected at JAKi initiation and follow-up visits (6 months, 12 months and a median of 21 months postinclusion), including chest high-resolution CT (HRCT), pulmonary function tests (forced vital capacity (FVC) and diffusing capacity of the lungs for carbon monoxide (DLCO)), acute exacerbations of ILD, respiratory infections and lung cancers.

Results We enrolled 42 patients (26 women, 62%) with RA-ILD with a mean age of 61±13 years and a mean disease duration of 16±10 years. Compared with the 778 RA patients without ILD from the MAJIK registry, RA-ILD patients were older, displayed more severe and active disease and had more prevalent comorbidities. Non-specific interstitial pneumonia and usual interstitial pneumonia accounted for 46% and 43% of the chest HRCT ILD patterns, respectively. No significant changes in FVC and DLCO were observed during the follow-up period. Chest HRCT lesions remained stable in 69% of patients. Progressive ILD was identified in 8 patients (19%). 16 (38%) respiratory tract infections were observed. Only one acute regressive exacerbation of ILD was noted, and no lung cancer was diagnosed. No deaths occurred. JAKi was discontinued in 17 patients including 8 for inefficacy on joint involvement and 5 for intolerance.

Conclusion The analysis indicates stability of RA-ILD in patients treated with JAKi. The tolerance profile of JAKi in this higher risk population did not reveal new safety signal.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Janus kinase inhibitors (JAKis) are an emerging class of targeted therapies primarily used in rheumatoid arthritis (RA). While they are effective in controlling RA's systemic inflammation, their impact on RA-associated interstitial lung disease (RA-ILD) is not as well established. Case reports and smaller observational studies suggest that JAKis may stabilise lung function and pulmonary symptoms in RA-ILD patients, but data is still emerging.

WHAT THIS STUDY ADDS

⇒ This national study provides a detailed description of RA-ILD patients treated with JAKis in France, including demographics, disease characteristics and treatment history. It shows stability in lung function parameters (forced vital capacity, diffusing capacity of the lungs for carbon monoxide) over a median follow-up of 21 months combined with a good therapeutic response on joint involvement. High-resolution CT lesions remained stable in 62% of patients, while 19% showed progression of ILD. No new safety signals were identified, with respiratory tract infections being the most common adverse events observed.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The results suggest that JAKis could be a viable treatment option for managing both systemic RA symptoms and the pulmonary complications associated with RA-ILD.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is characterised by joint inflammation and destruction. It affects approximately 0.5% of the adult population in Western countries.[1] In addition to joint involvement, RA can affect several organs and systems through the development of extra-articular manifestations. Pulmonary involvement in RA has recently attracted increasing interest, particularly interstitial lung disease (ILD), which represents one of the most severe extra-articular manifestations and can lead to progressive respiratory failure.[2] ILD occurs in about 6% of RA patients, resulting in a worse prognosis and mortality.[3–5] The management and treatment of RA-ILD are challenging due to the paucity of available information and the absence of dedicated clinical trials on the topic. However, this aspect is increasingly considered by guidelines.[6] The advent of targeted biologic or synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) has significantly altered the course of RA, markedly improving the control of synovitis and, consequently, reducing joint destruction and physical disability.[7 8] Janus kinase inhibitors (JAKis) are a class of tsDMARDs. These small molecules are orally administered and inhibit the activity of JAK, tyrosine kinase proteins that are involved in signal transduction of the JAK/signal transducer and activator of transcription (JAK/STAT) pathway, which is involved in critical cell functions, including survival, growth and differentiation. JAKi have demonstrated efficacy in the treatment of RA, either alone or in combination with methotrexate.[9 10] The safety and tolerability of JAKis in patients with RA-ILD remain poorly understood. This is evidenced by the limited data available in the literature. New data are emerging in favour of tofacitinib, the longest-used JAKi, which may slow the progression of ILD associated with connective tissue diseases.[11–13] This study aimed to examine the course of RA-ILD on JAKi together with their lung tolerance, using the French 'MAJIK-SFR' registry.

METHODS

Study design

This is an observational prospective study based on the 'MAJIK-SFR' registry. The MAJIK-SFR registry is a nationwide, multicentre, prospective study (NCT04602091) including adult patients initiating JAKis for RA, axial spondyloarthritis and psoriatic arthritis at 68 rheumatology centres in France that have been ongoing since October 2019. Treatment was chosen by the recruiting physicians, and patients are being followed up for 5 years, even if they change treatment during this time.

