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RESEARCH ARTICLE

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Safety risks of interstitial lung disease upon real-world usage of Janus kinase inhibitors and biologics for patients with autoimmune diseases: epidemiological study using nationwide electronic medical record database in Japan

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ABSTRACT

Although Janus kinase inhibitor (JAKi) therapy is used for patients with autoimmune diseases (AD), one safety concern, interstitial lung disease (ILD), is life-threatening. We evaluated actual usage of JAKi and safety upon JAKi treatment, in an epidemiological retrospective cohort study utilizing the electronic medical record database in Japan. Among 391,565 AD patients, we analyzed data of new-users receiving JAKi or tumor necrosis factor alpha inhibitor (TNFi)/biologics during the period July 2013–May 2022. ILD (ICD10: J70.2, J70.3, J70.4 and J84) criteria were defined: new-ILD (1) and new-ILD (2) which differed in the latter's prompter therapeutics cessation upon ILD development. We analyzed ILD occurrence and death, ILD cumulative incidence by the Kaplan–Meier method, and hazard ratio (HR) by the Cox model, for 957 JAKi and 3931 TNFi users. JAKi use has become widespread amidst additional drug-development. Among JAKi users, two-year new-ILD (2) incidence, at 1.4%, was higher than for TNFi users (risk ratio: new-ILD (2) 1.75, death 2.31). Cumulative incidence (2.9% in 20.48 days) was also significantly higher (log-rank test $p = .013$, HR 2.23 (95% CI 1.16–4.27)); risk factors estimated by HR included JAKi (2.14), rheumatoid arthritis (4.94), diabetes mellitus (2.67) and cerebrovascular disease (2.86). ILD screening is essential.

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KEYWORDS
Epidemiology; autoimmune disease; Janus kinase inhibitor; biologics; tumor necrosis factor alpha inhibitor; interstitial lung disease

1. Introduction

The treatment for autoimmune diseases (AD) by biological therapeutics (biologics) became more widespread over the past 20 years. For example, the first biologics, infliximab, was approved for rheumatoid arthritis (RA) in Japan in 2002 following the U.S. in 1998 [1], and since then, eight approved drugs have been used clinically in Japan [2]. More recently, a Janus kinase inhibitor (JAKi) was developed, followed by others, which are believed to inhibit intracellular signaling and effectively suppress inflammatory cytokine production by selectively binding kinases of the JAK family, i.e., JAK1 to JAK3, and tyrosine kinase 2 (TYK2) [3]. The first JAKi, tofacitinib, was approved for RA in Japan in 2013 following the U.S. in 2012 [3], and since then, five approved drugs have been added in Japan [4–8]. These new therapeutics have dramatically improved clinical effectiveness, but safety concerns remain [2].

Interstitial lung disease (ILD) is known as one of the fatal side effects of conventional biologics [9–15]. Curtis et al. reported that ILD incidence in biologics users was 0–0.47/100 patient-years (pt-yrs) which was not significantly different between biologics with the following cytokine or cell targets: tumor necrosis factor (TNF) alpha (etanercept, adalimumab, infliximab, certolizumab pegol and golimumab), interleukin-6 (IL-6) (tocilizumab), CD20 B-cells (rituximab) and CD80/86/CD28 T-cells (abatacept) [16]. In Japan, post marketing studies found that ILD occurred in less than 1.0% of biologics users, and possible host (patient) or environmental risk factors were identified such as older age, male sex, diabetes mellitus (DM), previous ILD (including pulmonary fibrosis), RA, elevated erythrocyte sedimentation rate

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and smoking [9–11,14,17]. ILD has also become known as life-threatening safety specification for JAKi [4–8,18–22]. Thus, collecting effectiveness/safety information is required for pharmacovigilance/risk minimization activities as regulated in the risk management plan (RMP) published at the time of each new JAKi approval [4–8,18–27].

Several randomized controlled trials (RCTs) examined efficacy/safety information in JAKi users: Khoo et al. reported from RCTs that the incidence of ILD in JAKi users was not significantly different from TNF alpha inhibitor (TNFi) users [28]. According to a combined analysis of RCTs from different countries, the incidence of ILD in JAKi users was 0.17/100 pt-yrs worldwide, with 0.24/100 pt-yrs in Asians [4] and did not exceed 0.1% from each RCT [18,19]. In contrast, non-interventional studies on post-marketing clinical practice (real-world data) have suggested a higher incidence of ILD in JAKi users, i.e., 2.86/100 pt-yrs in five observational studies [28], 0.5% [29,30], or 14 of 3929 patients (0.36%) [31]. As RCTs were conducted on a limited pre-marketing population [32], it is important to identify the actual incidence of ILD and risk factors among JAKi users in general, based on real-world data reflecting the actual usage of JAKi after marketing.

Considering JAKi's new mechanism of action (inhibiting intracellular signaling by selectively binding kinases of the JAK family) and suppression of various inflammatory cytokines in AD patients, drug cytotoxicity and a wide-range of immune responses (including possible unknown ones) can lead not only to effectiveness but also to safety concerns [14,33,34]. Therefore, we surmised that: (1) JAKi use has been widespread for treatment, (2) but ILD occurrence could be higher after JAKi than after biologics with higher risk of death due to its broad immune effects and ILD's lethal nature [12,13,35,36] and (3) diseases (RA, other immune diseases, DM, cerebrovascular disease (CVD) and lung diseases aside from ILD (other lung diseases)) could also be risk factors for ILD, because systemic inflammation and fibrosis in these diseases were shared with ILD and might make airway and/or alveolar epithelium more susceptible to drug cytotoxicity and altered immune responses to JAKi treatment [37,38].

To examine these hypotheses, we analyzed actual usage of JAKi and compared safety (ILD occurrence and mortality, and cumulative incidence and the risks) with TNFi for the same indications in Japanese AD patients, using real-world data upon JAKi treatment. Analyzing Japanese AD patients, who are considered to have a higher incidence of drug-induced ILD than other racial groups due to genetic factors that predispose them to ILD [10,39–41], may be particularly useful.

