Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.2226-18
Intern Med 58: 1703-1712, 2019
http://internmed.jp

【 ORIGINAL ARTICLE 】

Effect of Biological Disease-modifying Anti-rheumatic Drugs on Airway and Interstitial Lung Disease in Patients with Rheumatoid Arthritis

Izumi Kurata, Hiroto Tsuboi, Mayu Terasaki, Masaru Shimizu, Hirofumi Toko, Fumika Honda, Ayako Ohyama, Mizuki Yagishita, Atsumu Osada, Hiroshi Ebe, Hoshimi Kawaguchi, Hiroyuki Takahashi, Shinya Hagiwara, Hiromitsu Asashima, Yuya Kondo, Isao Matsumoto and Takayuki Sumida

Abstract:

Objective Biological disease-modifying anti-rheumatic drugs (bDMARDs) represent an important advance in alleviating rheumatoid arthritis (RA), but their effect on rheumatic airway disease (AD) and interstitial lung disease (ILD) is still unclear. This study was performed to evaluate the association of the use of different bDMARDs with new-onset or worsening of RA-AD/ILD.

Methods We performed a retrospective cohort study of RA patients who received bDMARDs and assessed their AD/ILD before and after drug initiation in our hospital over the past 10 years. We evaluated the serial changes in computed tomography (CT), classified patients according to AD/ILD progression, and analyzed associations between clinical characteristics and outcomes.

Results We enrolled 49 patients. Thirty patients received tumor necrosis factor inhibitors (TNFis), 12 received abatacept (ABT), and the remaining 7 received tocilizumab (TCZ). Seventeen patients had ILD, 10 had AD, and 6 had both AD and ILD before the initiation of bDMARDs. New emergence or exacerbation of AD/ILD was observed in 18 patients after drug initiation, while the remaining 31 remained stable or improved. Multiple logistic regression analyses revealed that pre-existing AD was an independent risk factor against the emergence or exacerbation of RA-AD/ILD, and ABT use was a protective factor against it.

Conclusion Our study showed that pre-existing RA-AD is associated with future worsening of RA-AD/ILD, and ABT over other bDMARDs was associated with a better prognosis. Future studies to confirm our results are needed.

Key words: rheumatoid arthritis, biological DMARDs, interstitial lung disease, airway disease, abatacept

(Intern Med 58: 1703-1712, 2019)
(DOI: 10.2169/internalmedicine.2226-18)

Introduction

Rheumatoid arthritis (RA) is a progressive, systemic autoimmune disease characterized by multiple synovitis. Respiratory abnormalities, such as airway disease (AD) and interstitial lung disease (ILD), are the common extra-articular manifestations. The prevalence of AD is reported to be 39-60% (1-3) in RA patients, and recent studies using high-resolution computed tomography (HRCT) reported that RA-ILD was detected in 27-67% (4).

With regard to the lower airways, RA-AD shows varied states from simple bronchiectasis to fatal constrictive bronchiolitis obliterans (5). Despite the fact that smoking and severe, recurrent lower respiratory infections are well-established risk factors for bronchiectasis, the actual etiopathogenic mechanism, including the possible role of RA-specific drugs, is still a matter of debate in the literature (6).

Department of Internal Medicine, Faculty of Medicine, University of Tsukuba, Japan
Received: October 4, 2018; Accepted: December 13, 2018; Advance Publication by J-STAGE: February 25, 2019
Correspondence to Dr. Takayuki Sumida, tsumida@md.tsukuba.ac.jp

The clinical, radiological and histological spectra of RA-ILD are also highly varied, ranging from conditions characterized by an inflammatory infiltrate (susceptible to corticosteroid/immune suppressants) to rapidly progressing fibrotic conditions with poor response to therapy. A higher prevalence of RA-ILD has been demonstrated in smokers, men, the seropositive and those who inherit shared epitopes (7, 8). Thus, local and systemic inflammation together with persistent underlying immune cell activation cooperate to induce the development of ILD. As far as the autoimmune response is concerned, rheumatoid factor (RF) is able to worsen pulmonary inflammation in experimental models, and anti-cyclic citrullinated peptide antibodies (ACPAs) have recently been associated with ILD (7). Although smoking and ACPA are linked (the enzyme responsible for protein citrullination is induced by smoking), the observation of ACPA in the bronchoalveolar lavage fluid (BALF) of non-smoking RA patients clearly indicates the possibility that an inflamed lung can be the initial site of ACPA production (9).

Both AD and ILD are recognized as causes of increased morbidity and mortality compared with RA patients free from respiratory involvement (10). However, an optimal treatment for RA-AD/ILD has not been established. Furthermore, several conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), such as methotrexate (MTX) and leflunomide, are considered to be involved in the development or exacerbation of respiratory abnormalities (11, 12).

Biological DMARDs (bDMARDs) have dramatically improved the outcome of RA joint inflammation in recent years (13). There are no reports on the influence of bDMARDs in RA-AD at present, but many studies have reported detailed analyses of bDMARDs in RA-ILD (14-18). Some reports, including a national multicenter study, have indicated a preferable effect of abatacept (ABT) for RA-ILD (16, 18) while tumor necrosis factor inhibitors (TNFis) and tocilizumab (TCZ) have been shown to increase the risk of ILD exacerbation (14, 15). Yusof et al. suggested that rituximab could be an acceptable choice for RA-ILD patients (17), but a definitive ruling on bDMARDs use for RA-AD/ILD patients has not been determined because of the difficulty of conducting randomized prospective studies.

Therefore, in this study, we retrospectively investigated the association of the use of bDMARDs with the development and worsening of RA-AD/ILD and aimed to identify factors associated with the outcome.