Inclusion and exclusion criteria

In June 2023, we selected patients with RA from the MAJIK registry with a pre-existing diagnosis of ILD, as defined by the presence of suggestive lung abnormalities (including ground-glass opacities, reticulations, honeycombing and traction bronchiectasis) on chest high-resolution CT (HRCT) scans performed prior to their entry into the registry. We excluded patients presenting other RA-related or non-related lung diseases.

Setting and data collection

Data were gathered at JAKi initiation and follow-up visits (6 months, 12 months and a median of 21 months postinclusion). They included demographic parameters (age, sex, smoking, body mass index (BMI)), RA characteristics (disease duration, antibody status, structural damages, extra-articular manifestations, current and past medication use, tender and swollen joints, Disease Activity Score-28 (DAS-28) with C reactive protein (CRP)) and ILD evaluation (dyspnoea, need for oxygen therapy, ILD pattern on HRCT, pulmonary function including forced vital capacity (FVC) and six-minute walk test).

Outcomes

The primary endpoint was the analysis of the change in FVC and diffusing capacity of the lungs for carbon monoxide (DLCO) between the inclusion visit (corresponding to the date of JAKi initiation) and evaluation at months 3, 6 and 12 and at the last follow-up date.

Secondary endpoints included the comparison of baseline characteristics of the 42 RA-ILD patients with 778 RA patients without ILD from the MAJIK registry with complete, cleaned and validated data. Outcomes include the course of ILD on chest HRCT (improvement, stability or progression according to the local expert radiologist) at months 3, 6 and 12 and at the last follow-up date, and the occurrence of ILD progression defined by a progressive worsening of FVC by more than 5% during follow-up and worsening of ILD lesions on chest HRCT according to the local expert radiologist or of their respiratory symptoms (worsening of the Borg dyspnea score). We also collected the analysis of JAKi discontinuations and respiratory (ILD exacerbation, respiratory infections, lung cancer) and extra-respiratory (other infections including herpes zoster, major cardiovascular events, venous thromboembolism, death) tolerance of JAKi in RA-ILD.

Statistical analysis

Quantitative variables were expressed as means±SD or median (95% CI), or numbers and percentages. Statistical analysis was performed using GraphPad Prism (V.9.1.2) and XLSTAT 2023.1.6.1410 softwares. Data were compared with χ^2 test or Fisher exact test (for qualitative variables) and with Mann-Whitney (for quantitative variables). An analysis of the power of our sample has been performed to determine its ability to detect the minimum annual decline in FVC in the general population: 33 patients were necessary to detect a minimal annual difference of 57 mL with a power of 0.8 and 44 with a power of 0.9. The course of FVC, DLCO and DAS-28 CRP at successive times was evaluated by the Wilcoxon matched-pairs signed rank test. Cox proportional hazards model was

