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Original

Tumor Necrosis Factor Blockade Fails to Improve Small Airway Obstruction in Rheumatoid Arthritis

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Summary

Objective: To determine whether tumor necrosis factor (TNF) blockade improves small airway obstruction in rheumatoid arthritis (RA) patients without apparent respiratory symptoms.

Methods: Pulmonary function tests were performed before and one year after TNF blockade therapy in 29 RA patients without apparent respiratory symptoms. As a control, pulmonary function was examined at a one-year interval in 27 RA patients with conventional disease-modifying antirheumatic drugs (DMARDs) alone. Small airway obstruction was diagnosed when one of maximal mid-expiratory flow rate (MMEF), forced expiratory flow at 50% (FEF50) or 75% (FEF75) of the vital capacity was decreased to less than 60%, 55%, or 45% of predicted values, respectively.

Results: Small airway obstruction was found in 62.5% of RA patients. No differences were found in age, sex, disease duration, or disease activities. TNF inhibitors dramatically reduced disease activities. However, TNF inhibitors failed to improve small airway obstructions but worsened them.

Conclusions: TNF blockade fails to improve small airway obstruction, suggesting that TNF-independent pathways play important roles in the development of small airway obstruction in RA.

Key Words: rheumatoid arthritis, TNF blockade, small airway disease, pulmonary function

Introduction

Rheumatoid arthritis (RA) is a disease characterized by destructive polyarthritis, and it can also cause systemic inflammation and damage various organs, including the lungs. Pulmonary involvement, such as interstitial pneumonia, parenchymal nodules, pleuritis, pulmonary vasculitis, and Caplan syndrome, often develops[1,2]. In particular, small airway obstruction, which is thought to be caused by bronchiolitis, is found in 10-70% of RA patients, even in those who do not complain of respiratory symptoms or have never smoked[3-8]. Moreover, recent studies suggest that airway inflammation is a primary where the immune response can cause RA[9].

The small airway is a primary site of inflammation in asthma and chronic obstructive pulmonary disease. However, the small airway inflammation(bronchiolitis)

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occurs in various diseases/conditions such as infection, autoimmune diseases including RA, and graft-versus-host disease[10]. Bronchiolitis can be pathologically classified into several categories: cellular bronchiolitis, granulomatous bronchiolitis, follicular bronchiolitis and Obliterative Bronchiolitis[11]. Obliterative bronchiolitis is irreversible with subepithelial fibrosis and poor prognosis[12]. Bronchiolitis obliterans rarely occurs in RA, while cellular bronchiolitis and follicular bronchiolitis are common subtypes[10,13]. Surgical lung biopsy is necessary to distinguish these subtypes of bronchiolitis, although pulmonary function tests and CT scans help detect bronchiolitis.

Tumor necrosis factor (TNF) inhibitors dramatically suppress articular and systemic inflammation and prevent joint destruction in RA[14,15]. However, the effects of TNF blockade on pulmonary involvement remain to be elucidated. We examined whether TNF blockade improves small airway obstruction.

Patients and Methods

Study design

We conducted a retrospective cohort study. Pulmonary function was evaluated before and one year after TNF blockade treatment. As a control, pulmonary function tests were performed at 1-year intervals in age- and sex-matched RA patients treated with conventional disease-modifying antirheumatic drugs (DMARDs) alone.

Patients

This study was conducted on consecutive Japanese RA patients who started anti-TNF therapy at Dokkyo Medical University Hospital between February 2004 and September 2007, had no cough or other pulmonary symptoms, and underwent pulmonary function tests at the start of anti-TNF therapy and one year later. The control group consisted of patients with RA who were treated with conventional DMARDs and underwent pulmonary function tests at 1-year intervals during the above period. All patients fulfilled the American College of Rheumatology (ACR) 1987 revised criteria for the classification of RA[16]. According to the Declaration of Helsinki, this study was conducted and approved by the Bioethics Committee of Dokkyo Medical University (#2114).

Pulmonary function tests

Pulmonary function tests included forced vital capacity (FVC), forced expiratory volume in 1 second (FEV 1.0), FEV1/FVC, maximal mid-expiratory flow rate (MMEF), forced expiratory flow at 50% (FEF50) and 75% (FEF75) of the vital capacity, and diffusing capacity of lung for carbon monoxide (DLCO).

Definition of small airway obstruction

Small airway obstruction was diagnosed when one of %MMEF, %FEF50, or %FEF75 was decreased to less than 60%, 55%, or 45% of predicted values, respectively[17].