Materials and Methods

Patients

All RA patients who initiated bDMARDs in our hospital between April 2008 and March 2017 were retrospectively evaluated. Study drugs that were classified as bDMARDs included TNFis (adalimumab, certolizumab-pegol, etanercept, golimumab, and infliximab), ABT, and TCZ. The inclusion criteria were consecutive adult patients (>20 years old), who received at least 2 courses of bDMARDs without switching to other ones, fulfilling the revised 1987 American College of Rheumatology (ACR) criteria (19) or the 2010 ACR-European League Against Rheumatism (EULAR) classification criteria for RA (20), and underwent chest evaluations by HRCT before and after bDMARD initiation.

This retrospective observational study was approved by the local ethics committee of the Tsukuba Clinical Research & Development Organization (H29-77, August 2017), and the patients had the chance to be excluded through our website. Because of the noninvasive, observational nature of our study, the ethics committee has permitted us to waive the need for written informed consent from each patient.

The evaluation of the clinical and HRCT findings

Clinical findings and laboratory data were collected from medical records. The presence or progression of AD/ILD on HRCT was visually evaluated and assessed by a rheumatologist with reference to the reports from one or two radiologists who have expertise in pulmonary CT and assessing AD/ILD. We categorized reticular shadow, honeycombing, and ground-glass opacity (GGO) as ILD and thickened bronchial walls, bronchiolitis, bronchodilation and mucoid impaction as AD. Exacerbation of AD was defined as the expansion of the affected areas and/or thickening of the bronchial walls with/without peribronchial infiltrates/peripheral airway obstruction.

Statistical analyses

We divided the patients into two groups: those whose HRCT findings were improved or stable after bDMARDs treatment and those who showed worsened images or had new AD/ILD lesions. We compared their clinical parameters, treatment received, and pre-treatment scans. In addition, we performed multivariable analyses on the parameters for which p values were <0.2 in the univariate analysis (number of concomitant csDMARDs: p=0.181, use of TNFi: p=0.127, use of ABT: p=0.035, and pre-existing AD before bDMARDs initiation: p=0.026) to identify the factors that independently affected the deterioration of the AD/ILD status.

We used Fisher's exact test for categorical variables and Mann-Whitney U testing for continuous variables to compare the two groups. The selected parameters were used in multiple logistic regression testing. All statistical analyses were performed using the SPSS software program, Version 24 (IBM, Armonk, USA). Data were expressed as mean values with standard deviations. For all statistical analyses, a p value of <0.05 was considered significant.

Table 1. Baseline Characteristics of the 49 Patients at the Initiation of BDMARDs.

Age at bDMARDs initiation, years	64.1±11.2
Gender Male/Female,n	11/38
Disease duration at bDMARDs initiation, years	9.45±8.45
Past or current smoker, n (%)	14/40 (35.0%)
Patients with respiratory symptoms, n (%)	9 (18.4%)
CRP (mg/dL)	2.36±2.41
RF positive, n (%)	36/45 (80.0%)
RF level among positive patients (U/mL)	328.06±450.09
ACPA positive, n (%)	27/35 (77.1%)
ACPA titer among positive patients (U/mL)	203.84±148.56
Anti-SS-A antibody positive, n (%)	14/41 (34.1%)
Patients with Sjögren's syndrome, n (%)	4/41 (9.76%)
Concomitant PSL, n (%)	41 (83.7%)
PSL dose among users (mg/day)	9.87±7.36
Concomitant MTX, n (%)	15 (30.6%)
MTX dose among users (mg/week)	7.47±2.07
Concomitant other csDMARDs, n (%)	35 (71.4%)
The number of other csDMARDs among users	1.18±0.78
Initiated bDMARDs, n (%)	
TNFi	30 (61.2%)
Etanercept	17 (34.7%)
Adalimumab	6 (12.2%)
Infliximab	3 (6.4%)
Golimumab	3 (6.4%)
Certolizumab-pegol	1 (2.0%)
ABT	12 (24.5%)
TCZ	7 (14.3%)
Pre-existing respiratory abnormalities, n (%)	
ILD	17 (34.5%)
GGO	9 (18.4%)
Honeycombing	6 (12.2%)
Reticular shadow	5 (10.5%)
AD	10 (20.4%)
AD and ILD	6 (12.2%)
Other abnormality	1* (2.0%)
No abnormality	15 (30.6%)

Plus-minus values are means±S.D. *: This patient was diagnosed as non-tuberculous mycobacterial infection by bronchoscopy. bDMARDs: biological disease modifying anti-rheumatic drugs, CRP: C reactive protein, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibody, PSL: prednisolone, MTX: methotrexate, csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs, TNFi: tumor necrosis factor inhibitor, ABT: abatacept, TCZ: tocilizumab, ILD: interstitial lung disease, GGO: ground glass opacity, AD: airway disease, S.D.: standard deviations

Results

Baseline characteristics at the initiation of bDMARDs

A total of 49 patients were included in the analysis (Table 1). Thirty-eight (77.6%) were women, and the mean age was 64.1±11.2 years. The median disease duration at the initiation of bDMARDs was 9.45 years. The mean C-reactive protein (CRP) value, which reflected the disease activity, was 2.36 mg/dL. Among these 49 patients, 36/45 patients (80.0%) were rheumatoid factor (RF)-positive, and 27/35 (77.1%) were ACPA-positive. Furthermore, 14/41(34.1%) patients were anti-SS-A antibody-positive. Of these anti-SS-A antibody-positive patients, 4 were diagnosed with comorbid Sjögren's syndrome according to the revised Japanese Ministry of Health criteria for the diagnosis of Sjögren's syndrome (21). No other comorbid connective tissue diseases were found in this study.

Thirty (61.2%) patients were treated with TNFis, 12 (24.5%) with ABT (6 intravenously, 6 subcutaneously), and 7 (14.3%) with TCZ (6 intravenously, 1 subcutaneously). All bDMARDs were prescribed primarily for articular symptoms under the approved dosage in Japan, and no patient was treated solely with bDMARDs. With regard to csDMARD co-administration, 41/49 (83.7%) patients were treated with concomitant prednisolone (PSL) and 15/49 (30.6%) patients with MTX. Other csDMARDs were used in 35/49 (71.4%) patients, and the average number of non-MTX csDMARD prescriptions overall was 1.18±0.78.