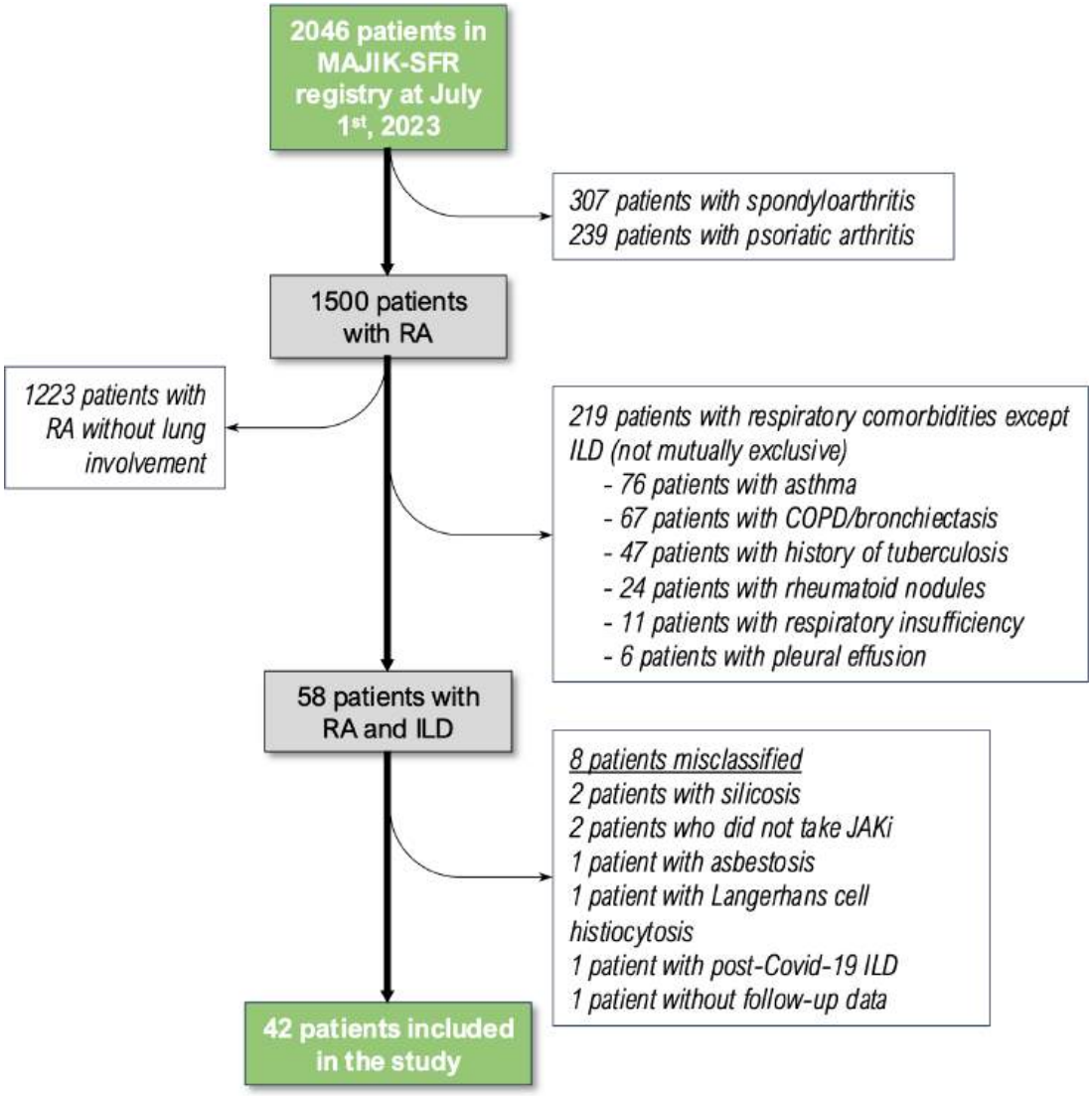

Figure 1 Flow chart of the study. ILD, interstitial lung disease; JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis, COPD: chronic obstructive pulmonary disease.

generated to identify predictive factors for ILD progression. A p value <0.05 was considered as significant.

Ethics

The protocol and the informed consent document have received Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval before the initiation of the study ('Comité de Protection des Personnes' Sud-Méditerranée II). All patients agreed to participate in this study after written informed consent, which was recorded in the medical source file.

RESULTS

On 1 July 2023, from the 2046 patients included in the MAJIK-SFR registry, 1500 patients had RA. We identified 277 patients with RA and respiratory diseases, including 58 with RA-ILD. After the analysis of medical history, we finally included 42 patients with RA-ILD receiving JAKi (18 baricitinib, 11 upadacitinib, 9 tofacitinib and 4 filgotinib) (figure 1).

Study population

These patients were mainly women (n=26, 62%) with a mean age of 61 years (SD: 13 years). BMI was 27.7 kg/m² (SD 4.1 kg/m²), including 12 (29%) with a BMI >30 kg/m². 20 patients (48%) had a history of smoking including 13 (31%) with active smoking. Mean disease duration was 16 years (SD: 10 years); positive rheumatoid factor and anti-citrullinated protein antibodies (ACPA) were detected in 37/41 (90%) and 39/41 (95%), respectively; 29 (69%) had bone erosions and 12 (29%) had at least one extra-articular manifestation other than ILD (table 1). Regarding background therapy in association with JAKi, 27/36 (75%) patients received conventional synthetic DMARDs, including 21/36 (58%) on methotrexate, and 28/36 (78%) were treated with a low dose of corticosteroids (<10 mg/day). The mean number of prior targeted therapies was 4.4 (SD 2.6). Mean DAS28-CRP at JAKi initiation was 4.7 (SD 1.5), and disease activity was significantly reduced on JAKi, with a significant decrease in DAS28-CRP at 6 months (−1.3 points, p=0<0.001) and

Table 1 Baseline characteristics of RA-ILD patients and comparison with non-RA-ILD from the MAJIK registry