2. Materials and methods

2.1. Data source

This study utilized a nationwide electronic medical healthcare record 'RWD database' provided by the Health, Clinic, Education Information Evaluation Institute (HCEI, Kyoto, Japan) [42], with the support of Real World Data, Co., Ltd. (Kyoto, Japan) [43]. The database has accumulated approximately 24 million patients' electronic medical record (EMR) data from 225 hospitals (including clinics) that covered 20% of the total population, under the universal healthcare system in Japan (as of May 2022). The data were anonymized (without a correspondence table) and standardized by International Classification of Diseases 10th Revision (ICD 10) and has also been utilized in various studies [44,45]. Medical information such as clinically diagnosed disease name, treatment and examination results were suitable for medical evaluation and/or research; this let us scientifically compare collected data among groups based on uniform criteria.

From this database, we obtained the subset 'AD patients' dataset' provided through public offering and review by the HCEI (reception no. 020) (data period, January 2001–May 2022). Informed consent was waived because of data-anonymization [46]. Although anonymized, if there was a category where an aggregate result could show less than 10 patients, the category was not to be public considering protection of patients' personal information [47]. This study was approved by the Institutional Review Board of Juntendo University (project no. E21-0234).

2.2. Patients included in this study

As shown in Figure 1, patient flow diagram, the dataset included 462,610 AD patients, from which 71,045 provisionally diagnosed patients (without ICD 10) were excluded. This study thus included a total of 391,565 AD patients with the following diseases (ICD 10) (with duplicate): 324,167 (82.8%) with RA (M05 and M06), 2246 (0.6%) with juvenile idiopathic arthritis (M08.0), 9,402 (2.4%) with Crohn's disease (K50), 27,432 (7.0%) with ulcerative colitis (UC) (K51), 33,888 (8.7%) with psoriasis vulgaris (L40.0 and L40.9), 1507 (0.4%) with psoriasis arthritis (L40.5) and 6,848 (1.8%) with Behcet's disease (M35.2) [48–50].

Some of the AD patients received JAKi or TNFi/biologics (TNFi alone, or TNFi and other non-TNFi biologics). JAKi included tofacitinib, baricitinib,

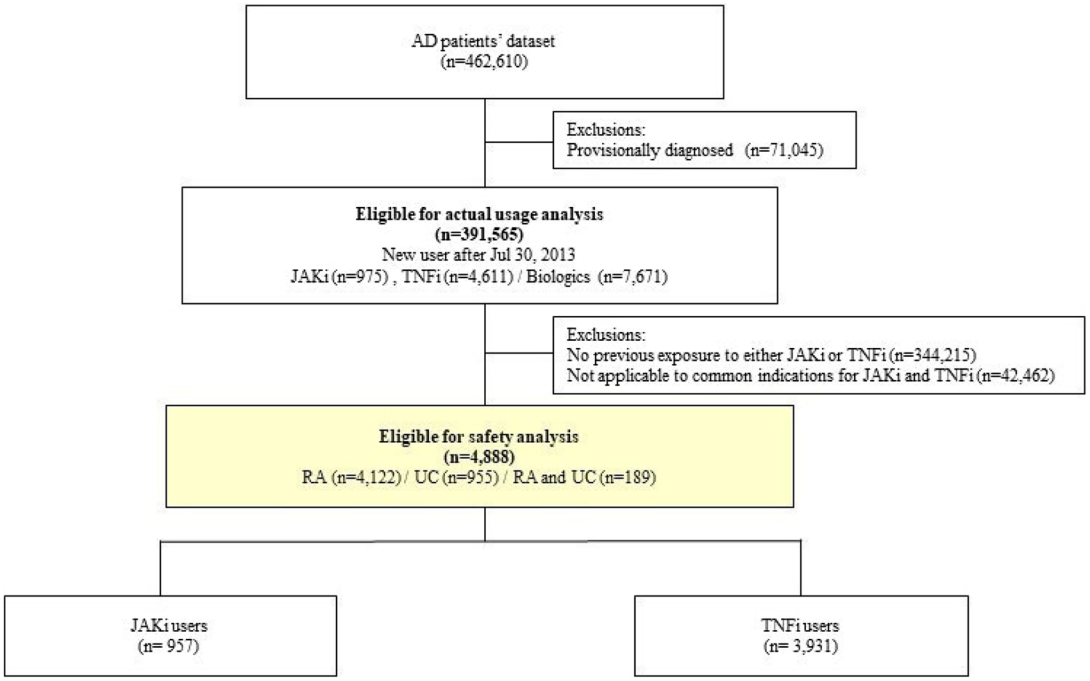


Figure 1. Patient flow diagram. The subset "AD patients' dataset", obtained from RWD database, included data of AD patients who were clinically diagnosed during the period January 2001 to May 2022. Eligible for actual usage analysis were selected as newly treated after July 2013, from which eligible for safety analysis were identified and divided into two groups. Some of RA or UC included patients with both diseases. AD: autoimmune diseases; JAKi: Janus kinase inhibitor; TNFi: tumor necrosis factor alpha inhibitor.

peficitinib, upadacitinib and filgotinib. TNFi were infliximab, etanercept, adalimumab, golimumab and certolizumab pegol. Biologics other than TNFi were abatacept, tocilizumab, salirumab, canakinumab, vedolizumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab and tildrakizumab. Adopting a new user design, AD patients received JAKi for the first time after its marketing-start date (30 July 2013) were handled as JAKi users. Similarly, AD patients received TNFi/biologics for the first time after 30 July 2013 (same with JAKi's marketing-start date) were handled as TNFi/biologics users for enhancing comparability in this study. In the case where TNFi/biologics users experienced JAKi even once, they were handled preferentially as JAKi users. Duration of treatment with JAKi or TNFi/biologics were the actual treatment period (date of treatment-start to treatment-end). The treatment-end refers to the end of each exposure including therapeutics-discontinuation.