HRCT was performed for these 49 patients at the discretion of rheumatologists. Twenty-two (44.9%) patients had their lungs scanned as a screening test at bDMARD initiation. Another 18 (36.7%) were scanned for chest X-ray abnormalities, and the remaining 9 (18.4%) were scanned because of complaints of pulmonary symptoms, such as cough and sputum.

Among the 49 patients, 17 (34.5%) had ILD before the initiation of bDMARDs, 10 (20.4%) had AD, and 6 (12.2%) had both AD and ILD. Another patient whose HRCT findings showed granular shadow was diagnosed with non-tuberculous mycobacterial (NTM) infection by bronchoalveolar lavage fluid culture. No abnormalities were found in the remaining 15 patients (30.6%). Typical findings on HRCT before bDMARD initiation are shown in Fig. 1. ILD included reticular shadow (Fig. 1A), honeycombing (Fig. 1A), and GGO (Fig. 1B) while AD included thickened bronchial walls (Fig. 1C), bronchiolitis (Fig. 1C), bronchodilation (Fig. 1D), and mucoid impaction (Fig. 1E). Among the 17 subjects who had pre-existing ILD, 9 (18.4%) showed GGO, 6 (12.2%) showed honeycombing, and 5 (10.5%) showed reticular shadows (several patients showed multiple abnormalities). Furthermore, 24 (49.0%) patients [19 (79.2%) with ILD, 3 (12.5%) with AD, 2 (8.3%) with both AD and ILD] had their lungs scanned by HRCT more than twice in order to perform follow-up of abnormalities before bDMARD initiation. Among these 24 patients, 18 (75.0%) [16 (88.9%) with ILD, 1 (5.6%) with AD, and 1 (5.6%) with AD and ILD] were found to have no remarkable changes, while the remaining 6 [25.0%; 3 (50.0%) with ILD, 2 (33.3%) with AD, and 1 (16.7%) with AD and ILD] showed progressive AD and/or ILD before the initiation.

