Comparative Study of Serum Surfactant Protein-D and KL-6 Concentrations in Patients with Systemic Sclerosis as Markers for Monitoring the Activity of Pulmonary Fibrosis

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ABSTRACT. Objective. To clarify the clinical significance of surfactant protein-D (SP-D) and KL-6 in the diagnosis and monitoring of pulmonary fibrosis (PF) in patients with systemic sclerosis (SSc), and to evaluate the differences between SP-D and KL-6.

Methods. Serum SP-D and KL-6 concentrations were determined by ELISA in 42 SSc patients. In a retrospective longitudinal study, 83 serum samples from 6 SSc patients were analyzed during a followup period of 0.6–6.3 years.

Results. SP-D and KL-6 concentrations at the first visit were higher in patients with SSc, especially those with PF, compared with healthy controls. Increased concentrations of SP-D were associated with decreased DLCO and decreased vital capacity in SSc patients more strongly than those of KL-6. The sensitivity and specificity for PF were 91% and 88% for SP-D and 39% and 100% for KL-6, respectively. In the longitudinal study, both SP-D and KL-6 concentrations were associated with activity of PF in patients with SSc. SP-D concentrations changed more rapidly than KL-6 concentrations, in parallel with the PF activity.

Conclusion. SP-D was a more sensitive marker for PF than KL-6. By contrast, KL-6 showed higher specificity than SP-D. Combined use of these 2 serum markers would be more helpful to diagnose and monitor the PF activity in patients with SSc than single use of each marker. (J Rheumatol 2004;31:1112–20)

Key Indexing Terms:
SYSTEMIC SCLEROSIS
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Systemic sclerosis (SSc) is a generalized connective tissue disorder characterized by sclerotic changes in the skin and internal organs. Pulmonary fibrosis (PF) occurred in more than 50% of patients with SSc, and is the major cause of death in SSc1,2. To evaluate the activity of PF, previous studies have identified several important signs, including patchy areas with ground-glass or reticular appearance on high resolution computed tomography (HRCT) and a neutrophilic alveolitis determined by bronchoalveolar lavage (BAL) analysis1. However, repeated examination by HRCT or BAL is difficult for patients with SSc because of their high cost and invasiveness. Simpler and easier, non-invasive serological markers would be helpful to closely monitor the activity of PF in SSc.

Surfactant protein-D (SP-D) belongs to the collectin subgroup of the CC-type lectin superfamily3. SP-D is produced and secreted by alveolar type II pneumocytes in alveoli and Clara cells4. SP-D functions at the air-liquid interface to reduce surface tension and thereby prevents alveolar collapse and atelectasia. SP-D also plays important roles in the innate immune system of the lungs4. Increased serum SP-D concentrations were detected in patients with interstitial lung diseases, including idiopathic interstitial pneumonia (IIP), pulmonary alveolar proteinosis, and interstitial pneumonia related to collagen diseases5-9. Moreover, serum SP-D concentrations were correlated with the presence of PF in patients with SSc10-12.

KL-6, a glycoprotein antigen first described by Kohno, et al13, is expressed mainly on type II pneumocytes in alveoli and respiratory bronchiolar epithelial cells14. KL-6 concentrations are elevated in the sera from patients with interstitial lung diseases, including IIP, hypersensitivity pneumonia, radiation pneumonia, sarcoidosis, and interstitial pneumonia related to collagen diseases14-18. Recent studies have shown that serum KL-6 concentrations are increased in SSc patients with PF compared to those without
Further, we found rapidly increased serum KL-6 concentrations to correlate with the extent or severity of PF in SSc. In addition, KL-6 concentrations have been shown to be helpful to closely monitor the activity of PF in SSc. We investigated the clinical significance of SP-D and KL-6 in the diagnosis and monitoring of PF in patients with SSc and further evaluated the clinical differences between SP-D and KL-6. Our results indicate that the combined use of these 2 serum markers would be more helpful to diagnose and monitor PF in patients with SSc than single use of each marker.