2.3. ILD and risk factors

For primary outcome 'ILD occurrence', first, we identified ILD including drug-induced ILD and other ILD (ICD10: J70.2, J70.3, J70.4 and J84 (J84.0, J84.1, J84.4 and J84.9)). The latter were ILD with alveolar and perialveolar pathology, ILD with pulmonary fibrosis, other explicit ILD, and ILD details unknown [49]. Then, we defined new ILD (1) and new ILD (2) as a combination of the ICD 10 with additional criteria: new ILD (1) was defined as ILD that was first developed during the 2-year period from treatment-start through to 30 days after the treatment-end. New ILD (2) was ILD whose treatment was stopped within 14 days before or after the date of new ILD occurrence during the 2-year period. Both definitions of newly developed ILD stipulated there be no prior history of ILD, with clinical diagnosis of ILD based on EMR data, and any patient re-administered the drug after treatment-end [9–11,23]. To evaluate safety risk of newly developed ILD more specifically upon treatment, new ILD (2) included the concept of therapeutics cessation; this reflected undeniable causality with treatment. ILD cases identified as new ILD (2) were composed of a subset of new ILD (1). This concept let us broadly cover new ILD events that included mild cases. For causality with treatment and validity, consistency of dates, and data of patient characteristics (pre-therapy, concomitant medication and ILD diagnosis test) were checked for diagnostic confirmation in patients with new ILD (2) [9–11,23]. Also, we identified deceased patients and the date of death. Then, we defined death after new ILD (1) and death after new ILD (2) as death that occurred after either new ILD.

Aside from advanced age, male sex, as well as RA and JAKi, the data on the following comorbidities (ICD 10) (inflammatory and fibrotic diseases) were used as

potential independent risk factors for ILD (1) or ILD (2); other immune diseases (M33, L94 (L94.0 and L94.1), M05.2, M31.4, M31.5 and M35 (M35.0-M35.9, except for M35.2)) [38], DM (E10-E14) [14], CVD (I25.6, I20, I20.1, I20.8, I20.9, I20.0, I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I25.2, I64, I69.4, I50, I50.0 and I50.9) [23,25] and other lung diseases (J60-J70, J99, J43, J44 and J45) [9,10,37].

2.4. Statistical analysis

The real-world data were used for actual usage analysis upon JAKi in all 391,565 AD patients as follows: number and percentage of each diseases, number and percentage of JAKi or TNFi/biologics users, number and percentage of JAKi or TNFi/biologics users by hospital size, treatment period (days and pt-yrs) and annual JAKi market trends (number of JAKi or TNFi users and JAKi as a percentage of the therapeutics, and number of doses by JAKi brand) in 2013–2021 (for annual total, up to 2021).

For safety analysis, 344,215 patients without both JAKi and TNFi treatment and 42,462 patients without both JAKi and TNFi indications were excluded from the total AD patients, the remaining 4888 AD patients were used for following safety analysis (Figure 1): baseline characteristics (including ILD screening status), ILD occurrence and death (percentage and ratio), and KL-6 test results. Those with any risk for new ILD were considered at-risk patients and were included in the survival time analysis; the cumulative incidence of new ILD by the Kaplan–Meier (KM) method (log-rank test) and hazard ratios (HRs) by the Cox proportional hazards model were calculated.

SAS software version 9.4 (SAS Institute Inc., Cary, NC) was used for the above analyses.

3. Results

As new users, 975 JAKi users and 4611 TNFi users or 7671 biologics users were identified. JAKi accounted for 17.5% of 5586 JAKi and TNFi users, and 11.3% of 8646 JAKi and biologics users. Among 975 JAKi users, 337 (31.6%) had undergone with TNFi and 473 (48.5%) with biologics.

Table 1 shows JAKi or TNFi/biologics users by hospital size. A relative preference for JAKi over TNFi only or biologics for treating AD patients was clearest in hospitals with fewer than 500 beds.

Table 2 shows treatment period with JAKi or TNFi/biologics. The treatment period with JAKi (1.32 pt-yrs) was tremendously shorter, i.e., 59.4% of that with TNFi only or 53.3% of that with biologics.

Figure 2 illustrates annual trends in JAKi or TNFi users in 391,565 AD patients in Japan, 2013–2021.

Table 1. JAKi or TNFi/biologics users by hospital size.

No. of beds	JAKi[a]	Biologics[b]	
		TNFi only	TNFi + non-TNFi
	N (%)	*N* (%)	*N* (%)
≤99	56 (5.7)	228 (5.0)	409 (5.3)
100–299	148 (37.8)	614 (13.3)	1075 (14.0)
300–499	392 (40.2)	1717 (37.2)	2771 (36.1)
≥500	379 (38.9)	2052 (44.5)	3416 (44.5)
Total	975 (100.0)	4611 (100.0)	7671 (100.0)

No.: number; JAKi: Janus kinase inhibitor; TNFi: tumor necrosis factor alpha inhibitor.
[a]Patients treated with both JAKi and TNFi/biologics were counted as JAKi users.
[b]Biologics were analyzed as TNFi or biologics (TNFi and other non-TNFi biologics), respectively.

Table 2. Treatment period with JAKi or TNFi/biologics.

Treatment period	JAKi[a]	Biologics[b]	
		TNFi only	TNFi + non-TNFi
	N = 975	*N* = 4611	*N* = 7671
Days			
Total	432,280	3,432,042	6,398,285
Mean (SD)	443.36 (493.93)	744.32 (763.10)	834.08 (776.35)
Patient-years (pt-yrs)			
Total	1200.78	9533.45	17773.01
Mean (SD)	1.23 (1.37)	2.07 (2.12)	2.31 (2.16)

SD: standard deviation; JAKi: Janus kinase inhibitor; TNFi: tumor necrosis factor inhibitor.
[a]Patients treated by both JAKi and TNFi/biologics were counted as JAKi users.
[b]Biologics were analyzed as TNFi or biologics (TNFi and other non-TNFi biologics), respectively.

JAKi users increased to the right, as did JAKi as a percentage of the 5586 JAKi and TNFi users. Figure 3 represents annual trends in number of doses by JAKi brand in Japan, during the same period. The number of doses of each JAKi brand increased along with new approval and its total also increased.

Table 3 summarizes baseline characteristics of 4888 AD patients for the analysis of ILD occurrence. They consisted of 957 JAKi users (19.6%) and 3931 TNFi users (80.4%). Most of them (4122 patients) suffered from RA, i.e., 90.9% and 82.7% of JAKi and TNFi users, respectively. UC affected 955 patients, of whom 189 suffered from both diseases. Other AD were also observed in duplicate with RA and/or UC (data not shown).

