Effectiveness and safety of tofacitinib in rheumatoid arthritis-associated interstitial lung disease: TReasure real-life data

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Abstract

Objective

Rheumatoid arthritis associated interstitial lung disease (RA-ILD) is a major concern in RA. These patients have been included in clinical trials and in the post-marketing setting of RA patients using tofacitinib. We aimed to assess the real-life efficacy and safety of tofacitinib in patients with RA-ILD.

Methods

RA patients with ILD diagnosis based on the HRCT images of the lungs from eight different centres recruited to study. As a control group, RA patients without ILD under tofacitinib were included. Demographic data, patients' characteristics, available pulmonary function tests regarding RA and RA-ILD at the visit in which tofacitinib was initiated and for the last follow-up visit under tofacitinib were recorded. Reasons for tofacitinib discontinuation were also recorded. Drug retention rates were compared by log-rank test. p-value <0.05 was considered statistically significant.

Results

A total of 47(42.6% male) RA patients with RA-ILD and a control group of 387 (17.8% male) patients without RA-ILD were included in analysis. After the median of 12 (9-19) months follow-up, mean FEV1%; 82.1 vs. 82.8 (pre/post-treatment, respectively, p=0.08), mean FVC%; 79.8 vs. 82.8 (pre/post-treatment, respectively, p=0.014) were stable and worsening was observed in 2/18 (11.1%) patients. Retention rates were similar (p=0.21, log-rank). In RA-ILD group, the most common cause of drug discontinuation was infections (6.3 vs. 2.4 per 100 patient-years).

Conclusion

Treatment strategy of RA-ILD patients is still based on small observational studies. A high rate of discontinuation due to infections was observed in RA-ILD patients under tofacitinib; however, RA-ILD patients were older than RA patients without ILD.

Key words

tofacitinib, rheumatoid arthritis, interstitial lung disease

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Introduction

Joint is the primary target tissue in patients with rheumatoid arthritis (RA); however, extra-articular involvement can occur at the onset or during disease (1, 2). The lungs are the most important site of involvement among extra-articular regions. Respiratory system (such as airway or pleura) involvement and parenchymal involvement (such as interstitial lung disease ([ILD]) can be seen in RA patients (1, 3). ILD is mainly detected by high-resolution computed tomography (HRCT) of the lung. Usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP) are the most common pattern on HRCT imaging. While the frequency of subclinical ILD is 30–50% in RA patients, clinically apparent ILD is encountered at a frequency of 5–10% (4). In RA, ILD not only leads to morbidity but also is an important cause of mortality. Indeed, pulmonary complications account for 10–20% of RA-associated deaths (5).

What is the most appropriate treatment strategy when ILD is detected in RA patients has always been the matter of debate. Data on this topic mainly come from observational studies. A study comprising 156 RA patients with ILD who were followed in our centre within the last 10 years revealed that 46% of the patients received at least one biologic or targeted synthetic disease modifying anti-rheumatic drug (DMARD) (6). Requirement for a biologic DMARD (bDMARD) is approximately 2 times higher in RA patients with ILD than those without. The most frequently preferred advanced therapies both in our patient group and in the literature include rituximab and/or anti-tumour necrosis factor (TNF) drugs. There is quite limited data on the use of tofacitinib, which is an oral Janus kinase inhibitor to treat RA and has become available in routine practice in recent years, in patients with RA-associated ILD. In fact, in an animal model (SKG mice), it was demonstrated that tofacitinib reduced both arthritis and ILD by enhancing the expansion of myeloid derived suppressor cells (MDSC) (7). Tofacitinib remarkably suppressed the progression of ILD in mice as compared to controls (7). It is important to note that events of ILD have been reported in patients treated with tofacitinib in clinical trials and in the post-marketing setting. A recent *post-hoc* analysis from 21 tofacitinib trials showed that incidence rates for ILD events were 0.18 for both doses of tofacitinib and associated with known risk factors for ILD (8). Thus, the present study aimed to assess the changes in pulmonary signs in RA patients with ILD who received tofacitinib in any period of their lives and were followed in 10 different centres participated in the TReasure database.