MATERIALS AND METHODS

Patients. Serum samples were obtained from 42 Japanese patients with SSc (36 women, 6 men). All patients fulfilled criteria for SSc proposed by the American College of Rheumatology (ACR). These patients were grouped according to the classification system proposed by LeRoy, et al: 14 patients had limited cutaneous SSc (lSSc) and 28 had diffuse cutaneous SSc (dSSc). Anti-topoisomerase I (anti-topo I) antibodies were positive in 27 patients; anticientromere (ACA) in 11; and anti-RNA polymerase I in 3. The remaining patient showed negative antinuclear antibodies (ANA). The average age was 49 ± 18 years (mean ± standard deviation). The mean disease duration was 4.2 years (range 0.2–20). Duration of disease was calculated from the time of onset of the first clinical event (other than Raynaud’s phenomenon) that was a clear manifestation of SSc. At their first visit, 10 patients had been treated with low dose corticosteroid (prednisolone 5–20 mg/day) and 2 with low dose D-penicillamine (100–500 mg/day). No patient had received immunosuppressive therapy. Twenty patients with systemic lupus erythematosus (SLE) that fulfilled the ACR criteria were also examined as disease controls (17 women, 3 men, age 47 ± 15 yrs). PF was not detected in any patient with SLE. Thirty healthy age and sex matched Japanese individuals were used as healthy controls (26 women, 4 men, age 52 ± 19 yrs).

In a retrospective longitudinal study, we analyzed 83 serum samples from 6 SSc patients. The mean followup period was 2.3 (0.6–6.3) years with 13.8 (8–20) timepoints. Three patients were already treated with low dose corticosteroid (prednisolone 5–20 mg/day) at their first visit. Serum SP-D concentrations in patients with SSc at their first visit. Serum SP-D and KL-6 concentrations were measured with specific ELISA kits (SP-D kit, Yamasa, Chiba, Japan), according to the manufacturer’s protocol. Briefly, polystyrene cups coated with anti-SP-D mAb were incubated with 20 μl of serum samples diluted 1:11 at 4°C for 24 h. The cups were then washed and incubated at 25°C for 2 h with 100 μl of 110-fold diluted horseradish peroxidase-conjugated anti-SP-D antibodies. Then the cups were washed again, 100 μl tetramethylbenzidine was added, and incubation was performed at 25°C for 15 min. Finally, 2 mM Na2OBOH was added to terminate the peroxidase reaction, and absorbance was measured at 450 nm. In this assay system, the cutoff value was established as 110 nmol/ml by the receiver-operating characteristic analysis, as described.

Detection of serum KL-6. Serum KL-6 concentrations were measured with specific ELISA kits (Eistest KL-6, Eisai, Tokyo, Japan), according to the manufacturer’s protocol. Briefly, 96-well plates were coated with mouse anti-KL-6 mAb, and serum samples diluted 1:200 were added to duplicate wells for 2 h at 20°C. After washing, bound antibodies were detected with peroxidase-conjugated mouse anti-KL-6 mAb. In this assay system, the cutoff value was established as 500 U/ml by the receiver-operating characteristic analysis.

Statistical analysis. Comparisons between 2 groups of data were by Mann-Whitney U-test. Comparisons among 3 or more groups were by one-way ANOVA followed by a Bonferroni test. Spearman’s rank correlation coefficient was used to examine the relationship between 2 continuous variables. A p value < 0.05 was considered statistically significant.

RESULTS

Serum SP-D and KL-6 concentrations at the first visit. We first assessed clinical correlation of SP-D and KL-6 concentrations in patients with SSc at their first visit. Serum SP-D and KL-6 concentrations are shown in Figure 1. Serum SP-D concentrations at first visit were significantly elevated in total patients with SSc compared with healthy controls (p < 0.0001) and patients with SLE (p < 0.05). Elevated SP-D concentrations were observed in 57% (24/42) of SSc patients, and 87% (21/24) of them were positive for antitopo I antibodies. SP-D concentrations in SSc patients with PF were significantly higher than in those without PF (p < 0.01) and SLE patients (p < 0.0001) and healthy controls (p < 0.0001; Figure 1A). By contrast, serum SP-D concentrations were similar for SSc patients without PF, SLE patients, and healthy controls. Further, SP-D concentrations correlated inversely with VC (r = −0.61, p < 0.0001) and DLCO (r = −0.70, p < 0.0001) in SSc patients (Figure 2A). Use of fibrosis on chest radiographs, and ground-glass opacities, reticular opacities, or honeycomb on HRCT. Pulmonary function tests (PFT), including vital capacity (VC) and diffusion capacity for carbon monoxide (DLCO), were performed to evaluate the severity of PF. When DLCO and VC were < 75% and < 80%, respectively, of predicted normal values, they were considered to be abnormal. Activity of PF was assessed by changes in serial examinations by HRCT and PFT. We used a HRCT scoring system based on the method of Kazarounti and coworkers. Each lobe of the lung was scored for the extent of ground-glass opacity (HRCT-ground glass) and reticular opacities and honeycomb (HRCT-fibrosis) on a scale of 0–5 as follows: score 0 (absent), 1 (< 5%), 2 (5–25%), 3 (25–50%), 4 (50–75%), and 5 (> 75%). Mean value for all lobes was incorporated into a fibrotic (HRCT-fibrosis) and ground-glass (HRCT-ground glass) score for each patient and scores were then averaged for the 2 readers. SSc patients with a smoking habit or other respiratory disorders that could have affected DLCO or VC were excluded from this study.