There was a slight difference in age or comorbidities between JAKi and TNFi users; over 60% were female, over 40% were elderly (65 years or older), and around 20% were late elderly (75 years or older). The average age of JAKi users was slightly higher than that of TNFi users, but both averages were below 65. Previous ILD was observed in nearly half of users. Therapy period by JAKi was shorter, at only 63.1% of that by TNFi. Finally, JAKi users had undergone pre-therapy (biologics) than TNFi users. ILD screening (medical examination), if limited to within 90 days before treatment-start, was conducted for only approximately 30.0% of patients who needed it.

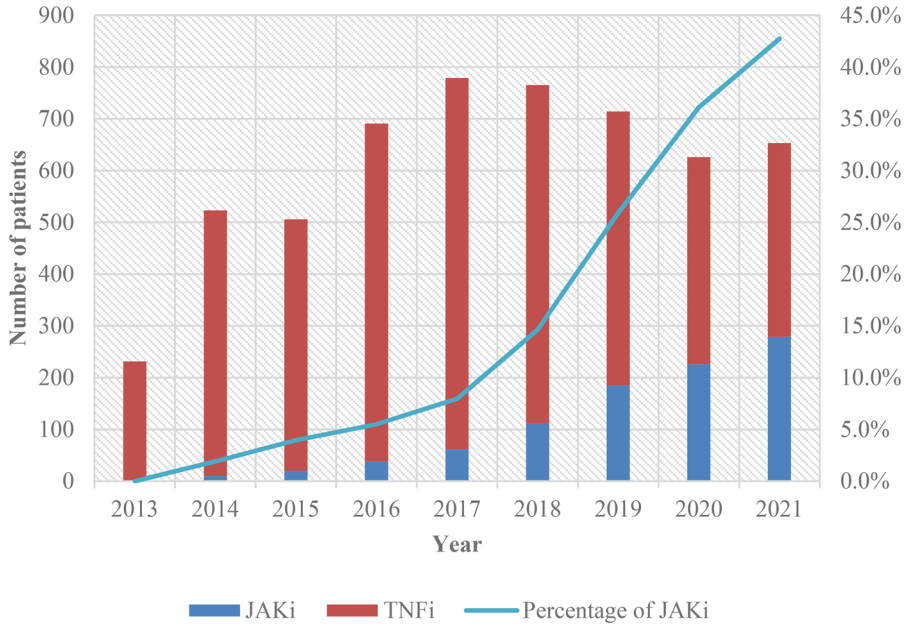
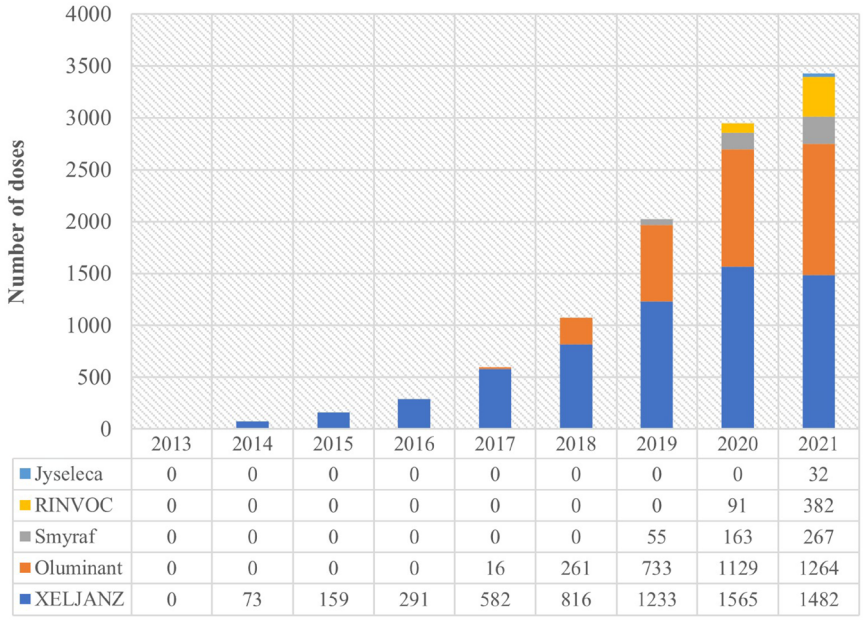


Figure 2. Annual trends in JAKi or TNFi users in 391,565 AD patients in Japan, 2013–2021. The bar shows number of new users of JAKi or TNFi; the line is JAKi as a percentage of the 5586 JAKi and TNFi users.



	2013	2014	2015	2016	2017	2018	2019	2020	2021
Jyseleca	0	0	0	0	0	0	0	0	32
RINVOC	0	0	0	0	0	0	0	91	382
Smyraf	0	0	0	0	0	0	55	163	267
Oluminant	0	0	0	0	16	261	733	1129	1264
XELJANZ	0	73	159	291	582	816	1233	1565	1482

Figure 3. Annual trends in number of doses by JAKi brand in Japan, 2013–2021. The bar shows number of doses of each JAKi brand and its total number of doses. XELJANZ: tofacitinib; Olumiant: baricitinib; Smyraf: peficitinib; RINVOC: upadacitinib; Jyseleca: filgotinib.

Two-year ILD occurrence and death in 4888 AD patients are shown in Table 4. ILD occurred in more than half of the patients in both JAKi and TNFi users; previous ILD was slightly more common in JAKi users. New ILD (2) occurred more in JAKi users than in TNFi users, showing the risk ratio of 1.75. All-cause death was 3.3% overall for both JAKi and TNFi users. However, death after new ILD (1) and new ILD (2) were higher than 3.3% and especially higher in new ILD (2) than in new ILD (1) (more than 6.0%, though not publishable due to there being fewer than 10 cases each). In particular, death after new ILD (2) was higher in JAKi users, showing a risk ratio of 2.31.

Table 5 presents results of KL-6 testing (within 90 days before treatment-start) in patients with and without new ILD. KL-6 testing, recognizing only tests done within 90 days prior to treatment-start, was not adequately conducted in patients with new ILD in either JAKi or TNFi group. KL-6 values in JAKi users were close to or over the abnormal value of 500 for new ILD (1) and new ILD (2). Furthermore, in contrast to TNFI users, especially in new ILD (2) in JAKi users, the KL-6 value was already close to 500 regardless of new ILD (2) occurrence.