Changes in HRCT findings by bDMARD administration

The first follow-up HRCT scans were obtained an average

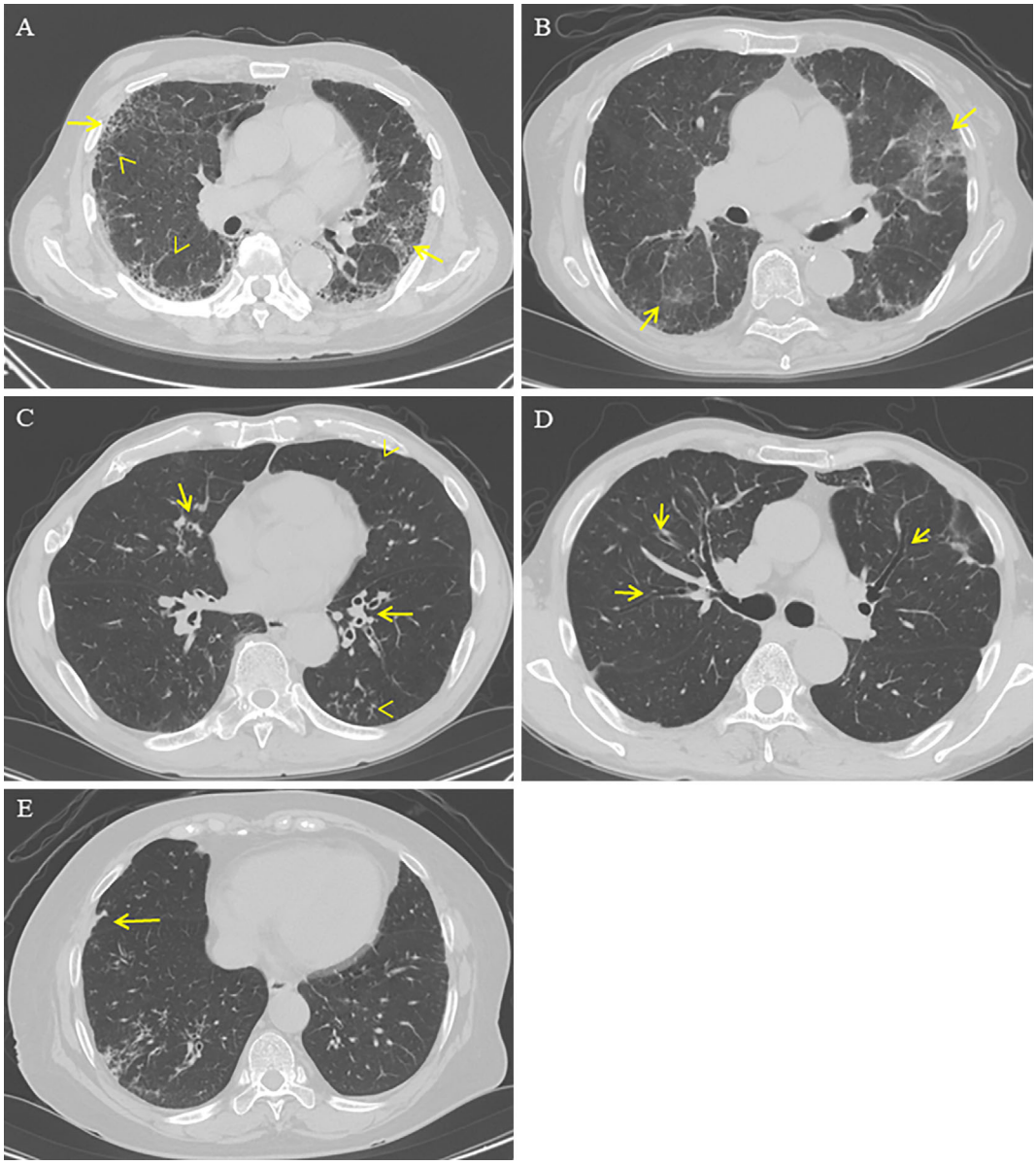

Figure 1. **Typical findings of HRCT at the initiation of bDMARDs. A) Lung HRCT of a man (78 years old) with RA-ILD demonstrating reticular shadow (arrows) and fibrosis (arrow heads) in the bilateral lower lobes. B) Lung HRCT of a woman (80 years old) with RA-ILD demonstrating ground-glass opacity (arrows) in the bilateral lungs. C) Lung HRCT of a man (64 years old) with RA-AD demonstrating thickened bronchial walls (arrows) and bronchiolitis (arrowheads). D) Lung HRCT of a man (59 years old) with RA-AD demonstrating bronchodilation (arrows). E) Lung HRCT of a woman (50 years old) with RA-AD demonstrating mucoid impaction (an arrow). Although pulmonary infection was suspected, subsequent bronchoscopy and bronchoalveolar lavage fluid culture revealed no infection. HRCT: high-resolution computed tomography, bDMARDs: biological disease-modifying anti-rheumatic drugs, RA: rheumatoid arthritis, ILD: interstitial lung disease, AD: airway disease**

of 69.6±72.2 weeks after bDMARD initiation (Fig. 2). Scans were performed to follow pre-existing AD/ILD in 30 (61.2%) patients. Another 7 (14.3%) patients underwent scanning due to their pulmonary symptoms, and 2 (4.1%) received scans for newly-emerged X-ray abnormalities. HRCTs were performed in the remaining 10 (20.4%) patients for other reasons, such as malignancy survey or suspicion of pulmonary thromboembolism. Among the 17 patients who had ILD before the initiation, 3 (17.6%) had improved, 9 (52.9%) remained stable, and 5 (29.4%) showed visible deterioration on imaging. Only GGOs were improved in the three patients whose ILD was recognized as improved. In addition, among the five patients whose ILD was exacerbated at follow-up HRCT, two showed exacerbation of both GGO and reticular shadow, another two showed exacerbation of honeycombing and reticular shadow, and the

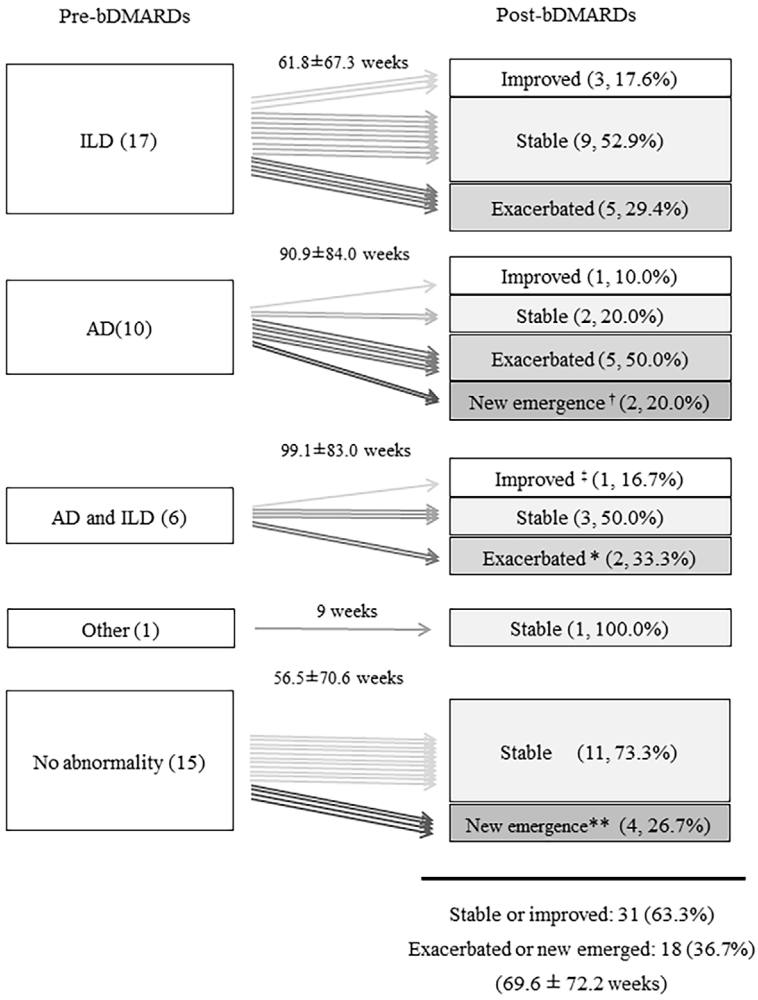

Figure 2. Changes in HRCT findings after bDMARD initiation. Parentheses indicate numbers and percentages of patients. Plus-minus values are means ± S.D. †: Two patients with pre-existing AD showed new emergence of ILD though AD lesions were unchanged. ‡: Improvement was observed only in ILD lesions. *: These 2 patients showed both AD and ILD exacerbation. **: Among these four patients, AD newly emerged in three, and one patient showed new ILD. bDMARDs: biological disease-modifying anti-rheumatic drugs, ILD: interstitial lung disease, AD: airway disease, HRCT: high-resolution computed tomography, S.D.: standard deviations

remaining one showed reticular shadow exacerbation. Furthermore, among the 10 patients who had pre-existing AD, 5 (50.0%) were revealed to have AD exacerbation, and 2 (20.0%) had developed new ILD. Of note, only 1 patient who showed improvement of AD was treated with ABT. In addition, in the 6 patients who had had both AD and ILD, improvement was observed in only 1 patient (16.7%) whose improvement was occurred only about ILD, whereas the AD status was unchanged. Two patients (33.3%) in that same group showed exacerbation of both AD and ILD on follow-up HRCT. Both AD and ILD were unchanged in the remaining 3 patients (50.0%).

Four out of 15 (26.7%) patients without pre-existing AD/ILD had newly emerged respiratory abnormalities on subsequent imaging; 3 showed AD emergence, and 1 showed new ILD, while the other 11 (68.8%) did not show any abnormalities before or after bDMARD treatment. In addition, the NTM infection found during bDMARD initiation that was treated with ABT and concomitant isoniazid, rifampicin and clarithromycin had not worsened on subsequent HRCT.