CT findings

CT findings were based on reports by an experienced respiratory radiologist.

Statistical analysis

All analyses were performed using JMP Version 7 (SAS Institute Japan Ltd., Tokyo, Japan). The unpaired chi-square and Fisher's exact test analyzed the values between groups. The paired t-test was used for statistical analysis of change in values of individuals, respectively. P values less than 0.05 were considered significant.

Results

Characteristics of patients

Fifty-six RA patients without respiratory symptoms such as cough, sputum, and dyspnea were enrolled in the present study. Details are shown in Table 1. Twenty-nine patients were treated with TNF inhibitors (infliximab in 16 cases, etanercept in 11 instances, infliximab to etanercept in 2 points), and the other 27 patients were treated with DMARDs. Of the 29 TNF blockade patients, 4 were males, 6 were smokers, and 26 were treated with prednisolone (mean ± SD: 7.0 ± 3.8 mg/day); at study entry, their age was 53.5 ± 9.4 (mean ± SD) years, and their disease duration was 9.3 ± 8.3 years. Of the 27 patients treated with DMARDs, 6 were males, 6 were smokers, and 20 were treated with prednisolone (3.6 ± 2.5 mg/day); at study entry, their age was 59.9 ± 9.2 years, and their disease duration was 7.3 ± 5.1 years. No patients were treated with D-penicillamine.

Table 1 Characteristics and clinical features of subjects

	Total (n = 56)	TNF blockades (n = 29)	DMARDs (n = 27)
Sex (M/F)	10/46	4/25	6/21
Age (year)	56.6 ± 9.7*	53.5 ± 9.4	59.9 ± 9.2
Disease Duration (year)	8.3 ± 6.9*	9.3 ± 8.3	7.3 ± 5.1
Smoking	12	6	6
RF positive	42	22	20
DAS28-CRP at the entry	5.41 ± 1.12*	5.69 ± 1.14	5.07 ± 1.04
DAS28-CRP1 year after	3.53 ± 1.30*	2.84 ± 0.87	4.35 ± 1.26
TNF Blockade (INF/ ETN/ INF to ETN)	16/11/2	16/11/2	0
PSL mean (mg/day)	5.4 ± 3.6*	7.0 ± 3.8	3.6 ± 2.5
(# of pt. with PSL)	(46)	(26)	(20)
DMARDs	MTX 39 SASP 14 BUC 4 CsA 2 TAC 2	MTX 20 SASP 7 BUC 2 CsA 2 TAC 1	MTX 19 SASP 7 BUC 2 CsA 0 TAC 1
CT findings			
# of examined patients	36	23	13
normal	12	8	4
interstitial lung disease	6	4	2
bronchiolitis	2	2	0
bronchiectasis	5	2	3
air trapping	11	8	3
others	3	1	2
Frequencies of abnormal results in pulmonary function tests			
%FVC < 80	3 (5.3%)	0 (0%)	2 (7.4%)
FEV1.0/FVC < 75%	10 (17.8%)	5 (17.2%)	5 (18.5%)
%FEF50 < 55	16 (28.5%)	9 (31.0%)	7 (25.9%)
%FEF75 < 45	34 (62.5%)	18 (62.0%)	16 (59.2%)
%MMEF < 60	19 (33.9%)	11 (37.9%)	8 (29.6%)
%DLCO < 75	9 (16.0%)	4 (13.7%)	5 (18.5%)
Small airway obstruction	34 (62.5%)	18 (62.0%)	16 (59.2%)

* mean ± standard deviation

BUC, bucillamine; CsA, cyclosporine; DAS28, disease activity score 28; DLCO, diffusing capacity of the lung for carbon monoxide; DMARDs, disease modified anti-rheumatic drugs; ETN, etanercept; FVC, forced vital capacity; FEV1.0, forced expiratory volume in 1 second; FEF50, forced expiratory flow at 50% of the vital capacity; FEF75, forced expiratory flow at 75% of the vital capacity; MMEF, maximal mid-expiratory flow rate; MTX, methotrexate; PSL, prednisolone; RF, rheumatoid factor; SASP, sulphasalazine; TAC, tacrolimus; TNF tumor necrosis factor-α.

Frequency of small airway obstruction in RA patients

At study entry, pulmonary function testing showed small airway obstruction in 62.5% of total RA patients (Table 1). All patients with small airway obstruction revealed reduced FEF75, suggesting FEF75 is the most sensitive marker for small airway disease. Airway trapping in expiratory CT scans was found in 11 out of 37(29.7%) patients (Table 1).

