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Jacobs Journal of Pulmonology

Research Article

Serum Biomarkers Predicting the Outcome in Patients with Acute Exacerbation of Idiopathic Pulmonary Fibrosis

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Received: 08-05-2015

Accepted: 08-21-2015

Published: 08-26-2015

Abstract

Objective

The aim of the study was to assess which biomarker was more predictive of early therapeutic effects of high-dose corticosteroids on patients with acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF).

Methodology

Seventeen consecutive patients with AE of IPF were enrolled and 12 patients responded to treatment and survived the acute stage. Serum levels of Krebs von den Lungen-6 (KL-6), surfactant protein-A (SP-A), surfactant protein-D (SP-D) and C-reactive protein (CRP) were evaluated before treatment and 1 week, 2 weeks and 4 weeks after the start of treatment.

Results

Levels of KL-6, SP-A, SP-D and CRP before treatment decreased significantly 1 week, 2 weeks and 4 weeks after the start of treatment in patients who survived the acute stage, but levels of KL-6, SP-A and SP-D tended to increase in patients who did not respond and survive acute stage. But levels of CRP in patients who did not respond to treatment tended to decrease. The reduction rates of SP-A and SP-D levels in responsive patients were significantly higher than that of KL-6 level at each point after the start of treatment. No differences were shown between those of SP-A and SP-D at every point. In 12 patients who responded to treatment, KL-6 level in one patient and SD-D levels in two patients elevated 1 week after the start of treatment, respectively.

Conclusions

Measurement of serum levels of biomarkers (KL-6, SP-A and SP-D) before and 1 week after the start of treatment, especially SP-A concerning the reduction rates and sensitivity in comparison with KL-6 and SP-D, might be effective to evaluate the outcome of treatment and management in AE of IPF, even early in the clinical course.

Key words: Acute Exacerbation of Idiopathic Pulmonary Fibrosis; Krebs Von Den Lungen-6; Surfactant Protein-A; Surfactant Protein-D

Introduction

Idiopathic pulmonary fibrosis (IPF) is the most common type of idiopathic interstitial pneumonia and carries a devastating prognosis of 2-3 years median survival from the time of diagnosis [1]. In the natural history of IPF, the disease usually progresses slowly, but some patients may suffer acute deterioration in respiratory status. Many of these cases are of unknown etiology and have been termed acute exacerbations (AE) of IPF, which are sometimes fatal. In a recent report, Song et al. demonstrated that 1- and 3-year incidences of AE of IPF were 14.2% and 20.7%, respectively [2].

Krebs von den Lungen-6 (KL-6), surfactant protein-A (SP-A) and surfactant protein-D (SP-D), which are produced and secreted by alveolar epithelial type Ⅱ cells, can be detected in serum and are elevated in patients with certain inflammatory lung diseases, including IPF. These biomarkers were demonstrated to be useful to predict the activity and prognosis of IPF [3,4]. They are far more easy to obtain and can also be measured frequently and are widely used in Japan.

KL-6 was the first biomarker applied in evaluating interstitial lung diseases and has been intensively studied in Japan [5]. Yokoyama et al. [6] demonstrated that monitoring the circulating levels of KL-6 in patients with AE of IPF could predict the efficacy of weekly corticosteroid pulse therapy for at least 3 weeks. They found that the circulating KL-6 levels decreased significantly even at 1 week after treatment in responsive patients when the overall clinical effect may not yet have been evident, whereas KL-6 levels tended to increase in patients who died. Levels of LDH decreased significantly at 1 week and tended to decreased at 3 weeks after treatment in responsive patients. However, those of LDH did not significantly change in patients who died. The effectiveness of monitoring of serum levels of SP-A and/or SP-D has not been evaluated in the patients with AE of IPF in the acute stage. In the present study, we evaluated the serum levels of KL-6, SP-A, SP-D and C-reactive protein (CRP) before treatment and at 1 week, 2 weeks and 4 weeks after the start of corticosteroid treatment in patients with AE of IPF to detect which biomarker is more useful to monitor as a prognostic predictor of AE of IPF in the acute stage.