Of the 49 total patients, 6 had infectious pneumonia at the first follow-up HRCT scan (Fig. 3). All six of these infected patients had respiratory symptoms, such as persistent cough, dyspnea or increased sputum, and their HRCT scans revealed accordant findings. Infections were diagnosed not only by radiological findings but also clinical parameters and disease courses. These six patients included one with pre-existing ILD, three with pre-existing AD and two whose previous HRCT scans had been normal. The four patients with pre-existing AD/ILD had pneumonia lesions similar to those seen on previous HRCT, and a radiological diagnosis pointed to the eventual exacerbation of pre-existing AD/ILD aside from pneumonia. In the two patients whose previous HRCT scans had revealed no abnormalities, neither AD nor ILD emergence were observed. All affected patients were treated with antibiotics, and bDMARD administration was

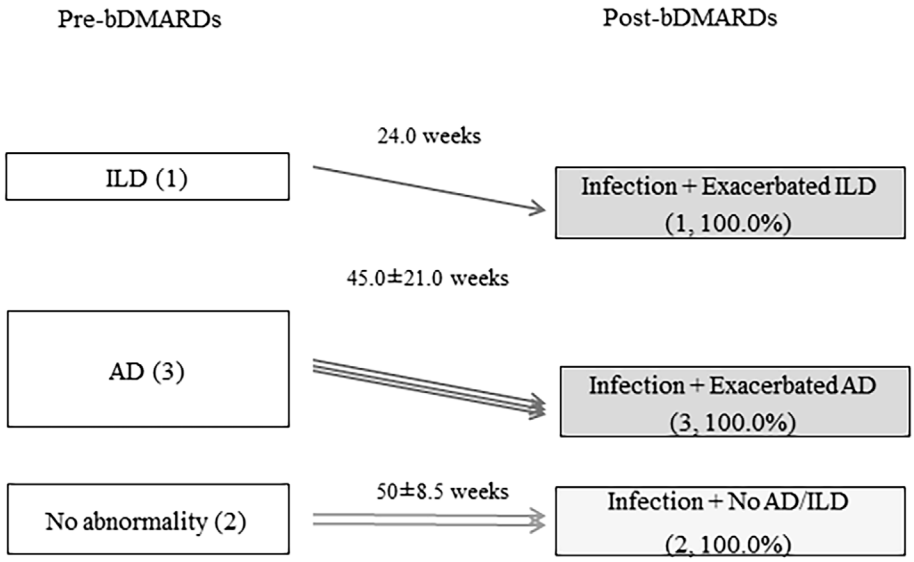

Figure 3. **Six patients with infectious pneumonia at the first follow-up HRCT scan. Parentheses indicate numbers and percentages of patients. Plus-minus values are means ± S.D. bDMARDs: biological disease-modifying anti-rheumatic drugs, ILD: interstitial lung disease, AD: airway disease, HRCT: high-resolution computed tomography, S.D.: standard deviations**

temporarily halted. All patients achieved symptomatic relief, and further HRCT revealed the radiological improvement of infectious pneumonia after the treatment, although the AD/ILD lesions were unchanged compared with the second HRCT scans. One patient with pre-existing ILD chose to cease bDMARDs, while the other five resumed the treatment.

Risk factors associated with AD/ILD exacerbation or emergence after bDMARDs initiation

To identify the risk factors associated with AD/ILD progression, we divided the patients into 2 groups: those who had improved or stable HRCT images (31 patients) and those who had exacerbated or newly emerged AD/ILD (18 patients) (Table 2). Patients whose AD/ILD deteriorated after bDMARD initiation more frequently had pre-existing AD (7/18, 38.9%) than those whose AD/ILD was stable or improved (3/31, 9.7%) (p=0.026). Furthermore, in the exacerbated or newly-emerged group, significantly fewer patients (1/18, 5.6%) received ABT than the stable group (11/31, 35.5%) (p=0.035). There were no significant differences between the groups in the age, sex, respiratory symptoms, baseline laboratory data, PSL usage and csDMARD status. In addition, no statistically significant difference was detected in the patient background data between ABT users and non-ABT users (Table 3).

Next, we took factors with p values of <0.2 in these univariate analyses and performed multiple logistic regression analyses with them (Fig. 4). Pre-existing AD (p=0.026), ABT use (p=0.035), TNFi use (p=0.127) and numbers of concomitant csDMARDs (p=0.181) were selected. Among these factors, the multivariate analyses revealed that pre-existing AD was a significant independent risk factor for (odds ratio=7.40, 95% confidence interval=1.28-42.8) while ABT use was a significant independent protective factor against (odds ratio=0.07, 95% confidence interval=0.01-0.99) exacerbation or new emergence of RA-AD/ILD.

Discussion

This study revealed two clinical important findings about the effect of bDMARDs on AD and ILD in RA patients.

First, pre-existing AD was an independent risk factor for the exacerbation of RA-AD or new emergence of RA-ILD after the initiation of bDMARDs. To our knowledge, this is the first study to analyze the influence of bDMARDs on RA-AD. As such, the concrete mechanism for this result remains unclear, but we speculate that subclinical infections of the lower airway associated with bDMARD administration may worsen pre-existing AD. Two studies (22, 23) bolster this theory with reports of increased pulmonary infection frequency in RA-AD patients versus patients with only RA on bDMARDs. In addition, infections are well known to exacerbate AD (24). Consistent with this hypothesis, HRCT of all three patients with RA-AD who had clinical pulmonary infections during bDMARD treatment experienced worsening of AD in addition to their infections.

