Rituximab therapy in primary Sjögren's syndrome with interstitial lung disease: a retrospective cohort study

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Abstract

Objective

Interstitial lung disease (ILD) is one of the major systemic manifestations of primary Sjögren's syndrome (pSS). The aim of this study was to evaluate the therapeutic effect of rituximab on pSS patients with ILD.

Methods

Pulmonary function test results, including diffusing capacity for carbon monoxide (DL_{CO}) and DL_{CO}/alveolar volume (Va) ratio, and high-resolution computed tomography (HRCT) findings/scores in ten pSS patients with ILD treated with rituximab were retrospectively investigated. Global disease, fatigue, dryness of eyes and mouth, shortness of breath, and cough were assessed by visual analogue scales (VAS, 0–100 mm).

Results

At 6 months after rituximab treatment, improvement in pulmonary function was observed (from 49.3±12.6 to 56.9±11.4% for DL_{CO}, p=0.011; from 74.4±15.8 to 85.6±10.3% for DL_{CO}/Va, p=0.021). Similarly, significant improvement of subjective symptoms were also noted after treatment (VAS global disease, from 62.0±11.4 to 26.0±10.8 mm, p<0.001; VAS fatigue, from 38.0±23.0 to 18.0±7.9 mm, p=0.006; VAS dryness of eyes, from 53.0±24.4 to 29.0±13.7 mm, p=0.004; VAS dryness of mouth, from 45.0±14.3 to 28.0±9.2 mm, p=0.001; VAS shortness of breath, from 64.0±16.5 to 31.0±16.0 mm, p<0.001; VAS cough, from 42.0±23.5 to 18.0±10.3 mm, p=0.011). The mean HRCT score decreased after rituximab therapy although to a lesser extent (from 8.7±4.1 to 7.6±4.6, p=0.419). An adverse event was observed in only one patient who had non-fatal pneumonia 4 months after rituximab infusion.

Conclusion

Rituximab was effective in improving clinical symptoms and gas exchange, and in stabilising HRCT score in pSS patients with ILD.

Key words

primary Sjögren's syndrome, interstitial lung disease, rituximab

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Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease that predominantly affects the function of exocrine glands due to focal lymphocytic infiltration (1, 2). pSS usually presents clinically as persistent dryness of the mouth and eyes. In addition, systemic nonexocrine manifestations including musculoskeletal, cutaneous, pulmonary, gastrointestinal, renal, and/or nervous involvement may occur in pSS patients. The frequency of lung involvement in patients with pSS varies, ranging from 9% to 90% in Caucasians (3, 4). The prognosis of pSS patients is favourable unless vital organ such as lung is involved. "Sicca lung" is a very important determinant of the patient's quality of life and clinical outcome. We have carried out an investigation on the effect of lung diseases on the outcomes of 44 patients with pSS and have found that patients with poor pulmonary function tests (PFT) and severe high-resolution computed tomography (HRCT) findings had a shorter median overall survival (5). Ito *et al*. analysed PFT and HRCT in 33 pSS patients, and revealed that low partial pressures of blood oxygen and presence of honeycombing lesions in lung were related to higher mortality (6).

Interstitial lung disease (ILD) has been reported to be the main pathologic presentation of pSS associated with autoimmune damage of the lung that carries poorest outcome (7-9). Current therapeutic options for these stetting are empiric and no controlled clinical trial results are available to guide management principle (10). Rituximab, a chimeric anti-CD20 monoclonal antibody, has demonstrated efficacy in patients with lymphoid malignancies, rheumatoid arthritis, and anti-neutrophil cytoplasmic antibody-associated vasculitis (11). Accumulating evidence has suggested that rituximab may be good alternative for these ill-defined connective disease (CTD)-associated ILD, including antisynthetase syndrome, polymyositis/dermatomyositis (PM/DM), systemic sclerosis, etc. (12-15). Significant improvement in PFT as well as in pulmonary architecture as demonstrated in HRCT has been observed after rituximab therapy. However, the effectiveness of rituximab on ILD in patients with pSS has yet to be appraised. To the best of our knowledge, only 3 pSS patients with ILD treated with rituximab have been reported previously (15). The aim of the present retrospective investigation was to evaluate the therapeutic effect of rituximab on pSS patients with ILD. Patient global assessment of disease status, fatigue, dryness of eyes and mouth, shortness of breath, cough, PFT results, and HRCT findings before and after receiving rituximab treatment were compared.