Methods

Study population

This multicentre observational study included RA patients who received at least 1 dose of tofacitinib, had ILD diagnosis based on the HRCT images of the lungs, and were followed in 10 different centres took part in the TReasure database. Diagnosis of RA was established by the treating physicians and all patients fulfilled the 1987 American College of Rheumatology (ACR) and/or the 2010 European League against Rheumatism (EULAR)/ACR classification criteria for RA. From the patients registered in the TReasure database, a control group was formed from those who were receiving tofacitinib for RA but had no ILD.

Data collection

The demographic data of the patients, including age, sex, educational status, smoking history, comorbidities, and body mass index (BMI) were recorded. For the evaluation of patients' characteristics regarding RA, the following data were obtained: disease duration, duration of tofacitinib use, seropositivity (presence of rheumatoid factor and/or anti-cyclic citrullinated peptides), rate of quantiFERON/purified protein derivative (PPD) positivity, reasons for discontinuation of tofacitinib (if discontinued), use of conventional synthetic (cs) DMARDs and corticosteroids before and while receiving tofacitinib treatment, and bDMARDs used before tofacitinib treatment. Scores of the disease activity indexes (the Disease Activity Score [DAS]-28, the Simplified Disease Activity Index [SDAI], and the Clinical

Disease Activity Index [CDAI]) were recorded for the visit in which tofacitinib was initiated and for the last follow-up visit. For evaluation of the effects of tofacitinib on laboratory parameters, following patients' data were recorded for the visit in which tofacitinib was initiated and for the last follow-up visit: anemia, leukopenia, thrombocytopenia, hyperlipidaemia, a high erythrocyte sedimentation rate (ESR), and a high C-reactive protein level.

The patients' data recorded for evaluation of ILD included duration and subtypes of ILD, initial ILD symptoms, presence of an ILD sign in the chest x-ray, presence of rheumatoid nodules and pleural effusion, presence of a change in rheumatoid nodules and pleural effusion as compared with control images, percent predicted forced expiratory volume in one second (FEV1%) and percent predicted forced vital capacity (FVC%) before and while receiving tofacitinib treatment, and presence of a lung infection while receiving tofacitinib treatment. Using the present study cohort, the RA patients with ILD receiving tofacitinib were compared with those without ILD receiving tofacitinib (controls) in terms of the general and disease-related characteristics and data concerning concomitant DMARD use. For the evaluation of retention rates of tofacitinib and reasons for discontinuation, data of the RA patients with ILD receiving tofacitinib in this study cohort were compared with the data of RA patients without ILD receiving tofacitinib who were followed in Hacettepe University.

Ethical approval and consent to participate

The study was conducted in compliance with the Helsinki Declaration and was approved by the Local Ethics Committee of Hacettepe University (KA-17/058) in May 2017 and by the Republic of Turkey Ministry of Health (93189304-14.03.01) in October 2017.

Statistical analyses

The statistical analysis was performed using the PASW Statistics for Windows, v. 18.0. (SPSS Inc., Chicago, IL, USA). Normality of the variables was tested using visual (histogram, probability plots) and analytical methods (Kolmogorov-Smirnov, skewness, and kurtosis). Descriptive variables were expressed as mean and standard deviation (SD) or median and 25th (Q1) and 75th percentile (Q3). Categorical variables were compared using the Chi-square test or Fisher's exact test, where appropriate. Non-normally distributed continuous variables between two groups were compared using the Mann-Whitney U-test. Wilcoxon signed-rank test was used to analyse the changes in FEV1% and FVC% between before and after the tofacitinib treatment. Kaplan-Meier survival analysis was used to calculate drug retention rates. Log-rank test was used to compare drug retention rates between RA patients with and without interstitial lung disease (ILD) who received at least 1 dose of tofacitinib. A p-value of <0.05 was considered statistically significant.

Table I. Demographic and clinical characteristics of the rheumatoid arthritis patients with and without interstitial lung disease receiving tofacitinib.

