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

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Abstract

Background/Aim:

Rheumatoid arthritis associated interstitial lung disease (RA-ILD) is a major concern in RA patients and events of ILD have been reported in patients treated with tofacitinib in RA clinical trials and in the post-marketing setting. The aim of this study was 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 centers recruited to study. As a control group, RA patients without ILD under tofacitinib was 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 of 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 the analysis. After the median of 12 (9–19) months follow-up period, mean FEV1%; 82.1 vs. 82.8 (pre and post-treatment, respectively, p = 0.079), mean FVC%; 79.8 vs. 82.8 (pre and post-treatment, respectively, p = 0.014) were stable and worsening was observed 2/18 (11.1%) patients. Retention rates were similar (p = 0.21, log-rank). In RA-ILD group, most common cause of drug discontinuation was infections (6.3 vs 2.4 per 100 patient-years).

Conclusion

The treatment strategy of RA-ILD patients are still based on small observational studies. High rate of discontinuation due infections was observed in RA-ILD patients under tofacitinib; however, RA-ILD patients were older than RA patients without ILD.

Introduction

Joints are the primary target tissue in patients with rheumatoid arthritis (RA) ; however, extra-articular involvement can occur at the onset or during the course of disease (1). 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 (2). 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% (3). 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 (4).

What kind of changes need to be done in treatment when ILD is detected in RA patients has always been the matter of debate. Most of the data on this topic have been derived from observational studies. A study comprising 156 RA patients having ILD who were followed in our center within the last 10 years revealed that 46% of the patients were received at least one biologic or targeted synthetic disease modifying anti-rheumatic drug (DMARD) (5). Accordingly, 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-tumor necrosis factor (TNF) drugs. There is quite limited data on the use of tofacitinib, which is an oral Janus kinase inhibitor for the treatment of 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 in a murine model by enhancing the expansion of myeloid derived suppressor cells (MDSC) (6). Moreover, tofacitinib remarkably suppressed the progression of ILD in mice as compared with controls (6). It is important to note that events of ILD have been reported in patients treated with tofacitinib in RA 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 (7). 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 centers participated in the TReasure database.

Methods

Study population

This multicenter 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 centers participated 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

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. Additionally, the 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, the presence of the following patients' data was recorded for the visit in which tofacitinib was initiated and for the last follow-up visit: anemia, leukopenia, thrombocytopenia, hyperlipidemia, 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. On the other hand, 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.

Statistical analyses

Statistical analysis was performed using the PASW Statistics for Windows, version 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. The Wilcoxon signed-rank test was used to analyze the changes in FEV1% and FVC% between before and after the tofacitinib treatment. The Kaplan Meier survival analysis was used to calculate drug retention rates. The 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.

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 summarized Table 1. 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 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.

Table 1
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
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

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.

Variables	RA patients with ILD n = 47	RA patients without ILD n = 387	p
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.

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. Accordingly, of these 44 patients, 16 (36.3%) had UIP, 24 (54.5%) had NSIP, and 4 (9.1%) had airway disease. Findings consistent with ILD were detected 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 as follows: 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-ups.

The values 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. The median time between two tests was 12 months (Q1-Q3, 9–19 months). The pre- and post-treatment FVC% and FEV1% values of the patients are shown in Fig. 1. During the follow-ups, 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 in Hacettepe University. Accordingly, the 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 was shown at Table 2. 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 2). 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 Fig. 2. Accordingly, the RA patients with and without ILD did not differ in terms of retention rate of tofacitinib (p = 0.21).

Table 2
Reasons for drug discontinuation in the patients receiving tofacitinib

	RA patients with ILD n = 47	**RA patients without ILD n = 239**	**p**
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.

Discussion

Rheumatoid arthritis with ILD has always been considered 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 (7). 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 (3). Data from several studies have suggested that rituximab might be superior to anti-TNF agents (8). On the other hand, data on the safety and efficacy of JAK kinase inhibitors, which were introduced into use for the treatment of 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.

Stabilization of pulmonary function test results in RA patients with ILD is one of the critical endpoints. In 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 (9). In 2017, Yusof et al. (10) 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, stabilization, and worsening of pulmonary function test results to be 19%, 65%, and 13% (10). In a study evaluating the efficacy of anti-TNF agents in detail in RA patients with ILD, pulmonary function tests were performed in 42 patients at baseline and after 1 year of treatment (11). It was reported that while the mean FVC% remained stable, a numerical decrease by 4 units was observed in the FEV% (11). In the present study, pulmonary function tests were also evaluated before and after treatment in 18 of the 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 more than 5% in 11% of the patients; these rates were similar to those obtained with other bDMARDs. Although it is an indirect comparison, absence of a remarkable worsening of pulmonary function test results of the patients receiving tofacitinib for RA-associated ILD is 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 had frequent steroid use. Moreover, 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 events in Tofacitinib with RA patients were published (7). In this analysis, almost seven thousand patients from 21 different studies assessed. Of note, older age, current smoking and disease activity score were as significant risk factors for ILD events 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 efficacy 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. 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 (9). As the 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. 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. Despite the presence of pre-treatment HRCT images of the lungs of the patients, lacking data on the follow-up images is also one of the limitations.