Patients and methods

Patients

pSS patients with ILD treated with rituximab between 2010 and 2012 in Taipei Veterans General Hospital were retrospectively analysed. All patients fulfilled the 2002 American-European Revised Classification Criteria for pSS (16). Patients with other CTD that may induce secondary SS, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), PM/DM, scleroderma, primary biliary cirrhosis (PBC), and mixed connective tissue disease (MCTD) were excluded (17). ILD was diagnosed according to the British Thoracic Society Interstitial Lung Disease guidelines (18). Other medical illnesses that could cause ILD, such as drugs, infections, etc, were excluded according to the clinical assessment and other laboratory investigations. The study was approved by the institutional review board of Taipei Veterans General Hospital, Taiwan.

Assessment in clinical appearance, PFT, and radiologic findings

Patient global disease activity, fatigue, dryness of eyes and mouth, shortness of breath, and cough were assessed by visual analogue scales (VAS) (score range: 0–100 mm). European League Against Rheumatism (EULAR) SS outcome measures, the disease activity index (ESSDAI) (19), and the patient-reported index (ESSPRI) (20) were used to evaluate systemic activity and patients' symptoms in pSS, respectively. PFT and HRCT of the lung were used to investigate the presence and se-

Table I. Demographic and immunologic profiles, pulmonary function tests, and extraglandular manifestations in 10 patients with primary Sjögren's syndrome with interstitial lung disease.

Characteristic	
Age at diagnosis of pSS (years ± SD)	51.1 ± 10.4
Female [n (%)]	10 (100%)
Smoker [n (%)]	0 (0.0%)
ANA > 1:160 [n (%)]	8 (80.0%)
Anti-SSA or SSB antibody (+) [n (%)]	10 (10.0%)
Rheumatoid factor (+) [n (%)]	6 (60.0%)
DL_{CO} ≤ 75% of the predictive [n (%)]	10 (100.0%)
DL_{CO}/Va ≤ 75% of the predictive [n (%)]	4 (40.0%)
FVC ≤ 60% of the predictive [n (%)]	2 (20.0%)
HRCT score (years ± SD)	8.2 ± 3.7
Extraglandular manifestations	
Musculoskeletal [n (%)]	5 (50.0%)
Gastrointestinal [n (%)]	2 (20.0%)
Neurologic [n (%)]	0 (0.0%)
Renal [n (%)]	0 (0.0%)

pSS: primary Sjögren's syndrome; ANA: antinuclear antibodies; DL_{CO}: carbon monoxide-diffusing capacity; Va: alveolar volume; FVC: forced vital capacity; HRCT score: high-resolution computed tomography score.

verity of pulmonary involvement. PFT included diffusion capacity of carbon monoxide (DL_{CO}), DL_{CO})/alveolar volume ratio (DL_{CO})/Va), and forced vital capacity (FVC). The predicted value of PFT was adjusted for age, height, and sex. HRCT has been proven to be very sensitive for lung involvement in patients with pSS, even in patients without overt symptoms (8, 21). All HRCT examinations were performed using contiguous axial beam, 5 mm thick in resolution, through the lungs on a Toshiba Aquilion 64 scanner (Toshiba, Tokyo, Japan). HRCT findings were read by two experienced chest radiologists and categorised according to the classification of CT patterns described by the American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias (22). HRCT scoring method has been used to evaluate severity of ILD and calculated according to the definitions reported previously by Schurawitzki *et al*. (23). All patients underwent two doses of rituximab 1000 mg, intravenous infusion, 14 days apart, and repeated the same protocol every half a year depending on individual responsiveness. However, our assessments focused on the status before the 1st and the second course of rituximab treatment (6 months apart).

Statistical analysis

The changes in VAS scores for clinical appearances, PFT results, HRCT scores before and after receiving rituximab treatment were compared by non-parametric Wilcoxon's sign-rank test. The Mann-Whitney *U*-test was used to compare differences between two groups. Spearman's correlation was used to assess the association between different parameters. *p*-values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS v. 15.0 (Statistical Package for the Social Sciences, SPSS, Inc., Chicago, IL, USA).