Variables	RA patients with ILD n=47	RA patients without ILD n=387	p-value
Male sex	20 (42.6)	69 (17.8)	<0.001
Age, years	64 (57-69)	56 (46-64)	<0.001
Disease duration for RA, months	128 (78-212)	110 (64-183)	0.171
Smoking status			
Never smoker	26 (55.3)	211 (56.4)	0.259
Current smoker	7 (14.9)	85 (22.7)	
Former smoker	14 (29.8)	78 (20.9)	
Educational status (high school and above)	13 (44.8)	112 (30.7)	0.115
RF positive	36 (78.3)	249 (68.8)	0.187
Anti-CCP positive	30 (65.2)	196 (61.6)	0.640
RF positive or CCP positive	41 (87.2)	242 (76.3)	0.094
QuantiFERON positivity	8 (25.8)	35 (17.9)	0.301
PPD positivity	12 (42.9)	74 (47.4)	0.655
Presence of comorbidity	33 (70.2)	203 (52.5)	0.021
DAS-28 score before tofacitinib	5.4 (4.6-6.22)	4.36 (3.22-5.58)	<0.001
ESR before tofacitinib, mm/h	38 (19-73)	29 (17-45)	0.029
CRP before tofacitinib	6.75 (1.63-24)	9.95 (4.18-25.1)	0.065
csDMARDs used before tofacitinib			
Methotrexate	37 (78.7)	305 (78.8)	0.989
Sulfasalazine	33 (70.2)	179 (46.3)	0.002
Hydroxychloroquine	28 (59.6)	271 (70)	0.144
Leflunomide	30 (63.8)	223 (57.6)	0.415
Steroids	46 (97.9)	179 (46.3)	<0.001
Concomitant csDMARDs used under tofacitinib			
Methotrexate	14 (29.8)	116 (30.0)	0.979
Sulfasalazine	3 (6.4)	24 (6.2)	1.000
Hydroxychloroquine	19 (40.4)	193 (49.9)	0.221
Leflunomide	18 (38.3)	115 (29.7)	0.228
Steroid	37 (78.7)	288 (74.4)	0.520
Duration of follow-up during tofacitinib treatment	15 (7-32)	7 (3-12)	<0.001

Data are presented as number (percentage, %), median (25th and 75th percentile [Q1 and Q3]), where appropriate. CCP: anti-cyclic citrullinated peptide; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; CRP: C-reactive protein; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; ILD: interstitial lung disease; PPD: purified protein derivative; RA: rheumatoid arthritis; RF: rheumatoid factor.

Results

Characteristics of the study population

The present study included a total of 47 RA patients with ILD and a control group including 387 RA patients who received tofacitinib but had no ILD. The demographic and clinical characteristics of these groups are summarised Table I. The RA patients with ILD receiving tofacitinib were mostly male, older, and had higher baseline disease activity as compared with those without ILD receiving tofacitinib. While 31 (66.0%) of 47 RA patients with ILD

Table II. Demographic and clinical characteristics of the rheumatoid arthritis patients with and without interstitial lung disease receiving tofacitinib (n=44).