Conclusion

In conclusion, although the present study is not a head-to-head comparative study, worsening of pulmonary functions found in the patients receiving tofacitinib for RA-associated ILD was comparable to those for other advanced therapies. This older patient group with high number of comorbidities are at the risk of treatment-related serious adverse events, hence, it should be kept in mind that drug discontinuation due to infections is relatively higher. Even though pulmonary functions remained stable during the one-year follow-up in the majority of our patients, it is important to note that events 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.

Abbreviations

ACR: American College of Rheumatology

BMI: Body mass index

CDAI: Clinical Disease Activity Index

DAS-28: Disease Activity Score 28

DMARD: Disease modifying anti-rheumatic drug

ESR: Erythrocyte sedimentation rate

EULAR: European League against Rheumatism

FEV1: forced expiratory volume in one second

FVC: forced vital capacity

HRCT: High-resolution computed tomography

ILD: Interstitial Lung Disease

MDSC: Myeloid derived suppressor cells

NSIP: Non-specific interstitial pneumonia

PPD: Purified protein derivative

RA: Rheumatoid arthritis

SDAI: Simplified Disease Activity Index

TNF: Tumor necrosis factor

UIP: Usual interstitial pneumonia

Declarations

- Ethical Approval and Consent to participate: The present 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.

- Consent for publication: A written informed consent form was completed by all participants.

- Availability of supporting data: Data is available upon request.

- Competing interests: UK received honorary from Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB. AE received honorary from Amgen, Novartis, Pfizer, Roche, UCB. ED received honorary from Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB. VY Abbvie, Actelion, Amgen, MSD, Novartis, Pfizer, Roche, UCB. GK received honorary from Abbvie, Amgen, Novartis, Pfizer, UCB. CB received honorary from Abbvie, Amgen, MSD, Novartis, Pfizer, Roche, UCB. HE received honorary from Novartis, Roche. İE received honorary from Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB. SK received honorary from Abbvie, Amgen, Johnson and Johnson, MSD, Novartis, Pfizer, Roche, UCB. CSB, SA and TYC are employee and shareholders of Pfizer Inc. Other authors declare no conflict of interest.

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- Authors' contributions: All authors contributed to conceptualization, data gathering, data analyses, writing of the manuscript and final approval of the manuscript.