Results

Clinical features and PFT parameters of patients with pSS with ILD

Ten pSS patients with moderate to severe ILD who received rituximab treatment were assessed. All of them were women and their mean age at diagnosis was 51.1 years (Table I). None of them gives a history of smoking or other comorbidities that may affect the lung function. Six (60.0%) of our patients underwent minor salivary gland biopsy for diagnosis. Antinuclear antibodies (ANA) with a titer of more than 1:160 and rheumatoid factors (RF) of more than 30 IU/ml were present in 8 (80.0%) and 6 (60.0%) patients, respectively. All (100%) patients were positive for anti-SSA and/or SSB antibodies. Five (50.0%) pSS had extraglandular manifestation other than lung involvement. The most popular one was musculoskeletal disease (5 out of 10, 50.0%), including arthralgia and myalgia. The second popular one was gastrointestinal in 2 (20.0%) patients including oesophageal dysmotility and gastritis. None of them suffered from neurologic or renal abnormalities. The mean ESSDAI and ESSPRI scores were 4.6 and 15.5, respectively. Prior to rituximab therapy, all patients had received immunosuppressants including more than one conventional non-biologic DMARD and corticosteroid treatment, including steroid pulse therapy in 4 patients (Table II). During and after rituximab treatment, 4 patients continued their hydroxychloroquine, 2 continued hydroxychloroquine in combination with low dose glucocorticoids (prednisolone 2.5–5mg), while another 4 patients had low dose glucocorticoids alone (prednisolone 5–10mg). In the study period, none of our patients received high dose glucocorticoids, or non-biologic DMARDs other than hydroxychloroquine, including cyclophosphamide, mycophenolate mofetil, etc. VAS for global disease, fatigue, dryness of eyes and mouth, shortness of breath, and cough were 62.0 mm, 38.0 mm, 53.0 mm, 45.0 mm, 64.0 mm, and 42.0 mm, respectively. All patients underwent PFT within one month before rituximab treatment, which revealed 100% (10/10) with restrictive-type impairment characterised by 49.3% in average of reduced DL_{CO} (p<75% of the predicted value). In addition, 4 (40.0%) presented with reduced DL_{CO}/Va (p<75% of the predicted value) and 2 (20.0%) had a reduced FVC (<60% of the predicted value).

HRCT findings

HRCT scans were carried out in all 10 pSS patients with ILD within one month before rituximab treatment and were repeated in 7 of them 6 months after first course of rituximab. The HRCT findings before rituximab are summarised in Table II, which shows a mixed pattern in all patients. The most frequent feature was linear interstitial opacity (100%), followed by ground glass opacity

Table II. Baseline characteristics in 10 patients with primary Sjögren's syndrome and interstitial lung disease.

n.	Age at diagnosis of pSS (years)	Sex	Duration between ILD diagnosis and rituximab use (years)	HRCT finding	Pre-rituximab immunosuppression
1	53	F	8	ILO, IST, GGO, CYS, NO, ACO	iv MTP, pred, MTX
2	49	F	1	ILO, IST, GGO, BEC, RET, NO	pred, HCQ
3	57	F	1	ILO, GGO, RET, HON	pred, HCQ
4	52	F	6	ILO, IST, GGO, BEC, NO	pred, HCQ
5	60	F	3	ILO, IST, GGO, CYS, BEC, RET, HON, NO	pred, HCQ
6	34	F	7	ILO, RET, NO	iv MTP, pred, HCQ
7	63	F	1	ILO, IST, GGO, BEC, RET, HON, NO	pred, HCQ
8	57	F	1	ILO, IST, GGO, BEC, NO, ACO	pred, HCQ
9	54	F	0.3	ILO, IST, GGO, BEC, RET, NO, ACO	iv MTP, pred, HCQ
10	32	F	1	ILO, IST, GGO, BEC, RET, HON, NO	iv MTP, pred, HCQ

pSS: primary Sjögren's syndrome; ILD: interstitial lung disease; HRCT: high-resolution computed tomography; ILO: interstitial linear opacities; IST: interlobular septal thickening; GGO: ground-glass opacities; CYS: cysts; BEC: bronchiectasis; RET: reticular pattern; HON: honey combing; NO: nodular opacities; ACO: airspace consolidation; MTP: methylprednisolone; pred: prednisolone; MTX: methotrexate; HCQ: hydroxychloroquine.

(90.0%), nodular opacity (90.0%), and interlobular septal thickening (80.0%). The average score for HRCT findings of all 10 patients was 8.2. There was no significant correlation between HRCT score and PFT obtained before rituximab, including DL_{CO}, DL_{CO}/Va, and FVC (r=-0.226, p=0.530; r=0.031, p=0.932; r=-0.604, p=0.065, respectively). In addition, HRCT score did not correlate with the duration between diagnosis of ILD and evaluation by HRCT (r=-0.421, p=0.225).