Variables	NSIP (n=24)	UIP (n=16)	Airway disease (n=4)
Male sex	10 (41.7)	9 (56.3)	1 (25)
Age, years	61 (56-66)	67 (56-74)	68 (66-73)
Disease duration for RA, months	127 (79-201)	139 (55-224)	145.5 (99-170)
Smoking status			
Never smoker	15 (62.5)	8 (50)	2 (50)
Current smoker	3 (12.5)	4 (25)	0 (0)
Former smoker	6 (25)	4 (25)	2 (50)
Educational status (≥high school)	7 (41.2)	6 (60)	0 (0)
RF positive	16 (69.6)	14 (87.5)	3 (75)
Anti-CCP positive	16 (66.7)	11 (68.8)	1 (25)
RF positive or CCP positive	20 (83.3)	15 (93.8)	3 (75)
QuantiFERON positivity	5 (31.3)	2 (18.2)	0 (0)
PPD positivity	9 (64.3)	3 (37.5)	0 (0)
Presence of comorbidity	16 (66.7)	11 (68.8)	4 (100)
DAS-28 score before tofacitinib	5.42 (4.68-6.26)	5.4 (4.6-5.8)	5.9 (4.25-6.4)
ESR before tofacitinib, mm/h	35.5 (20-70)	45 (24-74.5)	24 (14-44)
CRP before tofacitinib	5.22 (1.51-25.5)	14.65 (6.45-25.85)	2.525 (1.45-31)
csDMARDs used before tofacitinib			
Methotrexate	20 (83.3)	10 (62.5)	4 (100)
Sulfasalazine	18 (75)	11 (68.8)	2 (50)
Hydroxychloroquine	16 (66.7)	6 (37.5)	4 (100)
Leflunomide	13 (54.2)	11 (68.8)	3 (75)
Steroids	23 (95.8)	16 (100)	4 (100)
Concomitant csDMARDs used under tofacitinib			
Methotrexate	6 (25)	5 (31.3)	2 (50)
Sulfasalazine	2 (8.3)	0 (0)	0 (0)
Hydroxychloroquine	11 (45.8)	5 (31.3)	1 (25)
Leflunomide	7 (29.2)	7 (43.8)	2 (50)
Steroid	22 (91.7)	11 (68.8)	2 (50)
Duration of follow-up during tofacitinib treatment	15 (8-28.5)	16 (7.5-26.5)	13 (8.5-35.5)

Data are presented as number (percentage, %), median (25th and 75th percentile [Q1 and Q3]), where appropriate.
AD: airway disease; CCP: anti-cyclic citrullinated peptide; csDMARD: conventional synthetic disease-modifying anti-rheumatic drug; CRP: C-reactive protein; DAS: Disease Activity Score; ESR: erythrocyte sedimentation rate; ILD: interstitial lung disease; NSIP: non-specific interstitial pneumonia; PPD: purified protein derivative; RA: rheumatoid arthritis; RF: rheumatoid factor; UIP: usual interstitial pneumonia.

receiving tofacitinib did not previously receive another advanced therapy, 16 (34%) were received tofacitinib after treatment together with at least one bDMARD (anti-TNF in 13 [27.7%] patients, abatacept in 7 [14.9%] patients, rituximab in 6 [12.8%] patients, tocilizumab in 2 [4.3%] patients). Shortness of breath was less prevalent in the tofacitinib-naïve patients as compared with those initiated on tofacitinib after treatment with at least one of the advanced therapies (10 [37.0%] *vs*. 11 [73.3%], p=0.024); no difference was determined in other parameters.

Pulmonary findings in the RA patients with ILD receiving tofacitinib

The disease pattern was available in 44 (93.6%) of 47 RA patients with ILD receiving tofacitinib based on their HRCT images of the lungs. Of these 44 patients, 16 (36.3%) had UIP, 24 (54.5%) had NSIP, and 4 (9.1%) had airway disease. Demographic and clinical characteristics of these patients were given in Table II. Findings consistent with ILD were visible on anterior-posterior chest x-ray in 33 (70.2%) of 47 patients. No ILD symptom was determined in 15 (31.9%) of the patients. The distribution of ILD-related initial symptoms was shortness of breath in 14 (29.7%) patients, cough in 20 (42.5%) patients, sputum in 1 (2.1%) patient, and chest pain in 1 (2.1%) patient. Shortness of breath occurred in 21 (44.6%) patients during the follow-up.

Data of FVC% and FEV1% were available in 22 patients before the treatment with tofacitinib, whereas these values were available in 18 patients both before and after the treatment with tofacitinib. Median time between two tests was 12 months (Q1–Q3, 9–19 months). Pre- and post-treatment FVC% and FEV1% of the patients are shown in Figure 1. Although the overall increase was statistically significant, it was not clinically significant. In the follow-up, worsening of FVC% by >5% was observed in 2 (11.1%) of 18 patients, one of them with UIP pattern had worsening of FVC% by >15%.