No differences were found in age, sex, disease duration, disease activities, or frequency of rheumatoid factors between patients with and without small airway obstruction (Table 2).

Table 2 Clinical features of patients with/without small airway obstruction

	Small airway disease (+) (n = 34)	Small airway disease (−) (n = 22)	p
Sex (M/F)	8/26	2/20	0.28
Age (year)	57.5 ± 8.9*	54.8 ± 9.9	0.35
Disease Duration (year)	8.0 ± 7.0*	8.9 ± 6.8	0.65
Smoking	8	4	0.74
RF positive	27/7	15/7	0.36
DAS28 at the entry	5.44 ± 1.17*	5.26 ± 1.10	0.65
PSL mean (mg/day)	5.3 ± 3.8*	5.5 ± 3.4	0.90
(# of pt. with PSL)	(28)	(18)	(0.99)
DMARDs	MTX 22	MTX 17	MTX 0.31
	SASP 8	SASP 6	SASP 0.76
	BUC 2	BUC 2	BUC 0.64
	CsA 2	CsA 0	CsA 0.51
	TAC 1	TAC 1	TAC 1

* mean ± standard deviation

BUC, bucillamine; CsA, cyclosporine; DAS28, disease activity score 28; PSL, prednisolone; RF, rheumatoid factor; SASP, sulphasalazine; TAC, tacrolimus.

Effect of TNF blockade on RA activities

TNF blockade dramatically reduced disease activities; the disease activity score 28 (DAS28)[12] decreased from 5.69 ± 1.14 to 2.84 ± 0.87 (Table 1), and 34% of patients achieved clinical remission (DAS28 <2.4). On the other hand, conventional DMARD treatment slightly improved; the DAS28 score changed from 5.07 ± 1.04 to 4.35 ± 1.26, and only two patients achieved clinical remission.

Effect of TNF blockade on small airway obstruction

In contrast to RA disease activities, TNF blockade failed to improve small airway obstruction similar to conventional DMARD (Table 3).

No significant changes were found in the pulmonary function test results at the entry between TNF blockade and DMARD groups. In the TNF blockade group, %MMF, %FEF50, and %FEF75 were decreased, while these parameters were not changed in the DMARDs group. This suggests that TNF blockade may worsen bronchiolitis and small airway obstruction. However, no differences were found in the change of %MMF, %FEF50, and %FEF75 between the TNF blockade group and the DMARDs group.

In addition, no significant differences were found in other pulmonary function parameters, including FVC, FEV1.0/FVC, and DLCO, between before and after treatment. Furthermore, there were no differences in pulmonary functions among good, moderate, and poor TNF blockade responders.

Therefore, the TNF blockade failed to improve small airway obstructions but rather tended to worsen them.

Discussion

The present study demonstrated that TNF blockade failed to improve small airway obstruction, although TNF blockade had controlled the arthritis in RA. This suggests that different mechanisms cause arthritis and small airway obstruction and that TNF-independent pathways might play important roles in the development of small airway obstruction.

The mechanisms responsible for the development of small airway obstruction in RA are not well understood. Begin et al. demonstrated peribronchiolar mononuclear cell infiltration in RA patients with small airway disease[5]. In addition, cellular bronchiolitis and follicular bronchiolitis are preferentially found in patients with RA, which is characterized by abundant lymphoid tissue, frequently with lymphoid follicles[10,13]. The histological findings described in Begin's report were consistent with cellular or follicular bronchiolitis.

Table 3 Effect of TNF blockade on pulmonary functions in patients with RA

	TNF Blockade	Before	One year after	Change	Difference between before and 1 year after	Difference between TNF blockades (+) and (−) groups
%FVC	TNF blockade	106.3 ± 16.8	107.0 ± 16.7	0.6 ± 7.3	P = 0.64	P = 0.41
	DMARDs	103.9 ± 18.4	106.3 ± 12.9	2.3 ± 8.3	0.15	
FEV1.0/FVC	TNF blockade	79.3 ± 8.5	78.2 ± 8.5	−1.1 ± 3.1	0.07	0.16
(%)	DMARDs	77.6 ± 6.7	78.7 ± 7.2	1.1 ± 7.6	0.45	
%MMEF	TNF blockade	74.3 ± 32.0	65.2 ± 30.2	−8.9 ± 10.8	< 0.001	0.20
	DMARDs	72.7 ± 20.7	68.1 ± 17.3	−4.1 ± 15.5	0.18	
%FEF50	TNF blockade	72.7 ± 31.0	68.3 ± 27.0	−4.3 ± 10.2	0.03	0.61
	DMARDs	67.9 ± 18.8	65.1 ± 16.6	−2.7	0.26	
%FEF75	TNF blockade	46.3 ± 24.5	38.3 ± 21.8	−8.0 ± 8.9	< 0.001	0.06
	DMARDs	46.2 ± 15.6	43.9 ± 15.3	−2.3 ± 12.4	0.33	
%DLCO	TNF blockade	89.1 ± 14.0	89.3 ± 16.6	0.6 ± 11.0	0.76	0.78
	DMARDs	92.5 ± 23.6	84.0 ± 22.0	1.4 ± 10.9	0.49	