Efficacy of rituximab

The mean interval between diagnosis of ILD and rituximab treatment was 2.93 years (range: 0.3–8 years). Six months after the 1st rituximab infusion, improvement in pulmonary function was observed, including DL_{CO} and DL_{CO}/Va, but not FVC (mean ± SD, from 49.3±12.6 to 56.9±11.4% in the predicted value of DL_{CO}, p=0.011; from 74.4±15.8 to 85.6±10.3% in the predicted value of DL_{CO}/Va, p=0.021; from 74.7±16.2 to 76.4±16.1 in the predicted value of FVC, p=0.484, Table III; Fig. 1). Similarly, significant improvement in objective symptoms were also noted (VAS global disease, from 62.0±11.4 to 26.0±10.8 mm, p<0.001; VAS fatigue, from 38.0±23.0 to 18.0±7.9 mm, p=0.006; VAS dryness of eyes, from 53.0 ± 24.4 to 29.0±13.7 mm, p=0.004; VAS dryness of mouth, from 45.0±14.3 to 28.0±9.2 mm, p=0.001; VAS shortness of breath, from 64.0±16.5 to 31.0±16.0 mm, p<0.001; VAS score for cough, from 42.0±23.5 to 18.0±10.3 mm, p=0.011, Fig. 2). Significant decrease in ESSDAI and ESSPRI scores were found in our pSS patients after receiving treatment with rituximab (ESSDAI score, from 4.6±1.3 to 2.4±1.1, p<0.001; ESSPRI score, from 15.5±4.3 to 7.6±2.0, p<0.001). A median improvement was 6.7% in FVC (p<0.01) and 0% change in stability of DL_{CO} (p<0.01) 6–12 months after rituximab treatment. The mean HRCT score of 7 pSS patients decreased after rituximab infusion although to a lesser extent (from 8.7±4.1 to 7.6±4.6, p=0.419). A significant improvement in HRCT appearances occurred in a pSS patient 6 months after rituximab therapy (Fig. 3A-B). There was no statistically significant difference in pre-rituximab HRCT score, PFT parameters, age at the diagnosis of pSS or ILD, presence of ANA (>1:160), antibodies against SSA, SSB and RF in 2 patients with improvement in HRCT findings and in 5 patients without improvement in HRCT findings (all p>0.05).

Table III. Median change in clinical appearances, disease activity, pulmonary function tests, and high-resolution computed tomography score in all 10 patients before and 6 months after rituximab treatment.

	Pre-rituximab	Post-rituximab	p value*
Patient global disease VAS (mm)	62.0 ± 11.4	26.0 ± 10.8	<0.001*
Fatigue VAS (mm)	38.0 ± 23.0	18.0 ± 7.9	0.006*
Dryness eye VAS (mm)	53.0 ± 24.4	29.0 ± 13.7	0.004*
Dryness mouth VAS (mm)	45.0 ± 14.3	28.0 ± 9.2	0.001*
Shortness of breath VAS (mm)	64.0 ± 16.5	31.0 ± 16.0	<0.001*
Cough VAS (mm)	42.0 ± 23.5	18.0 ± 10.3	0.011*
ESSDAI score	4.6 ± 1.3	2.4 ± 1.1	<0.001*
ESSPRI score	15.5 ± 4.3	7.6 ± 2.0	<0.001*
% predicted DL_{CO}	49.3 ± 12.6	56.9 ± 11.4	0.011*
% predicted DL_{CO}/Va	74.4 ± 15.8	85.6 ± 10.3	0.021*
% predicted FVC	74.7 ± 16.2	76.4 ± 16.1	0.484
HRCT score	8.7 ± 4.1	7.6 ± 4.6	0.419

VAS: visual analogue scales; ESSDAI: European League Against Rheumatism Sjögren's syndrome outcome measures-the disease activity index; ESSPRI: European League Against Rheumatism Sjögren's syndrome patient reported index; DL_{CO}: carbon monoxide-diffusing capacity; Va: alveolar volume; FVC: forced vital capacity; HRCT score: high-resolution computed tomography score. *p<0.05 = significant.

Tolerance and outcome

Rituximab was well tolerated in all 10 patients and no infusion reaction was recorded. Seven patients received subsequent maintenance rituximab therapy including 4 with 2 courses (4 doses), 2 with 3 courses (6 doses), and 1 with 5 courses (10 doses). No one died during the follow-up period (mean follow-up time after rituximab use, 26.1 months,