Detection of serum SP-D. Serum SP-D concentrations were measured with specific ELISA kits (SP-D kit, Yamasa, Chiba, Japan), according to the manufacturer’s protocol. Briefly, polystyrene cups coated with anti-SP-D mAb were incubated with 20 μl of serum samples diluted 1:11 at 4°C for 24 h. The cups were then washed and incubated at 25°C for 2 h with 100 μl of 110-fold diluted horseradish peroxidase-conjugated anti-SP-D antibodies. Then the cups were washed again, 100 μl tetramethylbenzidine was added, and incubation was performed at 25°C for 15 min. Finally, 2 mM Na2OBOH was added to terminate the peroxidase reaction, and absorbance was measured at 450 nm. In this assay system, the cutoff value was established as 110 nmol/ml by the receiver-operating characteristic analysis, as described.

Detection of serum KL-6. Serum KL-6 concentrations were measured with specific ELISA kits (Eistest KL-6, Eisai, Tokyo, Japan), according to the manufacturer’s protocol. Briefly, 96-well plates were coated with mouse anti-KL-6 mAb, and serum samples diluted 1:200 were added to duplicate wells for 2 h at 20°C. After washing, bound antibodies were detected with peroxidase-conjugated mouse anti-KL-6 mAb. In this assay system, the cutoff value was established as 500 U/ml by the receiver-operating characteristic analysis.
Serum SP-D for the diagnosis of PF in SSc patients gave a sensitivity of 91% (21/23) and specificity of 88% (21/24).

Serum KL-6 concentrations at the first visit were significantly higher in total patients with SSc than in healthy controls (p < 0.01) and patients with SLE (p < 0.05). KL-6 levels were elevated in 21% (9/42) of SSc patients, and 89% (8/9) of them were positive for anti-topo I antibodies. SSc patients with PF exhibited significantly increased KL-6 levels relative to those without PF (p < 0.05), SLE patients (p < 0.05), and healthy controls (p < 0.01; Figure 1B). In contrast, serum KL-6 levels were comparable in SSc patients without PF, SLE patients, and healthy controls. Further, KL-6 levels correlated inversely with VC (r = –0.33, p < 0.05) and DLCO (r = –0.34, p < 0.05) in SSc patients (Figure 2B). Serum KL-6 levels were strongly correlated with serum SP-D levels in SSc patients (r = –0.60, p < 0.0001; Figure 3). Use of serum KL-6 in the diagnosis of PF in patients with SSc yielded a sensitivity of 39% (9/23) and specificity of 100% (9/9). Thus, elevated serum levels of SP-D and KL-6 were associated overall with presence and severity of PF in SSc patients at their first visit. In addition, SP-D was a more sensitive marker for PF than KL-6. By contrast, KL-6 was more specific for PF than SP-D, although measuring KL-6 levels was much less significant than SP-D levels. Thus, measuring both SP-D and KL-6 levels would be more useful for correct evaluation of PF than either test separately.