Retention rates of tofacitinib and reasons for discontinuation

For evaluation of retention rates of tofacitinib and reasons for discontinuation, the RA patients with ILD receiving tofacitinib (n=47) in the present study were compared with the RA patients without ILD receiving tofacitinib (n=239) who were followed at Hacettepe University. Median follow-up duration for the RA patients with ILD receiving tofacitinib (n=47) was 15 (Q1–Q3, 7–32) months. During the follow-up period, tofacitinib was discontinued in 20 (42.6%) patients with ILD. The reasons for tofacitinib discontinuation were shown in Table III. In addition, reasons for drug discontinuation in patients with known RA-ILD pattern (n=44) were given in Table IV. The median follow-up duration for RA patients without ILD (n=239) was 11 months (Q1–Q3, 4–24 months). Tofacitinib was discontinued in 106 (44.3%) of these patients (Table III). Concomitant methotrexate use with tofacitinib therapy was more common in the RA patients with ILD who discontinued tofacitinib therapy during the follow-up than in those who did not discontinue tofacitinib therapy (45.0% *vs*. 18.5%, p=0.05). The rate of drug discontinuation due to infection in the RA patients with and without ILD was 6.3 per 100 patient-years and 2.4 per 100 patient-years, respectively. The retention rates of tofacitinib are shown in Figure 2. RA patients with and without ILD did not differ in terms of retention rate of tofacitinib (p=0.21).