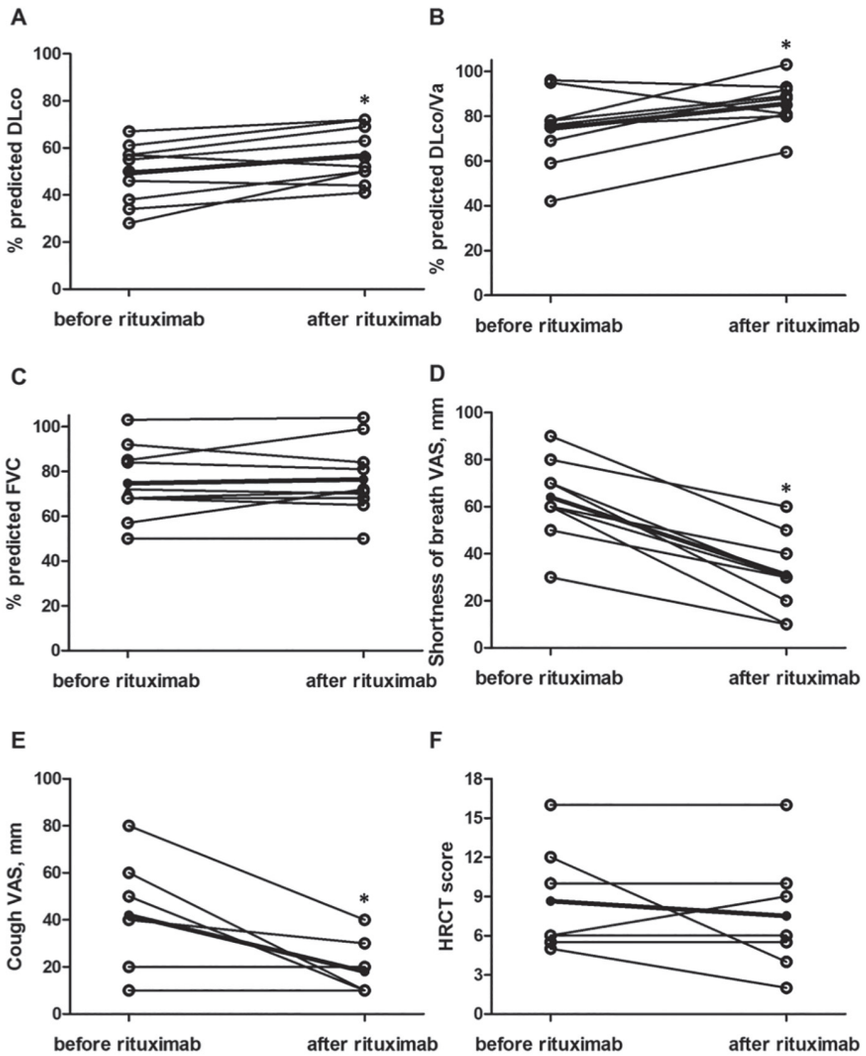

Fig. 1. Changes in pulmonary manifestation, pulmonary function test, and high-resolution computed tomography (HRCT) in 10 patients with primary Sjögren's syndrome and interstitial lung disease before and 6 months after rituximab therapy.
(**A**) Carbon monoxide-diffusing capacity (DL_{CO}) % predicted, (**B**) DL_{CO}/ alveolar volume (Va) % ratio predicted, (**C**) Forced vital capacity (FVC) % predicted, (**D**) Visual analogue scale (VAS) scores for shortness of breath, (**E**) cough, and (**F**) HRCT score before and 6 months after rituximab therapy. Average improvement in DL_{CO} % was 7.6 % (p=0.011), in DL_{CO}/Va % was 11.2% (p=0.021), in VAS scores for shortness of breath was 33.0 mm (p<0.001), and in cough was 24.0 mm (p=0.011). However, there was no statistically significant difference in FVC % predicted and in HRCT score before and after rituximab administration (p=0.484 and 0.419, respectively). Mean change for each group is represented by the solid black line. *p<0.05.

range: 9–60 months). However, one patient developed a serious infection (pneumonia) requiring hospitalisation 4 months after rituximab treatment.

Discussion

The clinical course of patients with pSS with lung involvement is not favourable (5). In the present investigation, we reported successful treatment of rituximab in 10 cases of moderate to severe ILD associated with pSS. These patients were previously refractory to conventional synthetic DMARDs. Rituximab offered a significant improvement in clinical symptoms, including dryness, global disease activity, and fatigue. In addition, PFT analyses revealed that rituximab improved restrictive-type impairment. Finally, rituximab improved or stabilised ILD as demonstrated by HRCT.