Table 3. Baseline characteristics of 4888 AD patients for the analysis of ILD occurrence.

		JAKi	TNFi
		N = 957 (100.0%)	*N* = 3931 (100.0%)
Disease name (duplicate)	RA	870 (90.9)	3252 (82.7)
	Seronegative (% of RA)	142 (14.8)	424 (10.8)
	Seropositive (% of RA)	844 (88.2)	3190 (81.2)
	Ulcerative colitis	123 (12.9)	832 (21.2)
Other disease name (duplicates RA and/or UC)	Juvenile idiopathic arthritis	–	22 (0.6)
	Crohn disease	12 (1.3)	22 (5.4)
	Psoriasis vulgaris	37 (3.9)	247 (6.3)
	Psoriasis arthritis	24 (2.5)	174 (4.4)
	Behcet's disease	–	126 (3.2)
Sex	Male	323 (33.8)	1331 (33.9)
	Female	634 (66.2)	2600 (66.1)
Age[a] (years old)	0–14	0 (0.0)	60 (1.5)
	15–64	410 (42.8)	2068 (52.6)
	65–74	272 (28.4)	958 (24.4)
	≥75	250 (26.1)	719 (18.3)
	Not applicable	25 (2.6)	126 (3.2)
	Age: mean (SD)	63.40 (15.90)	57.55 (18.23)
Region	Hokkaido/Tohoku	78 (8.2)	444 (11.3)
	Kanto	151 (15.8)	683 (17.4)
	Chubu	93 (9.7)	586 (14.9)
	Kinki	341 (35.6)	1230 (31.3)
	Chugoku	121 (12.6)	380 (9.7)
	Shikoku	66 (6.9)	81 (2.1)
	Kyushu/Okinawa	110 (11.5)	527 (13.4)
Hospital scale (number of beds)	<20, 20–99	56 (5.9)	228 (5.8)
	100–299	145 (15.2)	472 (12.0)
	300–499	384 (40.1)	1455 (37.0)
	≥500	372 (38.9)	1776 (45.2)
Treatment period (patient-years)	Total	1196.74	7790.27
	Mean (SD)	1.25 (1.38)	1.98 (2.08)
Pre-therapy[b] (duplicate)	Immunosuppressant	151 (15.8)	420 (10.7)
	Tacrolimus	136 (14.2)	300 (7.6)
	Cyclosporine; azathioprine; leflunomide	18 (1.9)	128 (3.3)
	Biologics	256 (26.8)	16 (0.4)
	TNFi	86 (9.0)	0 (0.0)
	Non-TNFi	183 (19.1)	16 (0.4)
Concomitant medication[c] (duplicate)	Oral corticosteroid (prednisolone)	236 (24.7)	798 (20.3)
	Dose: less than 5 mg/day; 5 mg/day	86 (36.4)	130 (16.3)
	Dose: over 5 mg/day	72 (30.5)	668 (83.7)
	Dose: mean (SD)	7.78 (9.0)	8.30 (9.5)
	MTX	379 (39.6)	2009 (51.1)
	Dose: less than 5 mg/day; 5 mg/day	261 (68.7)	1578 (78.7)
	Dose: over 5 mg/day	119 (31.3)	427 (21.3)[f]
	Dose: mean (SD)	6.80 (3.4)	6.13 (3.3)
Comorbidities[d,e] (duplicate)	Previous ILD	499 (51.2)	1620 (41.2)
	IMD	68 (7.7)	489 (12.4)
	DM	156 (16.3)	655 (16.7)
	CVD	110 (11.5)	450 (11.5)
	OLD	20 (2.1)	101 (2.6)
	Liver dysfunction	31 (3.2)	182 (4.6)
	Renal dysfunction	17 (1.8)	75 (1.9)
Medical examination[g] (duplicate)	ILD diagnosis test (all)	304 (31.8)	1002 (25.5)
	KL-6 test	287 (30.0)	892 (22.7)
	KL-6 negative (less than 500)	237 (72.6)	778 (87.2)
	KL-6 positive (500; over 500)	50 (17.4)	114 (12.8)
	SP-A/SP-D	56 (5.9)	131 (3.3)
	PaO_2	33 (3.5)	114 (2.9)
	β-D-glucan	306 (32.0)	1275 (32.4)
	β-D-glucan negative (less than 20)	297 (97.1)	1249 (98.0)
	Radiography test[h]	280 (29.3)	1120 (28.5)
	X-ray	96 (10.0)	360 (9.2)
	CT/HRCT	184 (19.2)	760 (19.3)

SD: standard deviation; ILD: interstitial lung disease; JAKi: Janus kinase inhibitor; TNFi: tumor necrosis factor alpha inhibitor; MTX: methotrexate; RA: rheumatoid arthritis; IMD: immune disease; DM: diabetes mellitus; CVD: cerebrovascular disease; OLD: other lung disease; hyphen (–): not to be public, in the case number was less than 10 patients. ILD: interstitial lung disease; JAKi: Janus kinase inhibitor; TNFi: tumor necrosis factor alpha inhibitor; KL-6: sialylated carbohydrate antigen KL-6; SP-A: lung surfactant protein-A; SP-D: lung surfactant protein-D; PaO_2: partial pressure of arterial oxygen; CT: computed tomography; HRCT: high resolution computed tomography.

[a]Age at treatment-start.

[b]Pre-therapies within 90 days before treatment-start.

[c]Concomitant medication within 30 days before to 30 days after treatment-start.

[d]Presence of disease within 30 days before to 30 days after treatment-start.

[e]Liver or renal dysfunction were counted based on each ICD10 (liver dysfunction K76.9 and R94.6, or renal dysfunction N28.4 and R94.4).

[f]Including MTX 2 mg capsule at dose 30 mg for 55 days.

[g]Presence of medical examination (abnormal values in examination results if it is necessary) within 90 days before therapy-start.