Correlation of serum SP-D and KL-6 concentrations with clinical and serologic features in SSc. To determine the correlations of serum KL-6 and SP-D concentrations with clinical and serologic features in patients with SSc, 42 SSc patients were grouped into the following 3 groups (Table 1). The first group included 18 SSc patients with normal levels of both KL-6 and SP-D. The second group included 15 SSc patients with normal KL-6 and elevated SP-D. The remaining 9 patients belonged to the group with elevated concentrations of both KL-6 and SP-D. There was no patient with elevated KL-6 and normal SP-D level. The presence of PF was significantly greater in patients with elevated SP-D and normal KL-6 or those with elevated SP-D and elevated KL-6 than in those with normal SP-D and normal KL-6 (p < 0.001). Similarly, the incidences of decreased VC and decreased DLCO were significantly higher in patients with elevated SP-D and normal KL-6 (p < 0.01) or in patients with elevated SP-D and elevated KL-6 than in those with normal SP-D and normal KL-6 (p < 0.001). Moreover, patients with elevated SP-D and normal KL-6 or those with elevated SP-D and elevated KL-6 had anti-topo I antibodies more frequently than those with normal concentrations of both SP-D and KL-6 (p < 0.01). Consistently, patients with elevated SP-D and normal KL-6 or those with elevated SP-D and elevated KL-6 had anticentromere antibodies less frequently than those with normal SP-D and normal KL-6 (p < 0.01). There was no significant difference between

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**Figure 1.** Serum SP-D (A) and KL-6 (B) concentrations in SSc patients with pulmonary fibrosis (PF+) and without pulmonary fibrosis (PF–), SLE patients, and healthy controls (CTL). Serum SP-D and KL-6 concentrations were determined by ELISA. Horizontal lines show mean values. Broken line indicates the cutoff value (110 ng/ml and 500 U/ml, respectively).
patients with elevated SP-D and normal KL-6 and those with elevated SP-D and elevated KL-6. However, the presence of PF, decreased VC, and decreased DLCO tended to be higher in patients with elevated SP-D and KL-6 levels than in those with elevated SP-D and normal KL-6 levels. Thus, SP-D is a sensitive PF marker, but it is necessary to account for false positive cases.

**Longitudinal study of serum SP-D and KL-6 concentrations.**

To determine whether the changes in serum SP-D and KL-6 concentrations correlated with new onset or deterioration of PF, we analyzed 83 serum samples from 6 SSc patients retrospectively. Five of 6 patients had anti-topo I antibodies and the remaining single patient was negative for ANA. The first patient (Case 1) had a normal KL-6 level (55 U/ml) and elevated SP-D (256 ng/ml), with mild PF and normal PFT at the first visit (Figure 4A). This patient was treated with 20 mg/day oral prednisolone for skin fibrosis. Six months after the first visit, KL-6 concentration suddenly rose to 956 U/ml and the patient began to have dry cough, while SP-D levels remained high around 250–300 ng/ml. Chest CT revealed ground-glass and reticular shadow in bilateral lower lobes, with decreased DLCO (39%) and VC (56%). After 3 years, the deterioration of PFT ceased and the progression of PF appeared to stop, although both serum KL-6 and SP-D concentrations stayed high. Five years after the first visit, SP-D levels gradually began to decline, and KL-6 levels also started to decrease about 6 months behind SP-D. After 6 years, this patient experienced complicated secondary pulmonary hypertension caused by PF that resulted in death.

Case 2 showed a slight increase in KL-6 concentration (554 U/ml) and a prominent increase in SP-D (210 ng/ml) with slightly decreased DLCO (56%) at the first visit (Figure 4B). Ground-glass shadow was observed in bilateral lower lobes on chest CT. This patient had been treated with 15 mg/day oral prednisolone for skin sclerosis and the same dose was continued after the first visit. Four months later,
KL-6 level suddenly increased to 1463 U/ml, with subacute deterioration of PF, dry cough, and dyspnea, whereas SP-D level remained high (205 ng/ml). Ground-glass and reticular shadow was increased in bilateral middle and lower lobes on chest CT relative to that observed at the first visit. In addition, 12 months after first visit, DLCO and VC were decreased to 37% and 59%, respectively. Then steroid pulse treatment was started, followed by 40 mg/day oral prednisolone, which resulted in stable KL-6 and decreased SP-D levels. However, PF persisted to deteriorate, and both SP-D and KL-6 levels were elevated again; 2.7 years after the first visit, this patient died of right heart failure.