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Figures

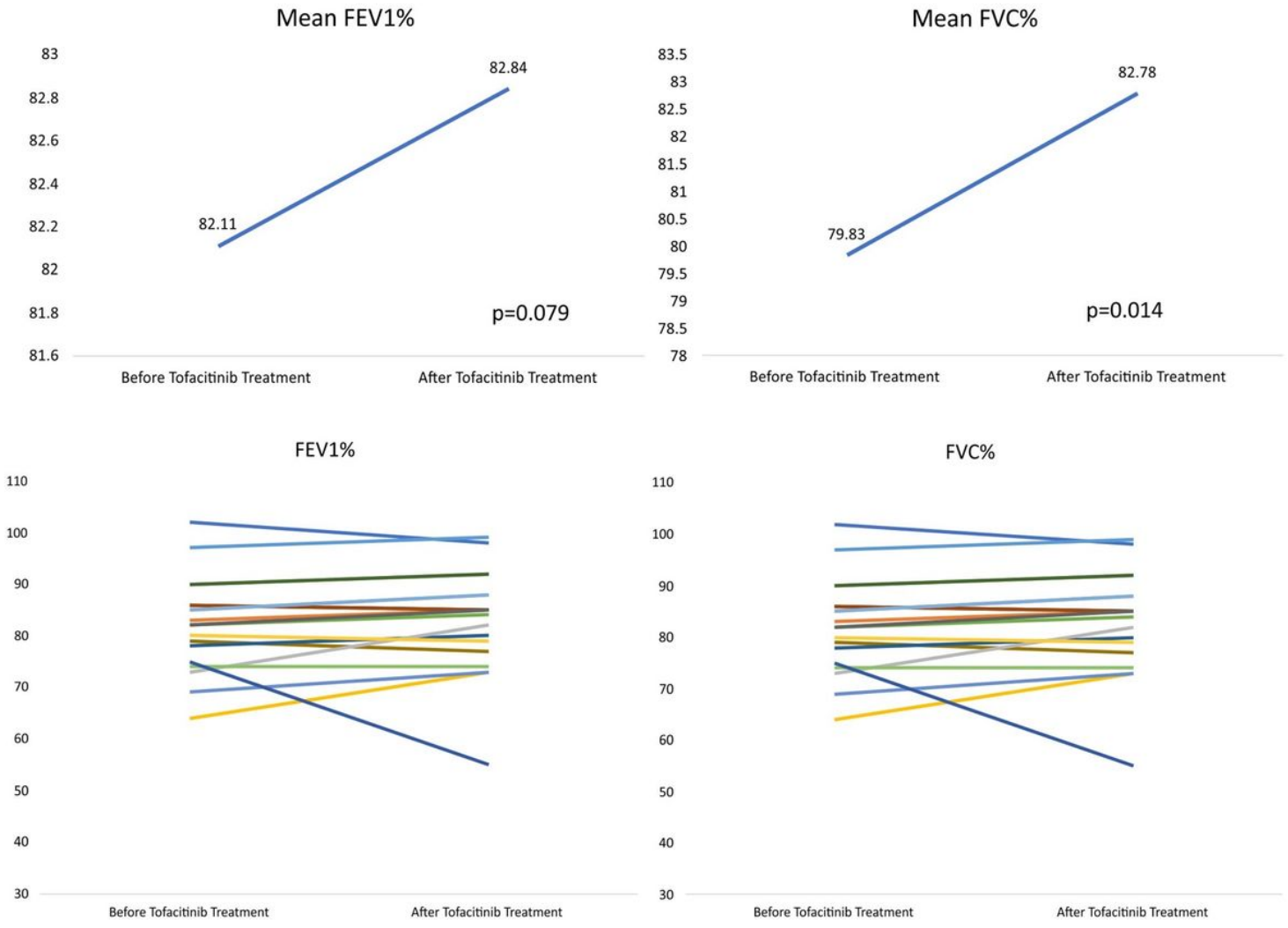
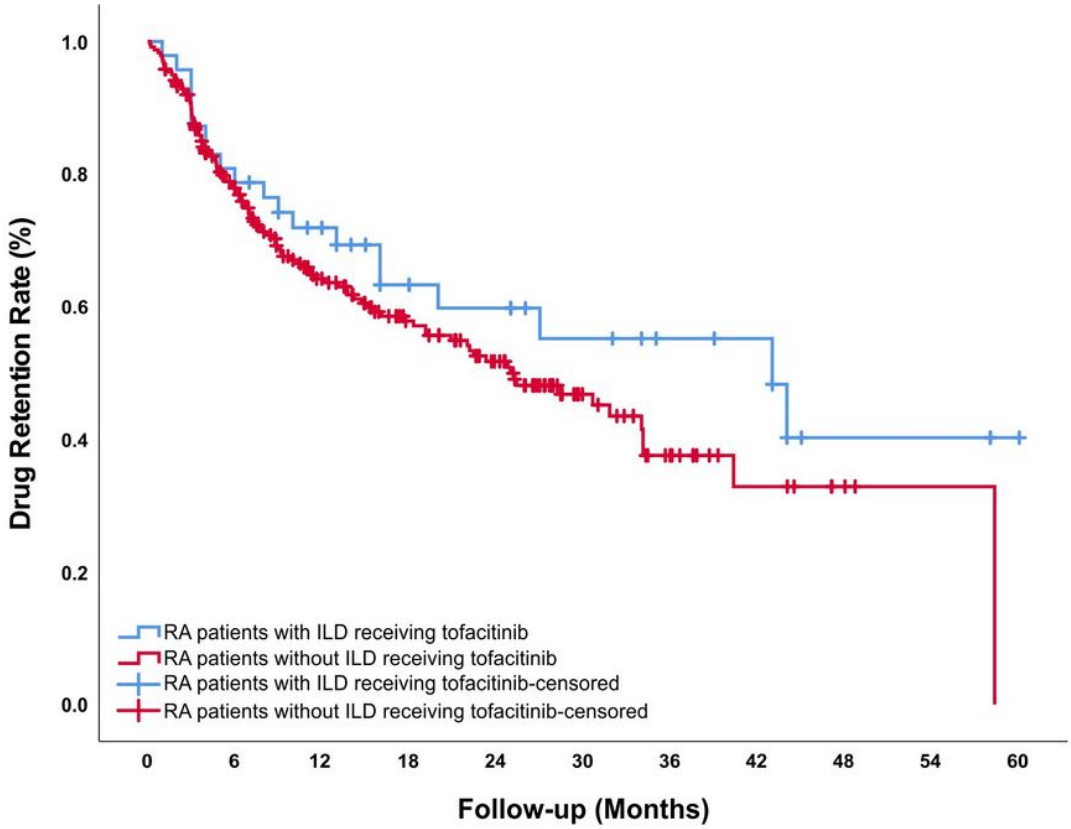


Figure 1

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.



N At Risk											
RA patients with ILD receiving tofacitinib	47	38	30	20	17	12	9	8	3	3	0
RA patients without ILD receiving tofacitinib	239	160	110	80	61	29	15	7	3	1	0

Figure 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)