	RA-ILD (n=42)	Non-RA-ILD (n=778)	P value*
Baseline demographics			
Age (years), mean±SD	61±13	58±14	0.18
Women, n (%)	26 (62)	553 (71)	0.21
Baseline disease characteristics			
Disease duration (years), mean±SD	16±10	12±10	0.012
Positive rheumatoid factor, n (%)	37/41 (90)	546 (70)	0.005
Positive anti-CCP2 antibodies, n (%)	39/41 (95)	531 (68)	<0.001
Erosions on hand/foot X-rays n (%)	29 (69)	379 (49)	0.017
Extra-articular manifestations	12 (29)	91 (12)	0.001
Baseline disease activity:			
Tender joints, mean±SD	9.8±7.1*	6.1±6.1	<0.001
Swollen joints, mean±SD	4.9±5.0*	4.5±4.6	0.58
DAS28-CRP, mean±SD	4.7±1.5*	4.2±1.4	0.025
CRP (mg/L), mean±SD	16.8±20.5	11.6±19.6	0.095
Baseline comorbidities			
Active smokers/former smokers, n (%)	13 (31) / 7 (17)	148 (19) / 156 (20)	0.058/0.63
High blood pressure, n (%)	15 (36)	205 (26)	0.20
Diabetes mellitus, n (%)	7 (17)	61 (8)	0.042
Hypercholesterolaemia, n (%)	7 (17)	114 (15)	0.72
BMI, kg/m^2, mean±SD	27.7±4.1	NA	–
BMI>30 kg/m^2, n (%)	12 (29)	114 (15)	0.015
Atherosclerotic cardiovascular disease, n (%)	3 (7)	41 (5)	0.57
History of venous thromboembolism, n (%)	1 (2.5)	15 (2)	0.82
History of severe infection, n (%)	3 (7)	46 (6)	0.79
History of herpes zoster, n (%)	2 (5)	35 (5)	>0.99
Previous neoplasia, n (%) (solid/haemopathy)	7 (17) / 1 (2.5)	53 (7) / 23 (3)	0.017/0.86
Treatments received at baseline JAKI received			
Baricitinib, n (%)	18 (43)	357 (46)	0.70
Tofacitinib, n (%)	9 (21)	127 (16.5)	0.39
Upadacitinib, n (%)	11 (26)	244 (31.5)	0.58
Filgotinib, n (%)	4 (10)	50 (6)	0.64
Current corticosteroid use, n (%)	28 (78)	174 (22)	<0.001
Current csDMARD use, n (%)	25 (59)	258 (33)	0.001
Current MTX use, n (%)	21 (50)	227 (29)	0.006
Number of previous targeted therapies			
One, n (%)	6 (14)	159 (20)	0.28
Two, n (%)	3 (7)	144 (19)	0.050
Three, n (%)	5 (12)	99 (13)	0.85
>3, n (%)	28 (67)	159 (21)	<0.001
Previous targeted therapies			
TNF inhibitors, n (%)	22 (52)	478 (61)	0.15
Rituximab, n (%)	19 (45)	136 (17)	<0.001

Continued

Table 1 Continued

	RA-ILD (n=42)	Non-RA-ILD (n=778)	P value*
IL-6 receptor inhibitors, n (%)	19 (45)	273 (35)	0.24
Abatacept, n (%)	26 (62)	243 (31)	<0.001

*Available for 38 patients.
BMI, body mass index; CRP, C reactive protein; csDMARDs, conventional synthetic disease-modifying anti-rheumatic drugs; DAS28, Disease Activity Score-28 ; DAS-28, Disease Activity Score-28; JAKi, Janus kinase inhibitor; MTX, methotrexate; RA-ILD, rheumatoid arthritis-associated interstitial lung disease.

12 months (−1.35 points, p<0.001) (online supplemental figure S1). Disease characteristics and comorbidities are detailed in table 1.

Compared with the 778 RA patients without ILD from the MAJIK registry, for whom data were validated and consolidated, RA-ILD patients were older, presented a higher frequency of rheumatoid factor and ACPA positivity, displayed more severe, active and refractory disease, had more prevalent comorbidities, were more frequently treated with corticosteroids and csDMARDs in combination with the JAKi and have received more likely rituximab and abatacept as previous therapies (table 1).

Characteristics of RA-ILD at baseline

The mean time since ILD diagnosis was 4 years (SD 2 years). At baseline, 17/36 patients (47%) presented with dyspnoea, 10/37 patients (27%) with cough and 2 patients (5%) were on long-term oxygen therapy. Non-specific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) accounted for 46% (n=16) and 43% (n=15) of the chest HRCT ILD patterns, respectively. Two patients were receiving nintedanib. Pulmonary function tests (PFTs) were available for 36 patients; the median FVC was 3.20 L (95% CI 2.91 to 3.47 L) and the median DLCO was 65% (95% CI 53%–69%). Six-minute walk test showed a functional limitation with a median distance walked of 390 m (95% CI 338 to 510 m) (table 2).