Case 3 had increased SP-D concentration (139 ng/ml) and normal KL-6 (368 U/ml), with slightly decreased DLCO (64%), while no lung fibrosis was observed on chest CT (Figure 4C). This patient was treated with 20 mg/day oral prednisolone for skin fibrosis. At 2 months after first visit, KL-6 level suddenly increased to 886 U/ml and SP-D also increased to 198 ng/ml. A slight ground-glass shadow appeared in bilateral lower lobes on chest CT. Eight months after the first visit, SP-D and KL-6 levels were elevated to 236 ng/ml and 1311 U/ml, respectively. Ground glass shadow was increased in bilateral lower lobes on chest CT, and DLCO and VC were decreased to 49% and 79%. At 8 months, after the first visit, CYC pulse therapy (1000 mg/month) was started, followed by 30 mg/day oral prednisolone, and 6 administrations of CYC pulse therapy (750–1000 mg/month) were performed in total. During the pulse therapy, there was no further elevation of SP-D or KL-6 level, and decrease of DLCO and VC also ceased (VC 85% and DLCO 47%). However, after the 6 treatments of
Figure 4. Serial changes in serum SP-D and KL-6 concentrations during follow-up period in 6 patients with SSc. Serum SP-D and KL-6 concentrations determined by ELISA. Black symbols represent serum SP-D, white symbols KL-6. Broken lines indicate cutoff values of SP-D and KL-6 (110 ng/ml and 500 U/ml, respectively).
CYC pulse therapy were finished, both SP-D and KL-6 levels started to increase again (> 300 ng/ml and 1500 U/ml, respectively).

Case 4 had elevated SP-D and KL-6 concentrations (233 ng/ml and 908 U/ml, respectively) at the first visit (Figure 4D). Reticular and fibrotic shadow was observed in bilateral lower lobes on chest CT, and DLCO and VC were decreased (51% and 66%, respectively). This patient had been treated with 5 mg/day oral prednisolone for skin sclerosis, and prednisolone dose was increased to 30 mg/day after the first visit. To prevent deterioration of PF, 1000 mg/month CYC pulse treatment was started 2 months after the first visit, and in total 6 pulses of CYC were performed until 1.5 years after the first visit. During this period, DLCO and VC remained stable, and no progression of lung fibrosis was observed on chest CT. In addition, KL-6 level stayed almost the same as at first visit, whereas SP-D level remained lower than at first visit.

Case 5 had high SP-D and KL-6 levels (231 ng/ml and 930 U/ml, respectively) at the first visit (Figure 4E). Reticular and ground-glass shadow was seen in the bilateral lower lobes on chest CT, and DLCO was slightly decreased (60%). CYC pulse therapy (750 mg/month) was started for PF one month after the first visit, followed by 30 mg/day oral prednisolone. Two months after the first visit, SP-D level started to decrease, and KL-6 also began to decrease 3 months behind SP-D. Moreover, 6 months after the first visit, both SP-D and KL-6 showed normal levels. In total, 6 pulses of CYC were given within 9 months after the first visit, and no progression of PF was observed with chest CT and PFT (VC 97% and DLCO 58%).

Case 6 showed increases in SP-D and KL-6 levels (186 ng/ml and 1009 U/ml, respectively) at the first visit (Figure 4F). Ground-glass and reticular shadow was observed in bilateral lower lobes on chest CT, and DLCO and VC were prominently decreased (46% and 64%, respectively). At first visit, this patient complained of dry cough and dyspnea, and these symptoms were getting worse. To prevent deterioration of PF, CYC pulse therapy (750 mg/month) was started one month later, followed by 10 mg/day oral prednisolone. In total, 3 pulses of CYC were given until 3 months after the first visit. However, the ground-glass and reticular shadow on chest CT was increased bilaterally and the dry cough and dyspnea did not remit at all. Moreover, both SP-D and KL-6 levels kept rising, to 344 ng/ml and 2490 U/ml, respectively. We thought CYC pulse therapy had no effect on PF in this patient. Thus 5 months after the first visit, steroid pulse therapy was performed, followed by 30 mg/day oral prednisolone and 100 mg/day cyclosporine. Five months after the first visit, SP-D suddenly started to decrease. One month behind SP-D, KL-6 level also began to decline and the progression of lung fibrosis appeared to cease (VC 67% and DLCO 43%). Collectively, fluctuations of SP-D were in accord with those of KL-6, and changes in SP-D and KL-6 levels overall were associated with the activity of PF in SSc.

Further, the SP-D level changed earlier and more rapidly than the KL-6, on a parallel with the PF activity.