Patients and Methods

Patients

Seventeen patients were enrolled for the present study from March 2012 to January 2015. The diagnosis of AE of IPF was based on the proposed diagnostic criteria of Collard et al.[7] that have been defined as follows: under a previous or concurrent diagnosis of IPF, 1) worsening of dyspnea within 30 days, 2) high-resolution computed tomography (HRCT) with new bilateral ground-glass abnormality and/or consolidation with a background reticular or honeycombing pattern consistent with the usual interstitial pneumonia pattern, 3) deterioration of hypoxemia by more than 10 mmHg from the previous level under the same conditions, 4) absence of apparent lung infection, pneumothorax, malignant tumor, pulmonary embolism or congestive heart failure. Significant decrease in oxygenation was confirmed using previous PaO_2 or SpO_2 in every patient. Cultures of sputum or tracheobronchial aspirate for bacteria, mycobacteria and fungi, Streptococcus pneumonia and Legionella pneumophila serotype 1 urinary antigens, influenza A and B antigens by nasopharyngeal swab, antigenemia for cytomegalovirus, serum antigen for Aspergillus, and a titer of serum β-D-glucan were carried out for every patient as screening examinations and showed negative findings. Echocardiogram was performed to rule out heart failure. Patients with connective tissue disease, drug-induced lung disease and hypersensitivity pneumonia were excluded. Written informed consent was obtained from each patient and the study protocol was approved by the institutional review board.

Treatment

Pulse therapy with intravenous methylprednisolone (1 g for 3 days) was performed, followed by oral prednisolone maintenance treatment at a dosage of 0.5-1.0 mg/kg. Pulse therapy was continued for at least 2 cycles. Oral prednisolone dose was gradually reduced for the responders. All patients received oxygen therapy with or without invasive mechanical ventilation (MV) and/or non-invasive ventilation (NIV). Treatment response was evaluated with an increase of PaO_2 under the same conditions (>10 mmHg) and/or chest HRCT examinations.

Biomarker evaluation

KL-6, SP-A, SP-D and CRP were evaluated prior to corticosteroid pulse therapy and 1 week, 2 weeks and 4 weeks after the start of initial therapy. Commercially available kits were used to evaluate the levels of KL-6 (Picolumi KL-6: Sanko Junyaku Co., Tokyo, Japan), SD-A (SP-A test-F: Sysmex Kokusai Shiyaku Co., Hyogo, Japan) and SD-D (SP-D kit Yamasa: Yamasa Syoyu Co., Tokyo, Japan). Normal values of KL-6, SP-A, SP-D and CRP were <500 U/mL, <43.8 ng/mL, <110 ng/mL and <0.3 mg/dL, respectively. All blood samples were immediately centrifuged, and plasma was used for analysis.

Statistical analysis

Data are expressed as the mean±SD. The survival rate after the start of treatment was obtained using Kaplan-Meyer survival curve. Mann-Whitney U-test or Wilcoxon's signed-rank test was used to examine differences between means of unpaired or paired samples. The significance of differences between groups was examined by analysis of variance followed by Tukey's test. P values <0.05 were considered statistically significant.

Results

Patient characteristics are shown in Table 1. In 4 of 17 referred patients, previous chest CT was not obtained, but HRCT in the patients showed peripheral and basal dominant reticular opacities, honeycombing and traction bronchiectasis with extensive diffuse ground-glass opacity. All enrolled patients showed significant hypoxemia with less than 60 mmHg PaO_2 or 90% SpO_2 in room air. None of the patients had been treated with oral corticosteroids or immunosuppressive agents. The duration of IPF is shown based on the time of onset of symptoms. In terms of smoking status, 8 of 17 patients were never smokers. Five of 17 patients failed to respond to treatment and died within the next 7 weeks. Twelve responsive patients survived the acute period and remained alive for at least the next 4 months after the start of treatment. The levels of KL-6, SP-A, SP-D and CRP before treatment were all above each normal value. The pretreatment levels of KL-6 in the responsive patients (2,077±744 U/mL) were significantly higher (p=0.013) than those of KL-6 in patients who did not respond to treatment (1,154±510 U/mL). However, serum levels of SP-A (96.6±44.8 ng/mL), SP-D (560.7±360.5 ng/mL) and CRP (4.72±4.19 mg/dL) in the responsive patients were not significantly different from those of SP-A (78.6±29.7 ng/mL, p=0.352), SP-D (460.8±336.5 ng/mL, p=0.600) and CRP (8.43±6.07 mg/dL, p=0.261) in the patients not responsive to treatment, the levels of SP-A and SP-D in the responsive patients tended to be higher than those in the patients not responsive to treatment. Invasive MV was carried out for only 2 of 5 patients who died. Eight of 12 patients who responded to treatment and 3 who failed to respond were managed with NIV. Six-month survival was 57% and median survival time after the start of treatment was 9 months (**Figure 1**).