[h]X-ray, CT or HRCT were counted based on each photography/diagnosis fee code: [X-ray, 170000410; 170000510; 170000610; 170000730; 170000910; 170001010; 170001250; 170001350; 170001650; 170001750; 170001910; 170021550; 170022730; 170023750; 170024250; 170027910; 170028310; 170031350; 170031550, or CT, 170011710; 170011810; 170019950; 170022290; 170028610; 170033410; 170015410; 170033410; 170034910].

Table 4. Two-year ILD occurrence and death in 4888 AD patients (957 for JAKi and 3931 for TNFi).

	JAKi	TNFi	
	N = 957	*N* = 3931	JAK/TNFi ratio
ILD occurrence and death	*N* (%)[a]	*N* (%)[a]	Percentage ratio
ILD occurrence	566 (59.1)	2011 (51.2)	1.15
Previous ILD	499 (52.1)	1620 (41.2)	1.27
New ILD (1)	58 (6.1)	274 (7.0)	0.87
New ILD (2)	13 (1.4)	30 (0.8)	1.75
No ILD occurrence	391 (40.9)	1920 (48.8)	0.84
Deceased	31 (3.3)	129 (3.3)	1.0
Deceased with previous ILD[b]	20 (4.1)	58 (3.6)	1.14
Deceased after new ILD (1)[c]	–	–	1.11
Deceased after new ILD (2)[c]	–	–	2.31

ILD: interstitial lung disease; JAKi: Janus kinase inhibitor; TNFi: tumor necrosis factor alpha inhibitor.
[a]Not to be public, in the case number of observation was less than 10 patients or could be calculated.
[b]Percentage was calculated using no. of previous ILD as the denominator.
[c]Percentage was calculated using no. of new ILD (1) or new ILD (2) as each denominator.

Table 5. Results of KL-6 testing (within 90 days before treatment-start) in patients with and without new ILD.

	JAKi				TNFi			
		KL-6 test				KL-6 test		
			KL-6 test value				KL-6 test value	
ILD occurrence[a]	*N* = 957	No. of conducted (%)[b]	Mean (SD)	Yes/no ratio	*N* = 3931	No. of conducted (%)[b]	Mean (SD)	Yes/no ratio
New ILD (1)								
No	849	43 (5.0)	390.7 (251.73)	–	3657	194 (5.3)	289.02 (194.09)	–
Yes	58	25 (43.1)	592.93 (557.78)	1.52	274	85 (31.0)	325.16 (266.36)	1.13
New ILD (2)								
No	944	60 (6.4)	456.16 (400.98)	–	3901	270 (6.9)	295.38 (214.33)	–
Yes	13	–	447.63 (136.89)	0.98	30	–	380.79 (290.13)	1.29

No.: number; SD: standard deviation; ILD: interstitial lung disease; JAKi: Janus kinase inhibitor; TNFi: tumor necrosis factor alpha inhibitor; KL-6: sialylated carbohydrate antigen KL-6.
[a]Yes or no meant that two-year ILD occurred or not, respectively.
[b]Not to be public, in the case number of KL-6 test conducted was less than 10 patients or could be calculated.

Figure 4(A,B) illustrates two-year cumulative incidence of new ILD (1) and new ILD (2) in patients at risk, respectively. The cumulative incidence of new ILD (1) in JAKi users (17.6% over 623 days, with a mean of 615.89 days) was not significantly different from that in TNFi users (15.5% over 644 days, with a mean of 620.17 days). In both groups of users, new ILD (1) occurred early after treatment-start and increased with treatment duration. In contrast, the cumulative incidence of new ILD (2) in JAKi users (2.9% over the first 21 days, with a mean of 20.48 days) was significantly higher than that in TNFi users (0.8% over 21 days, 1.8% over 560 days, with a mean of 551.85 days), and the events occurred particularly early after treatment-start.

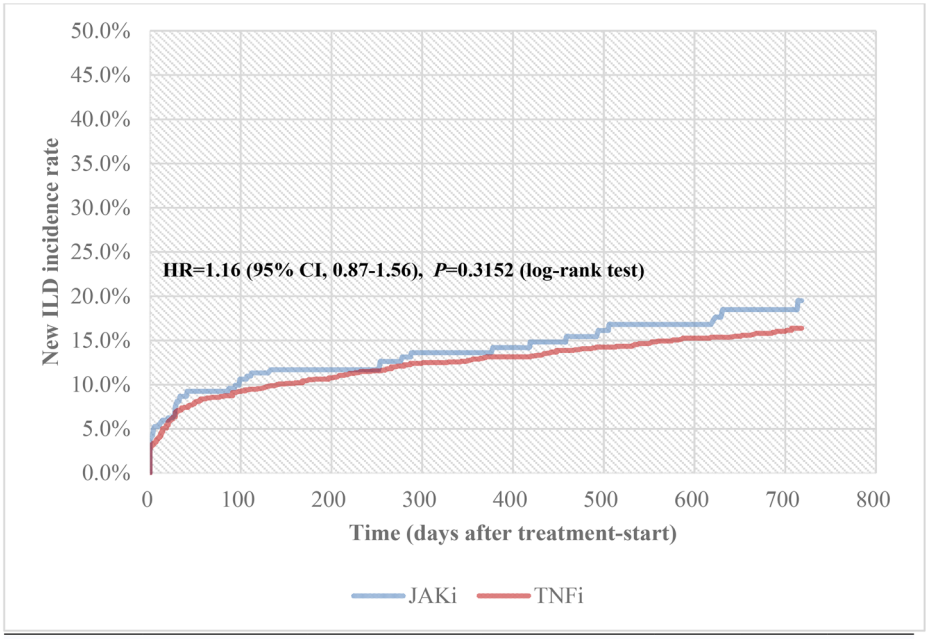
Table 6 summarizes two-year risk factors for new ILD in patients at risk. For new ILD (1), the significant risk factors suggested by HR were RA, other immune diseases, and DM. Similarly, for new ILD (2), the significant risk factors were presumed to be JAKi, RA, DM and CVD.