Outcome of RA-ILD treated with JAKi

Overall stability of FVC was observed during follow-up (figure 2A). At 12 months, median FVC was 3.12 L (95% CI 2.30 to 3.56 L) compared with 3.20 L (95% CI 2.91 to 3.47 L) at inclusion (p=0.38). Median FVC measured at the end of follow-up (median follow-up 21 months) was 3.03 L (95% CI 2.83 to 3.58 L), not significantly different from FVC at inclusion (p=0.34).

DLCO also remained stable over time (figure 2B): median DLCO measured at 12 months (63%, 95% CI 52%–71%) did not significantly differ from the value measured at inclusion (65%, 95% CI 53%–69%, p=0.21). At the end of follow-up, median DLCO was 60% (95% CI 35%–77%), not significantly different from the value measured at inclusion (p=0.75).

Chest HRCT lesions remained stable in 29 patients (69%). Regression of chest HRCT lesions (three NSIP and two organising pneumonia) was observed in five patients (12%), associated with an improvement of more than 5% in the initial FVC value at the last assessment. This was accompanied by an improvement in joint disease activity (decrease in median DAS28-CRP from 4.06 to 2.01). These patients had not received any antifibrosing therapy.

Progressive ILD was identified during follow-up in 8 patients (including three NSIP and three UIP) receiving JAKi (19%). Three were newly treated with nintedanib for fibrosis. This pulmonary progression contrasted with therapeutic efficacy on joint involvement, with a decrease in median DAS28-CRP from 4.29 to 2.30 (p<0.001). Univariate Cox proportional hazards analyses identified higher age at ILD diagnosis, active smoking, presence of extra-articular involvement and lower baseline DLCO as predictive factors for the progression of RA-ILD (table 3) in this population.

Table 2 Baseline characteristics of ILD

	RA-ILD (n=42)
Time since ILD diagnosis, mean±SD	4±2
Dyspnoea (n=36), n (%)	17(47)
Cough (n=37), n (%)	10 (27)
Long-term oxygen therapy, n (%)	2 (5)
Chest HRCT pattern	
Non-specific interstitial pneumonia, n (%)	16 (46)
Usual interstitial pneumonia, n (%)	15 (43)
Pulmonary function tests (n=36)	
TLC, median (95% CI)	4.87 (4.40–5.75)
FVC (L), median (95% CI)	3.20 (2.91–3.47)
DLCO (%),median (95% CI)	65 (53–69)
DLCO/AV, median (95% CI)	76 (54–96)
Median distance (m), median (95% CI)	390 (338–510)

AV, alveolar volume; DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution CT; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; TLC, total lung capacity.

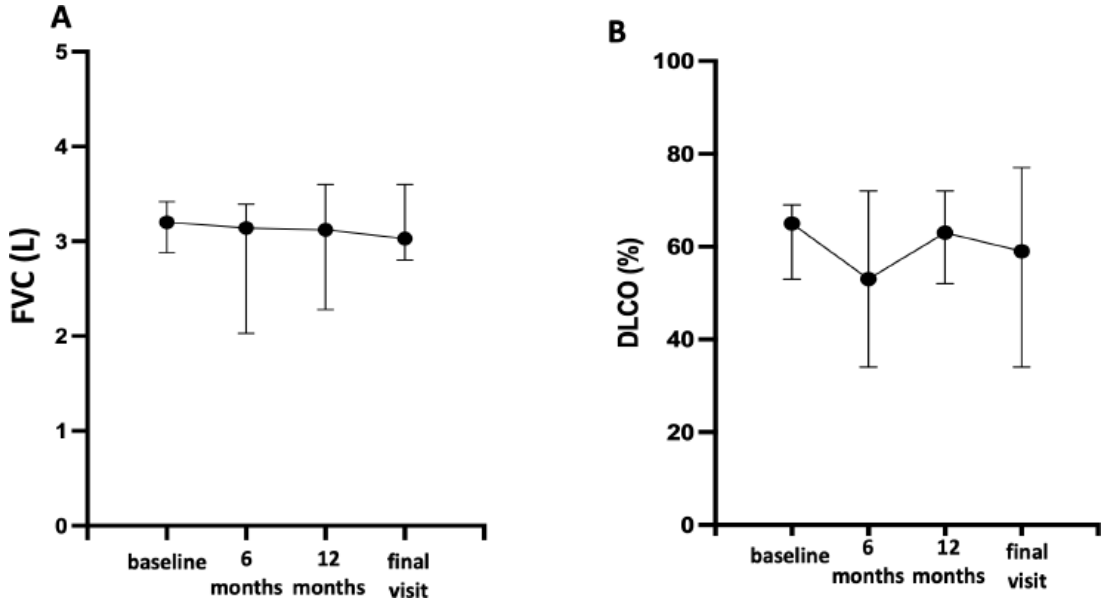

Figure 2 Changes in FVC (A) and DLCO (B) during follow-up (median, 95% CI). DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity.