Accumulating evidence has suggested that rituximab may offer benefits to patients with CTD-associated ILD. Sem and colleagues reported that rituximab stabilised and/or improved lung diseases in 7 of 11 patients with anti-synthetase antibodies associated with severe ILD who failed cyclophosphamide and/or other immunosuppressant therapies (12). A study described by Daoussis showed that FVC and DL_{CO} got more conspicuous improvement in 8 scleroderma patients receiving standard treatment and rituximab than in 6 patients receiving standard treatment only (13). Keir *et al*. analysed the PFT results and HRCT findings in 8 patients with CTD-ILD unresponsive to conventional immunosuppression, including 5 polymyositis/dermatomyositis, 2 undifferentiated CTD, and 1 systemic sclerosis, and found that 7 out of the 8 patients had a favourable treatment response to rituximab (14). The same group enrolled 33 patients with CTD-ILD including 10 polymyositis/dermatomyositis, 8 systemic sclerosis, 9 undifferentiated CTD, 2 MCTD, 2 RA, 1 SLE and 1 pSS, and revealed an improvement in FVC of 6.7% and stabilisation of DL_{CO} within the 6–12 months following rituximab therapies (15). In addition, two pSS patients with ILD treated with rituximab have been reported. Seror *et al*. described a patient with dyspnea and cough symptoms resulted from lymphocytic interstitial pneumonia, who was completely recovered after 2 months of treatment with rituximab (24). Another patient developed lymphocytic interstitial pneumonia with a predominant B-cell infiltration and had a significant improvement in dyspnea, dryness symptoms, PFT, and HRCT findings after receiving rituximab infusion (25). In the present investigation, improvement in DL_{CO} and DL_{CO}/Va was observed in all 10 pSS patients with ILD following rituximab infusion. Similarly, significant improvement of subject symptoms was also noted after the treatment; the mean changes in VAS for shortness of breath and cough were 33 mm and 24 mm, respectively.

Keir *et al*. has described a median improvement in FVC of 6.7% in 33 patients with CTD related-ILD after rituximab treatment (15). In contrast, we only observed a mild elevation in FVC with a mean change of 1.7%, which did not reach statistical significance. PFT in pSS can be restrictive or obstruc-

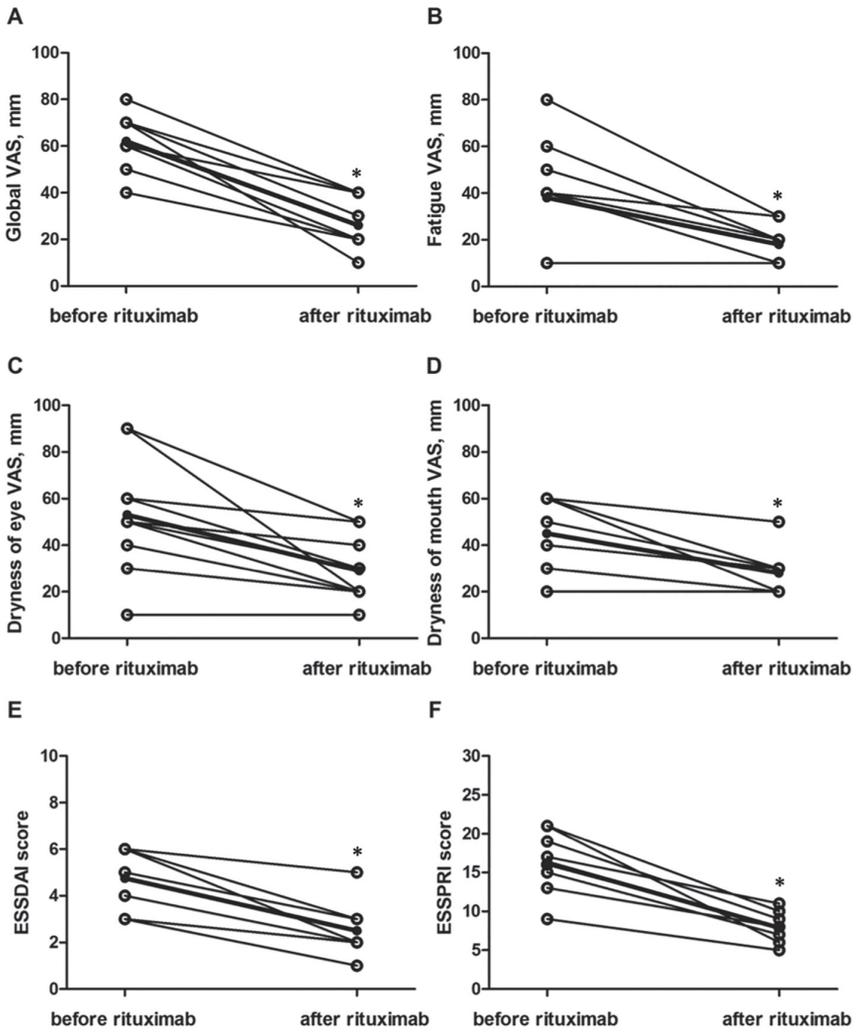

Fig. 2. Changes in clinical symptoms relevant to primary Sjögren's syndrome before and 6 months after rituximab therapy.
Visual analogue scale (VAS) scores for global disease (**A**), fatigue (**B**), dryness of eyes (**C**) and mouth (**D**), European League Against Rheumatism Sjögren's syndrome outcome measures-the disease activity index (ESSDAI), and the patient reported index (ESSPRI) scores before and 6 months after rituximab administration for each patient are shown. At the end of data collection, there was an improvement in mean global disease (36.0 mm, $p<0.001$), fatigue (20.0 mm, $p=0.006$), dryness of eyes (24.0 mm, $p=0.004$), dryness of mouth (17.0 mm, $p=0.001$), ESSDAI score (2.2, $p<0.001$), and ESSPRI score (7.9, $p<0.001$). Mean change for each group is represented by the solid black line. *$p<0.05$.