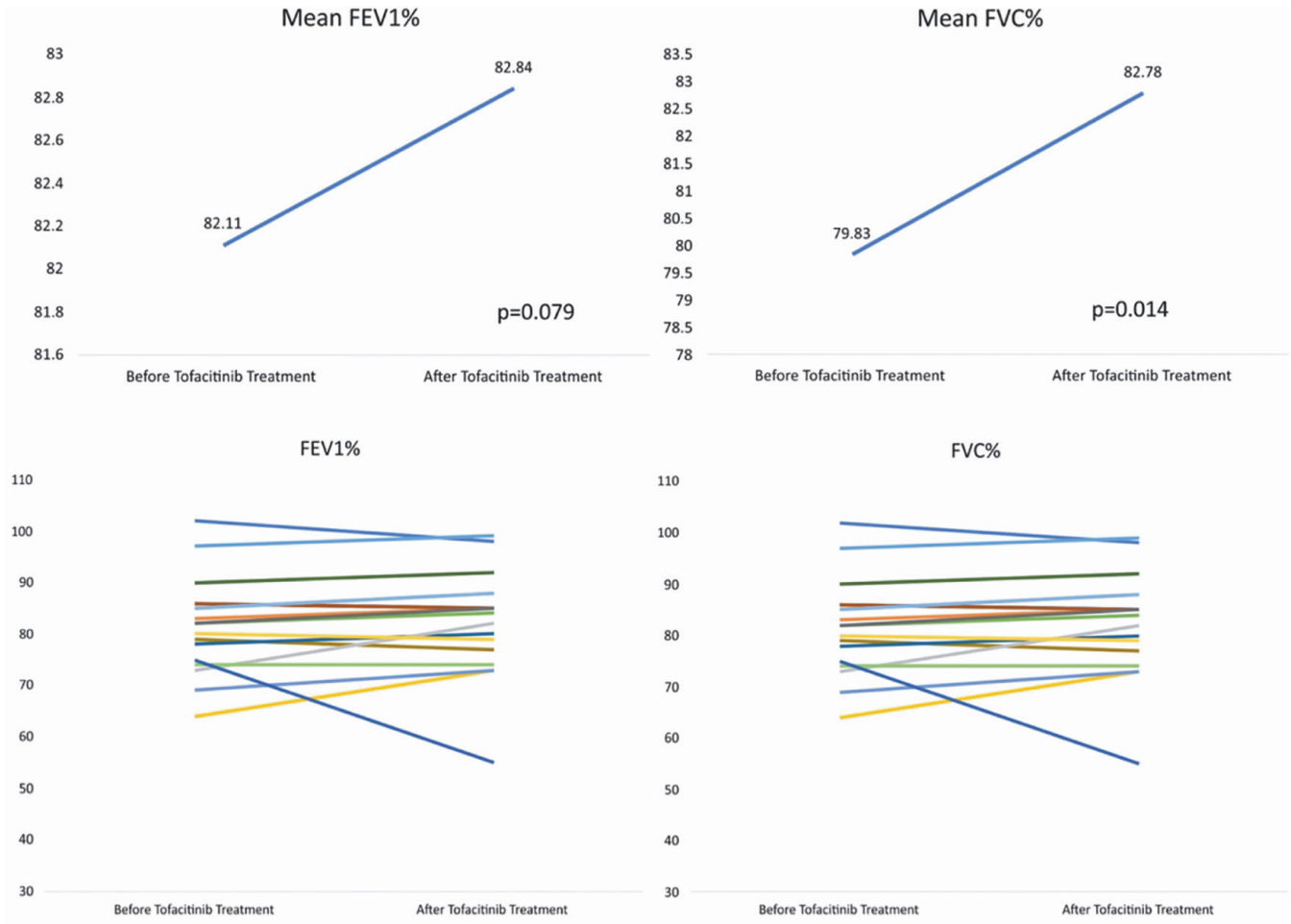

Fig. 1. Change in the percent predicted forced expiratory volume in one second (FEV1%) and percent predicted forced vital capacity (FVC%) values before and after treatment with tofacitinib in rheumatoid (RA) patients with interstitial lung disease (ILD) receiving tofacitinib.

Discussion

Rheumatoid arthritis with ILD has always been one of the problematic involvements from the perspective of rheumatology. In the last 25 years, a significant improvement has been observed in the prognosis of patients with RA-associated ILD; the median age of death has increased to 78 years from 63 years (8). Advancements in treatment modalities can be considered the main possible reason for this improvement. Fundamentally, rituximab (a B-cell blocker) and anti-TNF agents are among the most frequently employed preferred bDMARDs in RA and lung involvement (4). Data from several studies have suggested that rituximab might be superior to anti-TNF agents (9). Data on the safety and efficacy of JAK kinase inhibitors, which were introduced into use to treat RA in the last decade, are quite limited in the presence of RA and ILD. The present study retrospectively evaluated the efficacy and safety of tofacitinib in RA-associated ILD. Pulmonary functions remained stable after one year of treatment in the majority of patients receiving tofacitinib. Treatment change due to impairment in pulmonary functions was required in only a small proportion of patients. It was observed that infection was slightly more prominent as the reason for treatment discontinuation in the RA patients with ILD. However, it should be kept in mind that RA-ILD patients were older than RA patients without ILD. The retention rates of tofacitinib did not significantly differ between the RA patients with and without ILD.

Stabilisation of pulmonary function test results in RA patients with ILD is one of

Table III. Reasons for drug discontinuation in the patients receiving tofacitinib.

	RA patients with ILD n=47	RA patients without ILD n=239	*p*-value
Tofacitinib discontinuation	20 (42.6)	106 (44.3)	0.87
Reasons for tofacitinib discontinuation			
Inefficacy	7 (35.0)	56/106 (52.8)	
Patient's/physician's request	3 (15.0)	16/106 (15.1)	
Infection	5 (25.0)	7/106 (6.6)	
Worsening of pulmonary functions	2 (10.0)	0 (0)	
Other	3 (15.0)	27/106 (25.5)	

Data are presented as number (percentage, %).
ILD: interstitial lung disease; RA: rheumatoid arthritis.

Table IV. Reasons for drug discontinuation in the patients receiving tofacitinib in patients with known RA-ILD pattern (n=44).

	NSIP	UIP	AD
Tofacitinib discontinuation	10 (41.7)	7 (43.8)	2 (50)
Reasons for tofacitinib discontinuation			
Inefficacy	4 (16.6)	3 (18.8)	0 (0)
Patient's/physician's request	2 (8.3)	0 (0)	0 (0)
Infection	2 (8.3)	3 (18.8)	1 (25)
Worsening of pulmonary functions	1 (4.2)	0 (0)	1 (25)
Other	1 (4.2)	1 (6.3)	0 (0)

Data are presented as number (percentage, %).
AD: airway disease; ILD: interstitial lung disease; NSIP: non-specific interstitial pneumonia; RA: rheumatoid arthritis; UIP, usual interstitial pneumonia.