Tolerance of JAKi in RA-ILD

With regard to pulmonary tolerance, 16 episodes (38.1%) of respiratory tract infection were recorded, including six COVID-19 pneumonia without severity, five community-acquired pneumonia and one patient with pulmonary tuberculosis. Only one acute regressive exacerbation of ILD was noted requiring hospitalisation, oxygen and corticosteroids. No lung or other cancer was diagnosed during the 21-month follow-up period. No major cardiovascular event, venous thromboembolism and deaths occurred. JAKi was discontinued in 17 patients including 8 for lack of efficacy on joint involvement and 5 for intolerance (including one herpes zoster, one pulmonary tuberculosis and one non-HIV-related Kaposi). No discontinuation of JAKi was linked to a progression of ILD.

Table 3 Predictive factors for progressive RA-ILD identified by univariate Cox proportional hazards analyses

	P value	Hazard Ratio (CI 95%)
Age at diagnosis	**0.045**	**1.12 (1.02 to 1.24)**
Male gender	0.57	13.08 (0.02 to 10.28)
RA disease duration	0.36	0.93 (0.85 to 1.03)
DAS-28 CRP	0.82	5.17 (0.55 to 48.74)
Active smoking	**0.009**	**40.62 (2.56 to 644.78)**
Extra-articular manifestations	**0.012**	**17.28 (1.87 to 159.62)**
UIP pattern on chest HRCT	0.96	4.4 (0.01 to 442)
Baseline DLCO	**0.017**	**0.92 (0.86 to 0.98)**
Baseline FVC	0.78	1.13 (0.49 to 2.61)

ILD progression was defined by a progressive worsening of FVC by more than 5% during follow-up and worsening of ILD lesions on chest HRCT according to the local expert radiologist or of their respiratory symptoms (worsening of the Borg dyspnoea score). CRP, C reactive protein; DLCO, diffusing capacity of the lungs for carbon monoxide; FVC, forced vital capacity; HRCT, high-resolution CT; RA-ILD, rheumatoid arthritis-associated interstitial lung disease; UIP, usual interstitial pneumonia.

DISCUSSION

To date and to our knowledge, this study is one of the first ones to specifically focus on the evolution of RA-ILD in French patients with RA treated with one of the four JAKis available in France. Our study showed a stability of lung functional parameters and HRCT lesions on JAKi combined with a good therapeutic response on joint involvement, consistent with some studies suggesting an association between articular control and progression of RA-ILD.[14 15] However, there may be a dissociation between joint and lung status, with the eight patients with ILD progression in our sample exhibiting significant joint improvement.

Fundamental research data on mice in which RA-ILD was reproduced suggested an efficacy of baricitinib on lung fibrosis by the negative regulation of the JAK2/STAT3 complex and an inhibition of the transforming growth factor (TGF)-β.[16] Another study showed that tofacitinib increased the number of myeloid suppressive cells in lung interstitium and lowered Th17 lymphocytes and granulocyte-macrophage colony-stimulating factor (GM-CSF), leading to the inhibition of profibrotic mechanisms.[17] Data from 15 patients with RA (of which four with ILD) mention a reduction of inflammatory parameters and an enhancement of FVC with baricitinib, in particular in patients with RA-ILD.[18] Moreover, a

prospective multicentric study suggested that JAKi could be an interesting therapeutic option in RA-ILD by a short-term stability of respiratory parameters,[19] and a prospective Italian study including 75 patients comparing JAKi (tofacitinib, baricitinib) and abatacept showed a stability or an improvement of RA-ILD in more than 80% in the two groups.[20]

It is estimated that 40% of patients with RA-ILD develop a progressive fibrosing phenotype.[21 22] We identified eight patients (19%) with a progressive phenotype during the follow-up period, defined by a progressive worsening of FVC by more than 5% during follow-up and worsening of ILD lesions on chest HRCT or their respiratory symptoms. A previous study reported a comparable occurrence or progression rate of pre-existing ILD at 12 months between patients treated with baricitinib and abatacept.[23] We identified known independent predictors of progressive ILD in our cohort including age at ILD diagnosis, active smoking, extra-articular manifestations and lower baseline DLCO. UIP pattern was not identified as a predictive factor, and other factors including ACPA/rheumatoid factor (RF) values and extension in HRCT were not assessed in all centres.[24]

Acute exacerbations of ILD represent a major event in the history of RA-ILD, and a single case occurred in our cohort, despite the presence in our patients of several risk factors identified in a recent meta-analysis gathering approximately 2000 patients (male sex, old age, length of disease progression, smoking, immunopositivity at high titre for RF and ACPA, inflammatory syndrome).[25] This result should be interpreted in light of a small sample size and a quite short follow-up time and a possible lack of exhaustivity in data collection. However, in line with our data, only one patient experienced an acute exacerbation in the prospective Italian study including 75 patients of favourable evolution after corticosteroids and allowing the continuation of JAKi.