tive, even in patients without pulmonary symptoms (9, 21). All of our 10 pSS patients with ILD had restrictive pattern with low DL_{CO} (<75%), while only two presented with mixed type of obstructive and restrictive patterns (decreased FVC, <60%). At the initiation of rituximab infusion, predictive value of FVC in our patients seemed better than that in CTD patients enrolled in previous studies (median: 69.0% [50.0-103%] *vs*. 44.0% [24.0–99.0%]), suggesting that rituximab may bring more benefits in patients with serious obstructive-type impairment than in those with mild involvement. Other reasons for the different effect of rituximab on PFT between two studies may include diseases *per se*, ethnicities, genetic factors, or statistical power of the study resulted from limited sample sizes.

HRCT is a relatively non-invasive modality and is currently the most important tool to detect early parenchymal abnormalities and decreased lung function. The mean HRCT score of our 7 pSS patients decreased following rituximab therapy but not reached a statistical significant level. Reduction of the score was observed in 2 patients, while it tied in 4 and increased in one after the therapies. HRCT revealed regression of ground glass opacity, while the chronic changes persisted. These findings implied that rituximab may offer an effective therapeutic benefit for pSS patients during active phase of ILD. There was no significant difference between 2 groups of patients, those with HRCT improvement (n=2) and those without (n=5) before rituximab with regards to PFT and clinical profiles, including age at diagnosis of pSS or ILD, presence of ANA (>1:160), SSA/SSB, and RF (all $p>0.05$). Further large-scale studies are needed to find more reliable predictors of HRCT improvement in rituximab-treated pSS patients with ILD.

Some reports have suggested that rituximab may improve the symptoms relevant to dysfunction of the exocrine glands and systemic manifestations in pSS. An improvement in the subjective VAS score for dryness symptoms and an increase in salivary gland function was observed after infusions of rituximab in a woman with pSS associated MALT lymphoma (26). Devauchelle-Pensec *et al*. have reported VAS scores of fatigue and dryness were significantly improved in 16 patients with pSS (27). Dass and colleague analysed 8 pSS patients treated with rituximab and found 7 (87.5%) of them had more than 20% recovery in VAS fatigue (28). A prospective study enrolling 41 pSS patients with active disease reported by Carubbi *et al*. has demonstrated that compared to DMARDs, rituximab could more profoundly reduce glandular infiltrate and significantly attenuate global disease activity, fatigue, dryness, physician global assessment, and ESSDAI score (29). In a prospective cohort study of 28 pSS patients, the ESSDAI and ESSPRI scores improved significantly with rituximab therapy (30). Similar results were obtained in the present investigation; the mean changes in VAS score for global disease, fatigue, dryness of eye, dryness of mouth were 36 mm, 20 mm, 24 mm, 17 mm, while the mean ESSDAI and ESSPRI scores also decreased significantly (2.2 and 7.9, respectively). In contrast, two large randomised controlled studies failed to show similar results. In the Tolerance and Efficacy of Rituximab in pSS (TEARS) trial, improvement of at least

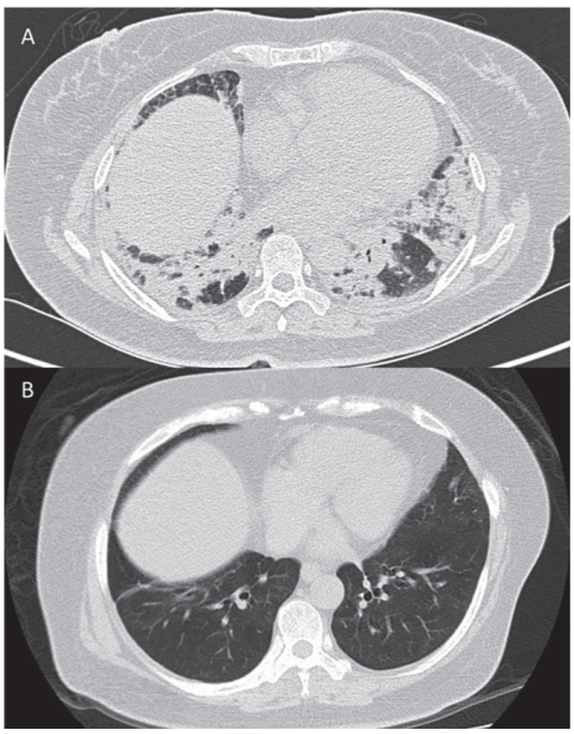

Fig. 3. Changes in the pulmonary architecture in a patient with primary Sjögren's syndrome as revealed by HRCT before and 6 months after rituximab therapy.
A) Consolidation and ground-glass opacity in bilateral lower lobes.
B) The lower lobe consolidation and ground-glass opacity almost completely resolved 6 months after rituximab therapy.