Second, we found that ABT was an independent protective factor for RA-AD/ILD exacerbation or emergence after the initiation of bDMARDs. ABT is a CTLA-4Ig that blocks T cell co-stimulation (25). The efficacy of ABT for RA synovitis (26, 27) has been verified by several reports that also indicated a beneficial effect on RA-ILD (16, 18, 28). To our knowledge, there are no reports detailing the mechanism of how ABT influences RA-AD/ILD. However, reports using murine models indicate that CTLA-4Ig has a protective effect against inflammatory lung diseases, supporting our findings. Ying et al. showed a beneficial effect of

Table 2. Comparison of Characteristics between 2 Groups.

Characteristics	RA whose AD/ILD were stable/improved (n=31)	RA whose AD/ILD were exacerbated/ newly emerged (n=18)	p value
Age at bDMARDs initiation, years	63.80±11.20	64.62±11.53	0.803
Gender Male/Female,n	8/23	3/15	0.724
Disease duration			
at bDMARDs initiation, years	9.00±9.15	10.24±7.23	0.297
Past or current smoker, n (%)	8/24 (33.3%)	6/16 (37.5%)	1.000
Patients with respiratory symptoms, n (%)	6 (19.4%)	3 (16.7%)	0.567
CRP (mg/dL)	2.59±4.31	1.62±1.70	0.647
RF positive, n (%)	22/26 (84.6%)	14 (77.7%)	0.451
RF level among positive patients (U/mL)	370.48±535.58	253.00±235.41	1.000
Anti-CCP antibody positive, n (%)	16/18 (88.9%)	11/13 (84.6%)	1.000
Anti-CCP antibody titer among positive patients (U/mL)	152.90±148.45	212.85±157.72	0.218
Anti-SS-A antibody positive, n (%)	10/27 (37.0%)	4/14 (28.6%)	1.000
Patients with Sjögren's syndrome, n (%)	3/27 (11.1%)	1/14 (7.1%)	1.000
Concomitant PSL at baseline, n (%)	26 (83.9%)	15 (83.3%)	1.000
PSL dose among users (mg/day)	11.06±8.61	7.80±3.90	0.429
Concomitant PSL at following CT, n (%)	20 (64.5%)	11 (61.1%)	1.000
PSL dose among users (mg/day)	6.75±3.72	6.38±5.17	1.000
Concomitant MTX, n (%)	9 (29.0%)	6 (33.3%)	0.759
MTX dose among users (mg/week)	8.00±2.00	6.66±2.07	0.456
Concomitant other csDMARDs, n (%)	23 (74.2%)	12 (66.7%)	1.000
The number of csDMARDs among users	1.35±0.88	0.88±0.49	0.181‡
Interval of following CTs (weeks)	69.39±72.16	69.96±74.44	0.707
Initiated bDMARDs, n (%)			
TNFi†	16 (51.6%)	14 (77.8%)	0.127‡
ABT	11 (35.5%)	1 (5.6%)	0.035*‡
TCZ	4 (12.9%)	3 (16.7%)	0.697
Pre-existing respiratory abnormalities, n (%)			
ILD	12 (38.7%)	5 (27.8%)	0.526
GGO	6 (19.4%)	3 (16.7%)	0.567
Honeycombing	4 (12.4%)	2 (11.1%)	0.616
Reticular shadow	4 (12.4%)	1 (5.6%)	0.386
AD	3 (9.7%)	7 (38.9%)	0.026*‡
AD and ILD	4 (12.9%)	2 (11.1%)	1.000
Other	1 (3.2%)	0 (0.0%)	0.581
No abnormality	11 (35.5%)	4 (22.2%)	0.754

Data were tested with Fisher's exact test (for categorical variables) and Mann-Whitney U test (for continuous variables). Plus-minus values are means±S.D. †: In patients with stable/improved AD/ILD, etanercept was used for 9 patients, adalimumab for 4 patients, infliximab for 2 patients, and certolizumab-pegol for 1 patient. In cases where AD/ILD was exacerbated or newly emerged, etanercept was used for 8 patients, adalimumab for 2 patients, infliximab for 1 patients, and golimumab for 3 patients. ‡: These factors were assessed in subsequent multiple logistic regression analyses. *: $p<0.05$, significant results. bDMARDs: biological disease modifying anti-rheumatic drugs, CRP: C reactive protein, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibody, PSL: prednisolone, MTX: methotrexate, csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs, TNFi: tumor necrosis factor inhibitor, ABT: abatacept, TCZ: tocilizumab, ILD: interstitial lung disease, GGO: ground glass opacity, AD: airway disease, S.D.: standard deviations

CTLA-4Ig in a murine asthma model, where it contributed to an increase of lung-infiltrating regulatory T cells (29). Israël-Assayag et al. also proved that CTLA-4Ig reduced the production of several cytokines in T cells and ameliorated hypersensitivity-mediated pneumonitis in mice (30). As T cell infiltration in the tissues has been observed in RA-ILD (4) and RA-AD, (4, 31) this opens up the potential use of ABT to downregulate these errant T cells. It is noteworthy that the use of CTLA-4 blockers, such as ipilimumab, has been reported to result in immune-related pneumonitis (e.g. ILD or sarcoidosis) (32) suggesting that CTLA-4 might exert a protective effect against these types of lung diseases. Furthermore, according to a report by Harigai et al., ABT may be associated with a lower risk for infection than other bDMARDs (33), as the reduced frequency of lower airway infections might contribute to the

Table 3. Comparison of Characteristics between ABT Users and Non-ABT Users.