All results except FEV1.0/FVC are expressed as a percentage of predicted for each individual adjusted for age, gender, and height. FEV1.0/FVC is the percentage of the measured value of FEV1.0/that of FVC. All values indicate mean ± standard deviation.

FVC, forced vital capacity; FEV1.0, forced expiratory volume in 1 second; MMEF, maximal mid-expiratory flow rate; FEF50, forced expiratory flow at 50% of the vital capacity; FEF75, forced expiratory flow at 75% of the vital capacity; DLCO, diffusing capacity of lung for carbon monoxide.

Rangel-Moreno et al. reported that inducible bronchus-associated lymphoid tissue (BALT), which is not formed in normal human lungs, is preferentially formed in the lungs of RA patients[18]. They also demonstrated that BALT formation was associated with airway collagen deposition and IL-13 production that enhances mucosal secretion. Based on these findings, subclinical small airway obstruction in RA could be due to peribronchial lymphoid infiltration or aggregation forming cellular and follicular bronchiolitis and BALT.

In the present study, we could not determine what subtypes of bronchiolitis caused small airway obstruction because we did not conduct a surgical biopsy. However, we assumed that small airway obstruction was due to cellular/follicular bronchiolitis rather than obliterative bronchiolitis. Cellular and follicular bronchiolitis are frequent in RA, while obliterative bronchiolitis is rare[7,13]. One study revealed that follicular bronchiolitis was found in 5 out of 26 RA patients who received surgical biopsy for ILD[19]. Moreover, the majority of RA patients with obliterative bronchiolitis present respiratory symptoms such as cough and dyspnea[20]. However, our study excluded patients with these symptoms. Thus, we believed that few patients had obliterative bronchiolitis in the present study.

Bronchial lymphoid infiltration and cellular or follicular bronchiolitis are observed in SjS and RA[18,21]. In the present study, SjS is characterized by lymphoid infiltration into various organs, particularly exocrine organs, and it has been reported to be resistant to TNF blockade therapy[22]. Moreover, Catrina et al. reported that TNF blockade with infliximab or etanercept induced apoptosis in synovial macrophages but not lymphocytes[23]. In addition, Baeten et al. have shown that rheumatoid nodules are resistant to TNF blockade therapy, suggesting the existence of TNF-independent lesions in RA[24]. We also reported that organizing pneumonia was developed in RA patients successfully treated with TNF blockade[25]. Therefore, small airway obstruction could be a TNF-independent lesion in RA and might be similar in pathogenesis to SjS, where lymphoid infiltration plays an important role.

In contrast to our results, one case report showed that etanercept improved the obliterative bronchiolitis associated with RA[26]. Obliterative bronchiolitis is a rare disease characterized by the destruction of bronchiolar walls by granulation tissue, effacement of lumens, and replacement of bronchioles by fibrous tis-

sue[6]. Obliterative bronchiolitis differs in pathology from follicular bronchiolitis or peribronchiolar lymphoid infiltration, which is assumed to have caused subclinical obstruction in the patients in the present study. TNF-dependent pathways might play an important role in the development of obliterative bronchiolitis, perhaps in the generation of granulation, but not in the development of small airway obstruction in RA.

The present study suggests that TNF blockade might worsen small airway obstruction because parameters of small airway obstruction were worsened in the TNF blockade group, not in the DMARDs group. This may be explained by the fact that TNF inhibition causes susceptibility to infection[27,28], and the inflammation by infection leads to the progression of airway obstruction.

In summary, the present study demonstrated that small airway obstruction is frequently found in RA patients, even those with early RA and that TNF blockade fails to improve small airway obstruction. These results suggest that TNF-independent pathways play important roles in the development of small airway obstruction in RA. However, the present study has several limitations, including a limited number of patients, a short observation period, and no histological and radiological evidence. Thus, further studies are needed to confirm our findings.

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