the critical endpoints. A recently published review, the rate of worsening of pulmonary findings in RA patients with ILD was found as 15.5%, 8.5%, 17.0%, and 16.9% in those receiving anti-TNF agents (n=96), abatacept (n=187), tocilizumab (n=41), and rituximab (n=201), respectively (10). In 2017, Yusof *et al.* (11) published a 10-year data of 56 RA patients with ILD who received rituximab and were followed in Leeds. In that patient group, the pulmonary function test results were available in 37 patients at the 6th and 12th months both before and after rituximab treatment. They observed a numerical improvement by +1.2% in FVC% and reported the proportion of patients with improvement, stabilisation, and worsening of pulmonary function test results to be 19%, 65%, and 13%, respectively (11). Another a study evaluating the efficacy of anti-TNF agents in RA patients with ILD, pulmonary function tests were performed in 42 patients at baseline and after 1 year of treatment (12). It was reported that, while the mean FVC% remained stable, a numerical decrease by 4 units was observed in the FEV1% (12). In the present study, pulmonary function tests were also evaluated before and after treatment in 18 patients receiving tofacitinib. In the present study, with a follow-up duration of median 12 months, the FVC% showed a numerical improvement by +3.0% from baseline, whereas the FEV1% remained stable. Evaluating the pulmonary function tests, the worsening of FVC% was over 5% in 11% of the patients; these rates were parallel to those obtained with other bDMARDs. Although it was an indirect comparison, absence of a remarkable worsening of pulmonary