Characteristics	RA treated with ABT (n=12)	RA treated with non-ABT (n=37)	p value
Age at bDMARDs initiation, years	66.83±11.21	63.22±11.20	1.000
Gender Male/Female,n	3/9	8/29	1.000
Disease duration at bDMARDs initiation, years	9.82±9.74	9.33±6.78	0.875
Past or current smoker, n (%)	4/12 (33.3%)	10/28 (35.7%)	1.000
Patients with respiratory symptoms, n (%)	3 (25.0%)	6 (16.2%)	0.383
CRP (mg/dL)	2.38±4.14	2.56±2.98	1.000
RF positive, n (%)	9/11 (81.8%)	27/34 (79.4%)	0.619
RF level among positive patients (U/mL)	243.78±224.14	356.15±503.95	0.674
Anti-CCP antibody positive, n (%)	9/12 (75.0%)	18/23 (81.5%)	0.571
Anti-CCP antibody titer among positive patients (U/mL)	201.03±172.60	204.69±147.27	0.752
Anti-SS-A antibody positive, n (%)	3/10 (33.3%)	11/31 (35.5%)	0.535
Patients with Sjögren's syndrome, n (%)	2/10 (20.0%)	2/31 (6.5%)	0.245
Concomitant PSL at baseline, n (%)	9 (75.0%)	32 (86.5%)	0.300
PSL dose among users (mg/day)	14.22±16.50	8.64±5.53	0.346
Concomitant PSL at following CT, n (%)	11 (91.7%)	32 (86.5%)	0.540
PSL dose among users (mg/day)	7.46±6.51	6.11±4.09	0.767
Concomitant MTX, n (%)	3 (25.0%)	12 (32.4%)	0.460
MTX dose among users (mg/week)	9.33±2.31	7.00±1.93	0.764
Concomitant other csDMARDs, n (%)	10 (83.3%)	25 (67.6%)	0.253
The number of csDMARDs among users	1.80±0.98	1.08±0.67	0.348
Interval of following CTs (weeks)	59.32±63.92	72.93±75.24	0.453
Pre-existing respiratory abnormalities, n (%)			
ILD	5 (41.7%)	12 (32.4%)	0.401
GGO	2 (16.7%)	7 (18.9%)	0.617
Honeycombing	2 (16.7%)	4 (10.8%)	0.460
Reticular shadow	2 (16.7%)	3 (8.1%)	0.356
AD	2 (16.7%)	8 (21.6%)	0.534
AD and ILD	1 (8.3%)	5 (13.5%)	0.540
Other	1 (8.3%)	0 (0.0%)	0.245
No abnormality	3 (25.0%)	12 (32.4%)	0.460

Data were tested with Fisher's exact test (for categorical variables) and Mann-Whitney U test (for continuous variables). Plus-minus values are means±S.D. bDMARDs: biological disease modifying anti-rheumatic drugs, CRP: C reactive protein, RF: rheumatoid factor, ACPA: anti-cyclic citrullinated peptide antibody, PSL: prednisolone, MTX: methotrexate, csDMARDs: conventional synthetic disease modifying anti-rheumatic drugs, TNFi: tumor necrosis factor inhibitor, ABT: abatacept, TCZ: tocilizumab, ILD: interstitial lung disease, GGO: ground glass opacity, AD: airway disease, S.D.: standard deviations

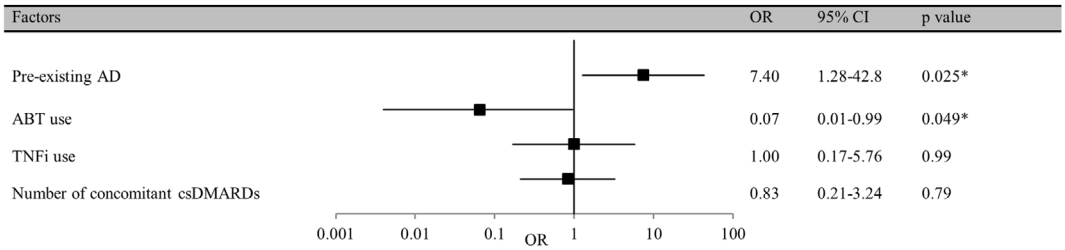

Figure 4. The independent factors associated with AD/ILD progression. Data were subjected to multiple logistic regression analyses. Factors with p values <0.2 at univariate testing were set as explanatory variables, and exacerbation or new emergence of AD/ILD was set as the dependent variable. *: p<0.05, significant results. OR: odds ratio, CI: confidence interval, AD: airway disease, ABT: abatacept, TNFi: tumor necrosis factor inhibitor, csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs

protective effect against AD/ILD.

This study has several limitations. First, the presence of RA-AD/ILD was assessed only by HRCT, limiting our ability to assess the actual pulmonary function. Second, as all patients were treated concomitantly with csDMARDs, any effects on respiratory progression could not be attributed to bDMARDs alone. Third, the inconsistent duration of follow-up HRCT was due to the retrospective design of the study. Finally, the lack of a control group made interpreting the effect of bDMARDs on the natural course of AD/ILD difficult. To account for this, patients were used as their own controls (with pre- and post-treatment HRCT trends) to highlight any effect attributable to bDMARDs.

Despite these limitations, we believe that our report contributes valuable findings to a field in which no prospective studies on RA-AD/ILD are currently available.

In conclusion, we herein report the influence of bDMARDs on RA-AD and ILD. Our findings suggest that physicians should be alert for RA-AD when patients are treated with bDMARDs. In addition, our results agree with previous papers that showed a better outcome with ABT for RA-associated lung disease than with other bDMARDs (16, 18, 28). Large, randomized prospective studies as well as mechanistic studies into the interactions between ABT and RA-AD/ILD are needed to confirm these promising initial results.

Author's disclosure of potential Conflicts of Interest (COI).
Hiroyuki Takahashi: Honoraria, Bristol-Myers Squibb Company. Isao Matsumoto: Honoraria, Bristol-Myers Squibb Company. Takayuki Sumida: Honoraria, Astellas Pharma, Chugai Pharmaceutical and Mitsubishi Tanabe Pharma Corporation; Research funding, Astellas Pharma, Bristol-Myers Squibb Company, Chugai Pharmaceutical, Mitsubishi Tanabe Pharma Corporation and Ono Pharmaceutical.

Acknowledgement

We thank Dr. Bryan J. Mathis of the Medical English Communications Center, University of Tsukuba, for his critical review of this manuscript.