4. Discussion

JAKi use from actual usage analysis has become widespread, partially replacing TNFi/biologics, is being used in smaller hospitals, and has been increasing over the years. The reasons behind the rise might include: (1) as an oral agent, JAKi was easier for both doctors and patients to use than injectable TNFi/biologics, (2) additional JAKi development after 2013 has brought new approval of JAKi brand and promoted JAKi use and (3) proper use information from each use has contributed to starting JAKi. Contrary to expectations, however, treatment period with JAKi was markedly shorter than with TNFi/biologics, which implied safety concerns in long-term use. Because JAKi use has been rising, elucidating its safety profile and proper use to balance benefits against risks have become increasingly important.

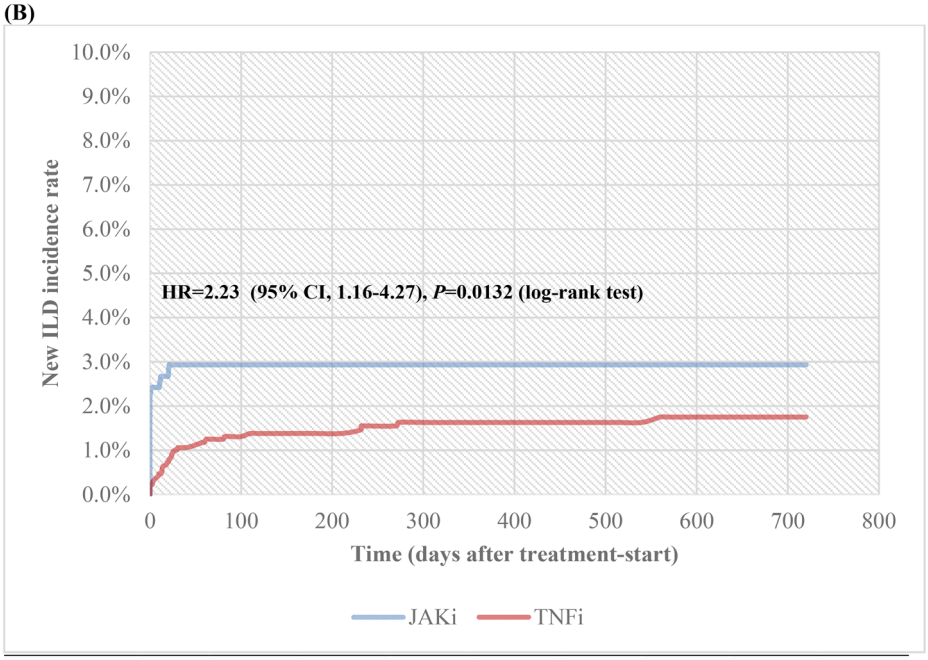
ILD occurrence and death from safety analysis were also in general agreement with expectations. Previous ILD was slightly more in JAKi than in TNFi users, and JAKi use showed a higher risk of new ILD (2) and subsequent death. Considering that previous ILD was common in RA, and a proven risk factor for ILD recurrence, exacerbation and death [9–11,35], much consideration (e.g., interview about symptoms, KL-6 test and radiography test) should be required for patients with previous ILD before starting JAKi, as strongly recommended in guides by Japan College of Rheumatology [23–27].

New ILD (2) occurred 1.4% of JAKi, and 0.8% of TNFi users. The 0.8% incidence among TNFi users



Time (days)		0	14	30	60	90	180	360	540	720
At risk (N)	JAKi	458	390	331	312	273	244	173	123	81
	TNFi	2311	1924	1740	1573	1482	1287	1035	858	708

(B)



Time (days)		0	14	30	60	90	180	360	540	720
At risk (N)	JAKi	458	390	331	330	270	218	150	116	81
	TNFi	2311	1924	1740	1573	1482	1287	1035	858	708

Figure 4. Two-year cumulative incidence of new ILD (1) (A) and new ILD (2) (B) in patients at risk. The line is the cumulative incidence rate of new ILD (1) and new ILD (2). ILD: interstitial lung disease; JAKi: Janus kinase inhibitor; TNFi: tumor necrosis factor alpha inhibitor.

was under 1.0%, consistent with previous post marketing study results (1.0% or less than 1.0% in biologics) [9–11]. The findings of less than 1.0% were said to include not only new ILD but also ILD recurrence and exacerbation, but this study's outcome focused on new ILD. If total ILD among TNFi users (including recurrence and exacerbation) in this study was almost 1.0% (i.e., within 1.3-folds of 0.8%), the 1.4% incidence among JAKi users yields a ratio of 1.75 (1.4%/0.8%), which could also be reasonable, though higher than ILD occurrence in previous studies (0.1–0.5%) [28–31]. Based on this study, therefore, JAKi seems to generate a higher risk of new ILD (2) than TNFi. In addition, in

Table 6. Two-year risk factors for new ILD in patients at risk.

	New ILD (1)			New ILD (2)		
Factor	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age: elderly	1.24	0.99–1.55	.07	0.94	0.95–1.77	.84
Sex: female	0.92	0.73–1.16	.48	0.87	0.46–1.65	.67
RA	9.1	5.04–16.41	<.0001**	4.94	1.45–16.85	.01*
IMD	2.78	2.22–3.65	<.0001**	1.31	0.55–3.12	.55
DM	1.92	1.45–2.54	<.0001**	2.67	1.30–5.47	.01*
CVD	1.11	0.76–1.61	.59	2.86	1.29–6.34	.01*
OLD	1.78	0.91–3.48	.09	1.1	0.15–38.32	.92
JAKi	1.14	0.85–1.52	.34	2.14	1.10–4.19	.02*

HR: hazard ratio; CI: confidence interval; ILD: interstitial lung disease; JAKi: Janus kinase inhibitor; TNFi: tumor necrosis factor alpha inhibitor; RA: rheumatoid arthritis; IMD: immune disease; DM: diabetes mellitus; CVD: cerebrovascular disease; OLD: other lung disease; elderly: 65 years or above.

*These *p* values in multivariate analysis using Cox proportional hazards model showed significant difference (*p* value < .5).

**These *p* values estimated by same method also showed significant difference (*p* < .01).

exploratory analysis in patients at risk for new ILD (458 JAKi and 2311 TNFi users), new ILD (2) occurred more in JAKi users (JAKi n = 13 (2.8%) or TNFi n = 30 (1.3%)), and the risk was greater (risk ratio, 2.19).