**DISCUSSION**

We observed serum SP-D and KL-6 concentrations were elevated in patients with SSc, especially those with PF at the first visit (Figure 1). Increased SP-D and KL-6 levels were associated with the presence of PF and decreased DLCO and VC (Figures 1 and 2). Further, SP-D levels were strongly correlated with KL-6 levels in SSc patients (Figure 3). Moreover, elevated levels of SP-D showed much higher sensitivity for PF than those of KL-6 (91% vs 39%). By contrast, increased levels of KL-6 gave higher specificity than those of SP-D (100% vs 88%). These results confirmed that both SP-D and KL-6 levels indicate the presence and extent of PF in patients with SSc. As well, SP-D is a sensitive marker for PF, but it is necessary to take account of false positive cases. In contrast, KL-6 was more specific to PF than SP-D, although measuring KL-6 levels was much less significant than SP-D levels. Collectively, measuring SP-D and KL-6 levels would be helpful for the evaluation of PF.

SP-D is a hydrophilic glycoprotein with reduced molecular weight of 43 kDa. SP-D is produced and secreted by type II pneumocytes in alveoli and Clara cells. Elevation of serum SP-D concentrations is induced by the destruction of alveolar epithelium followed by spillover of SP-D into the bloodstream, and may reflect the extent of injury of alveolar epithelium. On the other hand, KL-6 is a mucin-like glycoprotein of larger molecular weight, more than 200 kDa. KL-6 is expressed mainly on type II pneumocytes in alveoli and respiratory bronchiolar epithelial cells. In addition, KL-6 is expressed on regenerating and proliferating type II pneumocytes in pulmonary interstitial diseases more strongly than normal type II pneumocytes. KL-6 levels in BAL fluid are also increased and correlate with serum KL-6 concentrations. With an increase of epithelial and vascular permeability, KL-6 may flow into blood vessels in soluble form. Collectively, the increase in serum SP-D concentration is due to destruction of alveolar epithelium, whereas the elevation of serum KL-6 reflects the regeneration and proliferation of pneumocytes. Since SP-D has a lower molecular weight than KL-6, SP-D would leak more readily than KL-6. Consistently, in our longitudinal study, 2 of 6 cases (Cases 1 and 3) with PF had normal KL-6 levels at the first visit, while SP-D levels had already been elevated. A few months after the first visit, KL-6 levels started to increase over the cutoff value. In Case 2, the increase in KL-6 level seemed to be a few months behind, compared with SP-D. Moreover, in Cases 1, 5, and 6, the decline of KL-6 levels was observed a few months behind those of SP-D levels. These results indicate that SP-D levels reflect the activity of PF more sensitively than KL-6 levels, and that SP-D levels tend to change a few months earlier than KL-6 levels. However, studies...
with larger numbers of SSc patients will be needed to confirm our findings.

Treatment of SSc in general has been unsatisfactory, and PF is especially resistant to treatment. Steroid treatment alone is not effective for PF. Recently, several studies have shown that intravenous CYC pulse treatment in combination with steroid has a beneficial effect on early PF associated with SSc. In our study, 4 patients were treated with intravenous CYC pulse therapy in combination with steroid (Figure 4, Cases 3, 4, 5, and 6). In Cases 3, 4, and 5, after the introduction of CYC pulse treatment, SP-D and KL-6 concentrations started to decrease or were at least stable, with stable findings on HRCT and PFT. Moreover, in Case 3, after the CYC pulse treatment, SP-D and KL-6 levels began to be elevated again. Therefore CYC pulse therapy seemed to ameliorate the progression of PF, although its efficacy was transient. By contrast, in Case 6, CYC pulse treatment could not prevent the progression of PF and during the pulse therapy, SP-D and KL-6 levels continued to increase, with deteriorating HRCT and PFT results. Thus, CYC pulse treatment is to a certain extent effective to stabilize the progression of PF in some patients. In addition, longitudinal determinations of SP-D and KL-6 concentrations would be helpful to evaluate whether the treatment is effective or not. However, studies with larger numbers of SSc patients will be needed to clarify the usefulness of these markers. Larger controlled randomized studies should be undertaken to determine the efficacy and utility of the combination of CYC pulse therapy with corticosteroid for SSc associated PF.

Our results indicate that monitoring SP-D and KL-6 is useful to evaluate the activity and severity of pulmonary fibrosis. However, the fluctuations of SP-D and KL-6 concentrations occasionally show a discrepancy, especially in early-stage PF. It would be important to know the differences of characteristics of SP-D and KL-6 when the activity of PF is monitored by these markers longitudinally. It should be noted that SP-D and KL-6 concentrations must be interpreted in combination with other laboratory tests and radiological findings to precisely evaluate the activity or severity of PF.

REFERENCES