30 mm in 2 of 4 VAS for global disease, pain, fatigue, and dryness was not seen in 120 pSS patients after 24 weeks treatment with rituximab when compared to placebo group (31). TRACTISS study, another double-blind, randomised, controlled, parallel group trial, enrolled 133 patients with pSS but did not show any benefit of rituximab compared to placebo on global activity, dryness, and fatigue (32, 33). However, the mean decrease in the VAS scores for fatigue was larger with rituximab than with placebo at weeks 6 and 16 in the TEARS study. Also, a post-hoc analysis of the TEARS study revealed that pSS patients may actually be significantly improved by rituximab if treatment response was defined as a 30% improvement in at least two of five outcome measures, including patient-assessed VAS for fatigue, oral dryness and ocular dryness, un-stimulated whole salivary flow, and ESR (34). Therefore, we consider that rituximab may be an effective agent to ameliorate glandular as well as systemic diseases in pSS.

The mechanism underlying the improvement of ILD in pSS by rituximab remains unknown. PSS is characterised by lymphoplasmocytic infiltration in salivary glands. T cells were originally considered playing a main role in its pathogenesis. However, growing body of evidence has suggested that B cell is critical for the development of pSS and is a potential therapeutic target for amelioration of pulmonary inflammation (35-38). Compared to patients with secondary SS, a higher expression of CD20 bearing B cells in minor salivary glands was observed in pSS (39). B cells not only can produce autoantibodies, but also contribute to the secretion of cytokines and chemokines as well as to the presentation of antigens to autoreactive T cells (19, 40). Rituximab treatment depletes CD20 bearing B cells in peripheral circulation and salivary gland, leading to attenuation of autoantibody production and blocking of autoreactive T cell activation (41, 42). In addition to the influence of B cell functions, observations in the treatment of idiopathic thrombocytopenic purpura have suggested that rituximab may help revert the abnormalities of T-cell subsets and restore numbers of regulatory T cells (43). Finally, B cells, as well as plasma cells, were observed to infiltrate in interstitial septa and alveolar spaces in pSS patients with ILD, implying that rituximab may induce similar effects as described above in lung tissue (44). These may explain the benefit of rituximab in the management of ILD in pSS.

A limited amount of studies concerning the relationship between HRCT score and PFT have been conducted. Our previous investigaton revealed that impairment of DL_{CO} was associated with high HRCT scores in 44 pSS patients with lung involvement (5). Conversely, Yazisiz *et al*. analysed 14 Turkish pSS patients with lung involvement and found that there was negative correlations between HRCT scores and PFT profiles (45). In the present investigation, HRCT score did not have correlation with PFT scores in the pSS patients with ILD. This was probably because of tiny size of enrolment in the present investigation and the difference in ethnicity. In addition, HRCT score did not correlate with ILD duration. Previous studies observed that abnormal HRCT findings were seen in 24 of 37 pSS patients without pulmonary symptoms (8, 21), implying that ILD may exist early in asymptomatic patients. This may account for the absence of positive correlation between severity in HRCT findings and ILD duration in our pSS patients.

In addition to small sample size, there are some additional drawbacks in this retrospective study. First, our cohort had a relatively short follow-up period. The long-term efficacy of rituximab treatment was unavailable because of difficult in follow-up. Second, the heterogeneity of clinical characteristics, previous medications, and severity of HRCT in our patients might influence the response to rituximab. Another is that the normal control group was hard to include, resulting in that the efficacy of rituximab could not get a comprehensive comparison with the placebo as in a prospective study. So, whether rituximab is superior to conventional immunosuppressants for ILD associated with pSS remains unclear.

In conclusion, for pSS patients with ILD, rituximab may be safe and effective to improve clinical symptoms, PFT results, as well as HRCT findings. Nevertheless, more large-scale investigations are necessary to validate our findings. On the other hand, to clarify the exact role of B cell depletion in the improvement of pulmonary inflammation associated with pSS, further in-depth investigations are mandatory.

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