Death after new ILD (1) or new ILD (2) occurred more (over 6.0%, respectively) than death for all JAKi or TNFi users (3.3%). This was consistent with 'high risk of death in RA-ILD' noted in previous research [12,13,29,35,36]. The research presented the high risk of death not only after reoccurrence/exacerbation in patients with previous ILD, but also in newly developed cases, on which this study focused. Even though the two seem not to be entirely the same, the latter (death after newly developed ILD) were also at a higher risk of death upon receiving biologics than all RA patients. Especially, JAKi users had a higher risk of death after new ILD (2) (2.31) than after new ILD (1) (1.11); we should evaluate this finding cautiously and confidentially, because the total number of deaths subsequent to new ILD was under 10. However, this is an important finding in these rare ILD events. ILD was reconfirmed to be life-threatening, and preventing new ILD, especially new ILD (2) in JAKi users seems essential.

Cumulative ILD incidence and the risk factors from safety analysis were also in agreement with expectations. JAKi and some systemic inflammatory diseases increased risk for new ILD (2). Time to event analysis by KM-methods and 'multivariate analysis' by Cox proportional hazards model revealed the time to 'new ILD' in real-world and HRs (crude and adjusted). Propensity scores were not calculated due to the following: potential factors for estimating treatment-trends were lacking, multiple AD were included and with no large differentiation in ages among 4888 patients, and many non-elderly patients with new ILD were found, the methodology of this study provided reasonable real-world evidence, comparing JAKi with TNFi using clinical data collected based on uniform criteria from a nationwide large-scale EMR database. The results were consistent with previous information. Although the cumulative incidence of new ILD (1) in JAKi users was not significantly different from that in TNFi users, events increased with treatment duration and the timing of event-occurrence was consistent with published guidelines on ILD (from 1 to 2 weeks; within 100 days; from 2–3 weeks to 2–3 months; within several years) [9–11]. The risk factors included RA and DM, which are systemic inflammatory diseases, and other immune diseases associated with fibrosis. Patients with these factors should be monitored carefully over time. New ILD (1), defined as a more sensitive measurement, could reflect all adverse events occurring during therapy, including events whose causal relationship to the progress of inflammation and/or fibrosis in the underlying disease cannot be ruled out [37,38].

In contrast, cumulative incidence of new ILD (2) in JAKi users was significantly higher than in TNFi users. The timing of event-occurrence was very early after treatment-start, especially in JAKi users (mean, 20.48 days), consistent with published guidelines on ILD [9,11]. The risk factors were not only JAKi itself, but also RA, DM and CVD, which are systemic inflammatory diseases. HRs adjusted by the Cox proportional hazards model supported JAKi's causality and robustness. The records for pre and concomitant therapy indicated that almost no JAKi users with new ILD (2) had experienced TNFi/biologics. Also, none had experienced any immunosuppressant before or any concomitant methotrexate. New ILD (2), defined by a prompt treatment-stop, could reflect adverse drug reaction more specifically. That is, new ILD (2) could be induced by drug cytotoxicity and/or altered immune responses, because systemic inflammation had made the ultimately affected AD patients more susceptible [37].

For KL-6 value before treatment-start, results of already over 500 in patients developed new ILD (1) could teach highly susceptible lung condition potentially developing new ILD (1); although results of already close to 500 in those developed or did not develop new ILD (2) might reflect similar lung condition, it was under 500 difficult to judge starting JAKi. Furthermore, because the number of KL-6 test was under 10 among JAKi users with new ILD (2), the KL-6 value may not be adequately representative, and should be re-evaluated after accumulating more data. Exploratory analysis indicated that KL-6 was

monitored more after starting JAKi than before, and was used more than radiography testing in this study. Anyway, before starting JAKi, patients should be carefully examined.

There was no significantly different new ILD risk between the elderly and non-elderly, female and male, and patient with or without other lung diseases, among either JAKi or TNFi users. Several explanations, alone or together, might help explain this. First, the elderly could be in a state of higher inflammation, but one masked by random chance in who developed new ILD. Another possibility is that those with younger onset may indeed suffer from inherently more inflammatory conditions. In addition, 2.0–3.0% of database entries lacked age data. Relevant to the male to female ratio, the RWD database had no data on smoking, even though it carries a known risk of ILD in males [17], and such added risk may have offset the increased risk of new ILD attributable to higher AD susceptibility in females. Finally, the sample size of patients with other lung diseases was small.

It is important for rheumatologists to use JAKi properly, taking new ILD risks into considerations when treating RA, based on package inserts [18–22] and guidelines [23–27,33]. Also, this admonition is important for gastroenterologists as well because some patients with UC have RA and/or systemic inflammatory diseases that could predispose them to new ILD aside from the events (infection, herpes zoster, hepatitis B, tuberculosis and embolism) described in their guidelines [34].

Limitations to this study include the following. (1) Data were not prospectively collected because this is a database study, and some entries lacked specification of patient age, so further prospective studies are desired. (2) Possible bias of treatment-trends exists due to different approval timings of the therapeutics. Thus, we compared new users after July 2013 for both JAKi and TNFi to enhance comparability when analyzing effects by therapeutic class. (3) Although considering confounders is important in observational studies, unmeasured confounders (e.g., smoking) could not be analyzed. Despite the limitations, we could analyze risk factors for new ILD utilizing real-world EMR instead of relying only on claims data, and this study provided meaningful insights.

JAKi use has become widespread. AD patients had higher risk of new ILD (2) and subsequent death, along with a significantly higher cumulative incidence when treated with JAKi than with TNFi. JAKi and systemic inflammatory diseases increased risk. ILD screening should be conducted for pharmacovigilance/risk minimization. Further studies are expected to provide a safety profile for future AD management.

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Author contributions

MY designed this database study, prepared the statistical analysis plan, acquired the data, analyzed and interpreted the data, and drafted the manuscript. KY cooperated to the data interpretation and the draft development. All authors approved the final manuscript.

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The authors report there are no conflicts of interest to declare. MY is an employee of Pfizer R&D Japan G.K., but this study reflects only the personal views of authors.

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Data availability statement

Data are not publicly available because the database was obtained from the HCEI through public offering and their review.

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