Table 1. Chracteristics and Outcome of Patients

Case	Age/sex	Duration (mo)	Smoking※	Levels of Biomarkers				Outcome and survival time*
				KL-6 (U/mL)	SP-A (ng/mL)	SP-D (ng/mL)	CRP (mg/dL)	
1	71/M	12	N	845	52.4	210	9.77	survived acute stage, died 5 mo
2	64/M	8	S	2,424	144.0	109	4.31	survived acute stage, died 12 mo
3	63/M	37	EX	2,564	78.4	460	3.31	survived acute stage, died 6 mo
4	67/M	6	S	2,400	182.0	936	0.37	survived acute stage, died 25 mo
5	69/M	85	EX	2,414	41.3	955	5.08	survived acute stage, died 6 mo
6	64/F	34	N	2,548	132.0	498	2.82	survived acute stage, died 9 mo
7	88/F	24	N	1,265	46.4	322	1.51	suvived acute stage, alive 30 mo
8	71/F	46	EX	2,800	109.0	158	2.74	survived acute stage, alive 24 mo
9	79/M	30	N	1,244	50.3	380	0.56	survived acute stage, alive 15 mo
10	78/M	43	EX	1,027	129.0	716	6.38	survived acute stage, alive 12 mo
11	73/M	12	N	2,519	105.0	725	15.14	survived acute stage, alive 9 mo
12	63/F	5	N	2,876	89.9	1260	4.66	survived acute stage, alive 8 mo
13	70/M	23	EX	1,900	110.0	529	0.73	died 5 wk
14	84/M	24	EX	861	46.7	318	14.75	died 2 wk
15	65/M	2	EX	1,474	52.7	199	3.26	died 4 wk
16	91/F	45	N	725	107.8	1018	11.69	died 3 wk
17	74/F	33	N	814	75.9	240	11.75	died 7 wk

※Smoking status: current smoker: S, ex-smoker: EX, never smoker: N.

* Survival time is shown from the start of treatment to death or last follow-up.

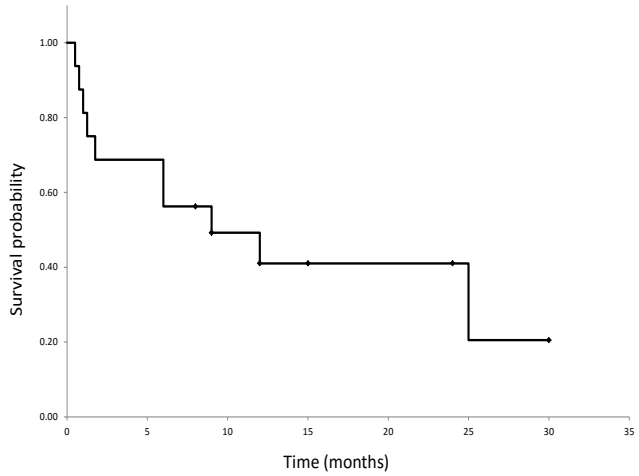

Figure 1

Figure 1. The Kaplan-Meier survival curve of patients with AE of IPF from the start of treatment to death or last follow-up is shown.

The serum levels of KL-6, SP-A, SP-D and CRP in each patient before treatment and 1 week, 2 weeks and 4 weeks after the start of treatment are shown in **Figure 2** (A: KL-6, B: SP-A, C:SP-D, D:CRP). In patients who failed to respond to treatment, the Kl-6, SP-A and SP-D levels tended to increase at 1 week after the start of treatment. However, the levels of CRP in those patients showed the tendency to decrease. In the patients who responded to treatment, the serum levels of KL-6 and SP-D increased in one patient and two other patients, respectively, at 1 week after the start of treatment, however, decreased at 2 weeks and 4 weeks after the start of treatment. SP-A levels in all responders decreased at 1 week.