References

1. Geddes DM, Webley M, Emerson PA. Airways obstruction in rheumatoid arthritis. Ann Rheum Dis **38**: 222-225, 1979.
2. Hassan WU, Keaney NP, Holland CD, Kelly CA. Bronchial reactivity and airflow obstruction in rheumatoid arthritis. Ann Rheum Dis **53**: 511-514, 1994.
3. Fischer A, Brown KK, Du Bois RM, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J Rheumatol **40**: 640-646, 2013.
4. Suda T. Up-to-date information on rheumatoid arthritis-associated interstitial lung disease. Clin Med Insights Circ Respir Pulm Med **9**: 155-162, 2016.
5. Penny WJ, Knight RK, Rees AM, Thomas AL, Smith AP. Obliterative bronchiolitis in rheumatoid arthritis. Ann Rheum Dis **41**: 469-472, 1982.
6. Wilczynska MM, Condliffe AM, McKeon DJ. Coexistence of bronchiectasis and rheumatoid arthritis: revisited. Respir Care **58**: 694-701, 2013.
7. Kelly CA, Saravanan V, Nisar M, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics-a large multicentre UK study. Rheumatol (Oxford) **53**: 1676-1682, 2014.
8. Alunno A, Caneparo V, Bistoni O, et al. Circulating interferon-inducible protein IFI16 correlates with clinical and serological features in rheumatoid arthritis. Arthritis Care Res **68**: 440-445, 2016.
9. Reynisdottir G, Karimi R, Joshua V, et al. Structural changes and antibody enrichment in the lungs are early features of anti-citrullinated protein antibody-positive rheumatoid arthritis. Arthritis Rheumatol **66**: 31-39, 2014.
10. Vij R, Strek ME. Diagnosis and treatment of connective tissue disease-associated interstitial lung disease. Chest **143**: 814-824, 2013.
11. Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Methotrexate and lung disease in rheumatoid arthritis: a meta-analysis of randomized controlled trials. Arthritis Rheumatol **66**: 803-812, 2014.
12. Inokuma S. Leflunomide-induced interstitial pneumonitis might be a representative of disease-modifying antirheumatic drug-induced lung injury. Expert Opin Drug Saf **10**: 603-611, 2011.
13. Singh JA, Furst DE, Bharat A, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res **64**: 625-639, 2012.
14. Roubille C, Haraoui B. Interstitial lung diseases induced or exacerbated by DMARDS and biologic agents in rheumatoid arthritis: a systematic literature review. Semin Arthritis Rheum **43**: 613-626, 2014.
15. Curtis JR, Sarsour K, Napalkov P, Costa LA, Schulman KL. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor aα agents, a retrospective cohort study. Arthritis Res Ther **17**: 1-13, 2015.
16. Fernández-Díaz C, Loricera J, Castañeda S, et al. Abatacept in patients with rheumatoid arthritis and interstitial lung disease: a national multicenter study of 63 patients. Semin Arthritis Rheum **48**: 22-27, 2018.
17. Md Yusof MY, Kabia A, Darby M, et al. Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. Rheumatol (Oxford) **56**: 1348-1357, 2017.
18. Nakashita T, Ando K, Takahashi K, Motojima S. Possible effect of abatacept on the progression of interstitial lung disease in rheumatoid arthritis patients. Respir Investig **54**: 376-379, 2016.
19. Arnett FC, Edworthy SM, Bloch DA, et al. Revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum **31**: 315-324, 1988.
20. Aletaha D, Neogi T, Silman AJ, et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum **62**: 2569-2581, 2010.
21. Fujibayashi T, Sugai S, Miyasaka N, Hayashi Y, Tsubota K. Revised Japanese criteria for Sjögren's syndrome (1999): availability and validity. Mod Rheumatol **14**: 425-434, 2004.
22. Goeminne PC, Verschueren P, Scheers H, Dupont LJ. Safety of immunomodulatory therapy in patients with bronchiectasis associated with rheumatic disease and IBD: a retrospective and cohort analysis. Clin Rheumatol **31**: 367-373, 2012.
23. Geri G, Dadoun S, Bui T, et al. Risk of infections in bronchiectasis during disease-modifying treatment and biologics for rheumatic diseases. BMC Infect Dis **11**: 304, 2011.
24. Alunno A, Gerli R, Giacomelli R, Carubbi F. Clinical, epidemiological, and histopathological features of respiratory involvement

in rheumatoid arthritis. Biomed Res Int, 2017 (Epub ahead of print).

25. Bonelli M, Scheinecker C. How does abatacept really work in rheumatoid arthritis? Curr Opin Rheumatol **30**: 295-300, 2018.

26. Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multicentre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. Ann Rheum Dis **67**: 1096-1103, 2008.

27. Westhovens R, Robles M, Ximenes AC, et al. Clinical efficacy and safety of abatacept in methotrexate-naive patients with early rheumatoid arthritis and poor prognostic factors. Ann Rheum Dis **68**: 1870-1877, 2009.

28. Mera-Varela A, Perez-Pampin E. Abatacept therapy in rheumatoid arthritis with interstitial lung disease. J Clin Rheumatol **20**: 445-446, 2014.

29. Ying L, Fu Z, Luo J, et al. Cytotoxic T lymphocyte antigen 4 immunoglobulin modified dendritic cells attenuate allergic airway inflammation and hyperresponsiveness by regulating the development of T helper type 1 (Th1)/Th2 and Th2/regulatory T cell subsets in a murine model of asthm. Clin Exp Immunol **165**: 130-139, 2011.

30. Israël-Assayag E, Fournier M, Cormier Y. Blockade of T cell costimulation by CTLA4-Ig inhibits lung inflammation in murine hypersensitivity pneumonitis. J Immunol **163**: 6794-6799, 1999.

31. Homma S, Kawabata M, Kishi K, et al. Diffuse panbronchiolitis in rheumatoid arthritis. Eur Respir J **12**: 444-452, 1998.

32. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer **54**: 139-148, 2016.

33. Harigai M, Ishiguro N, Inokuma S, et al. Postmarketing surveillance of the safety and effectiveness of abatacept in Japanese patients with rheumatoid arthritis. Mod Rheumatol **26**: 491-498, 2016.