The tolerance profile of JAKi was favourable in this cohort of RA patients with increased risk factors, including older age and increased cardiovascular risk factors. Respiratory tract infection was the most common infection observed in our patients. Enhanced by immunosuppressive treatments, they affect the prognosis of ILD whose mortality rate is already high.[26] A monocentric retrospective study highlighted that, compared with rituximab, baricitinib or tofacitinib did not increase the risk of respiratory events (infections, ILD acute exacerbations) or death in patients with RA-ILD or bronchiectasis during a follow-up time of 1–2 years, despite two deaths in each group (lung cancer and hospital-acquired pneumonia in JAKi group).[27]

With regard to the results reported in the ORAL Surveillance trial,[28] the follow-up period did not allow to detect lung cancer in a population with yet at high risk (active or former smoking, underlying ILD, treatment with JAKi). No ischaemic cardiovascular event and no venous thromboembolism were detected, but our sample size was probably too low to allow the detection of such rate events. Moreover, it is possible that clinicians may reasonably avoid using JAKi in RA patients who are older, smokers or have cancer or cardiovascular risk factors. Many of these patients would significantly overlap with patients with RA-ILD.

One of the strengths of this work is its national and multicentric nature. It reflects real-life data and considers all JAKis available in France through a multiparametric follow-up (clinical, imaging and functional characteristics). In addition to its descriptive nature, one of the main limits of our study is the presence of missing data for prospective variables, while characteristics at baseline were exhaustive and came from a standardised form. Because nearly 30% of our population had autoimmune diseases (especially secondary Sjögren syndrome) whose ILD CT scan pattern can be sometimes similar (NSIP or UIP), accountability of ILD to RA may not be certain. We acknowledge the limitation of not being able to evaluate the trajectories of FVC and DLCO values before and after treatment initiation due to a high proportion of missing data for these parameters prior to baseline. This prevented a direct comparison of changes over time relative to treatment start. Similar methodologies for evaluating the impact of antifibrotic treatments have been described in the literature, and future studies with more comprehensive datasets could provide valuable insights into these trajectories.[29] We did not perform a systematic screening of all RA patients from the registry for ILD, which may have resulted in some cases of subclinical or mild ILD remaining undiagnosed.

To sum up, this analysis indicates a stability of RA-ILD on JAKi during a median follow-up period of 21 months, combined with a marked reduction of disease activity in patients with established active disease with previous failure to several lines of advance therapies. We highlighted a group of patients with a progressive RA-ILD despite controlled joint disease whose independent risk factors of occurrence were age at diagnosis, active smoking, extra-articular manifestations and lower baseline DLCO. JAKi demonstrated an expected tolerance profile without new safety signal in a higher-risk population. Non-severe pulmonary infections occurred in 40% of our patients. We observed only one case of acute ILD exacerbation, and no lung cancer developed. These results need to be completed by further studies on a broader scale to confirm these results.