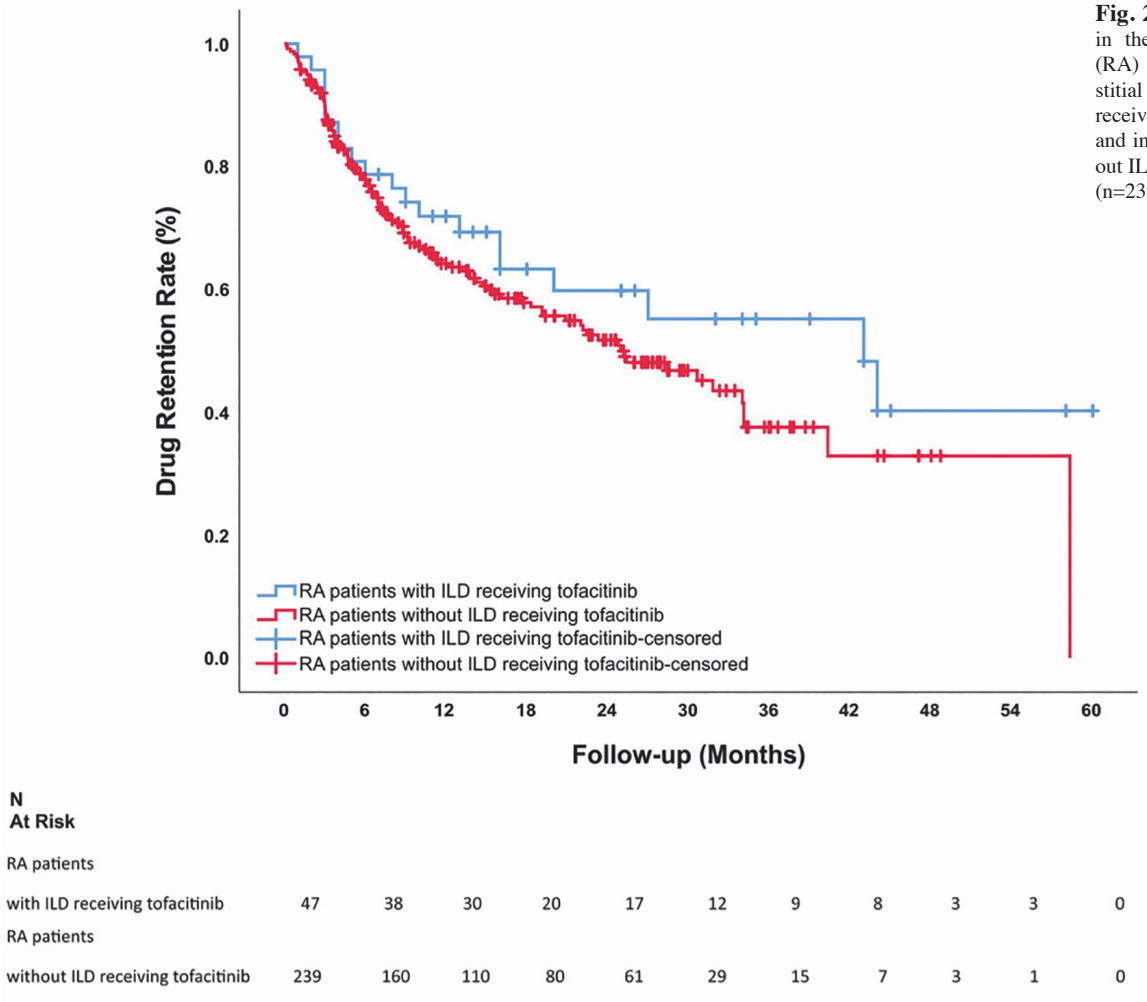

Fig. 2. Drug retention rates in the rheumatoid arthritis (RA) patients with interstitial lung disease (ILD) receiving tofacitinib (n=47) and in the RA patients without ILD receiving tofacitinib (n=239).

function test results of the patients receiving tofacitinib for RA-associated ILD was an important finding that needs to be confirmed in further prospective studies.

In our retrospective cohort, the RA patients with ILD receiving tofacitinib were mostly male, older, and were receiving steroids in higher frequency than without ILD. Baseline disease activity was slightly higher in the RA patients with ILD than in those without ILD. Recently, *post-hoc* analysis of incidence rates of ILD occurrence in RA patients receiving tofacitinib was published (8). In this analysis, almost seven thousand patients from 21 different studies were assessed. Of note, older age, current smoking, and disease activity scores were significant risk factors for ILD occurrence and these findings were consistent with our results. In addition, no difference was determined between the RA patients with and without ILD in terms of tofacitinib discontinuation rates. Drug retention is one of the important criteria for effectiveness and safety. The effects of ILD on drug retention rates have not been primarily evaluated in the earlier studies conducted with bDMARDs. From this point of view, drug retention rate is one of the important findings in RA patients regardless of the presence/absence of ILD. This issue requires accumulation of data from studies with other bDMARDs (13). One of the critical problems related to the advanced therapies in RA patients with ILD is particularly the infections of lower respiratory tract. In the present study, serious infection requiring drug discontinuation was also more prevalent in the RA patients with ILD receiving tofacitinib than in those without ILD receiving tofacitinib (6.3 per 100 patient-years and 2.4 per 100 patient-years, respectively). In a study conducted with rituximab, the incidence of severe infection was found to be 7.7 per 100 patient-years (10). As a consequence, this patient group is associated with an increased risk of infection. Therefore, this potential adverse event should always be kept in mind while initiating tofacitinib or other advanced therapies.

The present study has critical limitations. Since this study was a non-interventional observational study, baseline pulmonary functions of all patients could not be evaluated. Also, DLCO and TLC were not available for most of the patients. Also, number of the patients with control pulmonary function tests was very low. Besides, we did not collect data regarding possible toxic exposure other than smoking. Nevertheless, evaluation of pulmonary functions before and after tofacitinib therapy was available in 18 patients; thus, the study is valuable as it is the first to provide such data specific to tofacitinib. Although we had pre-treatment HRCT images of the lungs of the patients, the lack of data on the follow-up images is also one of the limitations.

Conclusion

In conclusion, although the present study was not a head-to-head comparative study, worsening of pulmonary functions was comparable in patients receiving tofacitinib for RA-associated ILD and those receiving other advanced therapies. In current study, older patients with a high number of comorbidities had a higher risk of treatment-related serious adverse events, hence, it should be kept in mind that drug discontinuation due to infections was relatively higher. Pulmonary functions remained stable during the one-year follow-up in the majority of patients with pre- and post-treatment pulmonary function tests. It is important to note that occurrence of ILD have been reported in patients treated with tofacitinib in RA clinical trials and in the post-marketing setting and and this issue warrants further large-scale, prospective controlled studies.

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