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REFERENCES

1 Salaffi F, De Angelis R, Grassi W, *et al*. Prevalence of musculoskeletal conditions in an Italian population sample: results of a regional community-based study. I. The MAPPING study. *Clin Exp Rheumatol* 2005;23:819–28.
2 Salaffi F, Carotti M, Di Carlo M, *et al*. High-resolution computed tomography of the lung in patients with rheumatoid arthritis: Prevalence of interstitial lung disease involvement and determinants of abnormalities. *Medicine (Baltimore)* 2019;98:e17088.
3 Fazeli MS, Khaychuk V, Wittstock K, *et al*. Rheumatoid arthritis-associated interstitial lung disease: epidemiology, risk/prognostic factors, and treatment landscape. *Clin Exp Rheumatol* 2021;39:1108–18.
4 Spagnolo P, Lee JS, Sverzellati N, *et al*. The Lung in Rheumatoid Arthritis: Focus on Interstitial Lung Disease. *Arthritis Rheumatol* 2018;70:1544–54.
5 Raimundo K, Solomon JJ, Olson AL, *et al*. Rheumatoid Arthritis-Interstitial Lung Disease in the United States: Prevalence, Incidence, and Healthcare Costs and Mortality. *J Rheumatol* 2019;46:360–9.
6 Holroyd CR, Seth R, Bukhari M, *et al*. The British Society for Rheumatology biologic DMARD safety guidelines in inflammatory arthritis. *Rheumatology (Oxford)* 2019;58:e3–42.
7 Nash P, Kerschbaumer A, Dörner T, *et al*. Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. *Ann Rheum Dis* 2021;80:71–87.
8 Fraenkel L, Bathon JM, England BR, *et al*. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res (Hoboken)* 2021;73:924–39.
9 Fleischmann R, Schiff M, van der Heijde D, *et al*. Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. *Arthritis Rheumatol* 2017;69:506–17.
10 Bae SC, Lee YH. Comparison of the efficacy and safety of tofacitinib and baricitinib in patients with active rheumatoid arthritis: a Bayesian network meta-analysis of randomized controlled trials. *Z Rheumatol* 2019;78:559–67.
11 Romero-Bueno F, Diaz Del Campo P, Trallero-Araguás E, *et al*. Recommendations for the treatment of anti-melanoma differentiation-associated gene 5-positive dermatomyositis-associated rapidly progressive interstitial lung disease. *Semin Arthritis Rheum* 2020;50:776–90.
12 Chen Z, Wang X, Ye S. Tofacitinib in Amyopathic Dermatomyositis–Associated Interstitial Lung Disease. *N Engl J Med* 2019;381:291–3.
13 Pineton de Chambrun M, Hervier B, Chauveau S, *et al*. Tofacitinib in antisynthetase syndrome-related rapidly progressive interstitial lung disease. *Rheumatology (Oxford)* 2020;59:e142–3.
14 Kronzer VL, Huang W, Dellaripa PF, *et al*. Lifestyle and Clinical Risk Factors for Incident Rheumatoid Arthritis-associated Interstitial Lung Disease. *J Rheumatol* 2021;48:656–63.
15 Zhang M, Yin J, Zhang X. Factors associated with interstitial lung disease in patients with rheumatoid arthritis: A systematic review and meta-analysis. *PLoS One* 2023;18:e0286191.
16 Liu H, Yang Y, Zhang J, *et al*. Baricitinib improves pulmonary fibrosis in mice with rheumatoid arthritis-associated interstitial lung disease

by inhibiting the Jak2/Stat3 signaling pathway. *Adv Rheumatol* 2023;63:45.
17 Sendo S, Saegusa J, Yamada H, *et al*. Tofacitinib facilitates the expansion of myeloid-derived suppressor cells and ameliorates interstitial lung disease in SKG mice. *Arthritis Res Ther* 2019;21:184.
18 d'Alessandro M, Perillo F, Metella Refini R, *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.
19 Venerito V, Manfredi A, Carletto A, *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.
20 Tardella M, Di Carlo M, Carotti M, *et al*. A retrospective study of the efficacy of JAK inhibitors or abatacept on rheumatoid arthritis-interstitial lung disease. *Inflammopharmacology* 2022;30:705–12.
21 Olson A, Hartmann N, Patnaik P, *et al*. Estimation of the Prevalence of Progressive Fibrosing Interstitial Lung Diseases: Systematic Literature Review and Data from a Physician Survey. *Adv Ther* 2021;38:854–67.
22 Wijsenbeek M, Kreuter M, Olson A, *et al*. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. *Curr Med Res Opin* 2019;35:2015–24.
23 Mochizuki T, Yano K, Ikari K, *et al*. Radiological evaluation of interstitial lung disease in patients with rheumatoid arthritis treated with abatacept or JAK inhibitors for 1 year. *Respir Investig* 2023;61:359–63.
24 Chen N, Diao CY, Gao J, *et al*. Risk factors for the progression of rheumatoid arthritis-related interstitial lung disease: Clinical features, biomarkers, and treatment options. *Semin Arthritis Rheum* 2022;55:152004.
25 Xie M, Zhu C, Ye Y. Incidence, risk factors, and prognosis of acute exacerbation of rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis. *BMC Pulm Med* 2023;23:255.
26 Azadeh N, Limper AH, Carmona EM, *et al*. The Role of Infection in Interstitial Lung Diseases: A Review. *Chest* 2017;152:842–52.
27 Cronin O, McKnight O, Keir L, *et al*. 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.
28 Ytterberg SR, Bhatt DL, Mikuls TR, *et al*. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. *N Engl J Med* 2022;386:316–26.
29 Juge PA, Hayashi K, McDermott GC, *et al*. Effectiveness and tolerability of antifibrotics in rheumatoid arthritis-associated interstitial lung disease. *Semin Arthritis Rheum* 2024;64:152312.