A**s** shown in **Table 2**, in 12 responsive patients, KL-6 levels before treatment (2,077±746 U/ml) significantly decreased at 1 week (1,986±724 U/mL, p=0.006), 2 weeks (1,809±649 U/mL, p=0.001) and 4 weeks (1,770±705 U/mL, p=0.004) after the start of treatment, and KL-6 levels at 1 week were significantly different from those at 2 weeks (p=0.006) and at 4 weeks (p=0.035); SP-A level before treatment (96.6±44.8 ng/mL) significantly decreased at 1 week (62.7±29.7 ng/mL, p<0.001), 2 weeks (47.7±20.8 ng/mL, p<0.001) and 4 weeks

Table 2. Serum biomarker levels in the responsive patients.

		After the start of treatment (p-values)		
Biomarker	Before treatment	1 wk	2 wk	4 wk
KL-6 (U/mL	2,077±746	1,986±725 (0.006)	1,809±649 (0.001)	1,770±705(0.004)
SP-A (ng/mL)	96.6±44.8	62.7±29.7 (<0.001)	47.7±20.8 (<0.001)	52.1±24.0 (0.002)
SP-D (ng/mL)	560.7±360.5	297.5±216.6 (0.003)	195.0±114.1 (0.001)	179.4±97.5 (0.001)
CRP (mg/dL)	4.72±4.19	0.83±0.96 (0.004)	0.59±0.83 (0.005)	0.32±0.64 (0.004)

Values are shown as mean ±S.D.
P-values are shown as before treatment vs. 1, 2 and 4 wk after the start of treatment.

Table 3. Reduction rates of serum biomarker levels in responsive patients

	Reduction rates (p-value)		
Biomarkers	1 wk	2 wk	4 wk
KL-6	4.5±4.2%	12.2±11.7%	14.7±15.2%
SP-A	34.4±12.3% (0.017)	49.4±9.4% (<0.001)	41.5±22.2% (0.005)
SP-D	39.4±31.0% (0.003)	55.7±24.7% (<0.001)	60.1±20.4% (<0.001)

P-values: reduction rates of KL-6 vs. those of SP-A or SP-D at 1 wk, 2 wk and 4 wk after the start of treatment.

(52.1±24.0 ng/mL, p=0.002) after the start of treatment, and there were significant difference between SP-A levels at 1 week and that at 2 weeks (p=0.012); SP-D levels before treatment (560.7±360.5 ng/mL) decreased at 1 week (297.5±216.6 ng/mL, p=0.003), 2 weeks (195.0±114.1 ng/mL, p=0.001) and 4 weeks (179.4±97.5 ng/mL, p=0.001) after the start of treatment, and there were significant differences between those at 1 week and 2weeks (p=0.009) and those at 1 week and 4 weeks (p=0.012), respectively. Each biomarker's reduction rate is shown in **Table 3.** The reduction rates of KL-6, SP-A and SP-D at 1 week after the start of treatment were 4.5±4.2%, 34.4±12.3% and 39.4±31.0%, respectively. The reduction rate of KL-6 at 1 week after the start of treatment was significantly lower than those at 2 weeks (p=0.027) and at 4 weeks (p=0.039); the reduction rate of SP-A at 2 weeks was significantly higher than that at 1 week (p=0.001); and that of SP-D at 1 week was significantly lower than those at 2 weeks (p=0.004) and at 4 weeks (p=0.004). Furthermore, the reduction rates of SP-A and SP-D in responsive patients were significantly higher than that of KL-6 at 1 week (SP-A vs. KL-6, p=0.017; SP-D vs. Kl-6, p=0.003), 2 weeks (SP-A vs. KL-6, p<0.001; SP-D vs. KL-6, p<0.001) and 4 weeks (SP-A vs. KL-6, p=0.005; SP-D vs. KL-6, p<0.001) after the start of treatment. However, the reduction rates of SP-A and SP-D in responsive patients did not significantly differ from each other at 1 week (p=0.975), 2 weeks (p=0.892) and 4 weeks (p=0.099) after the start of treatment.

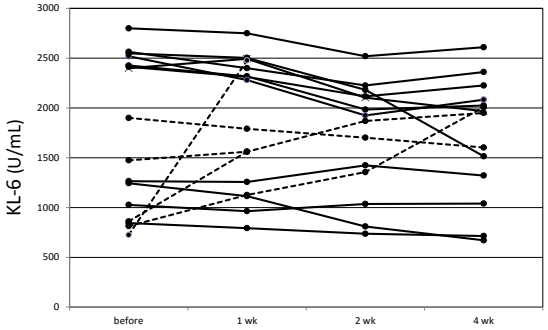

Figure 2A

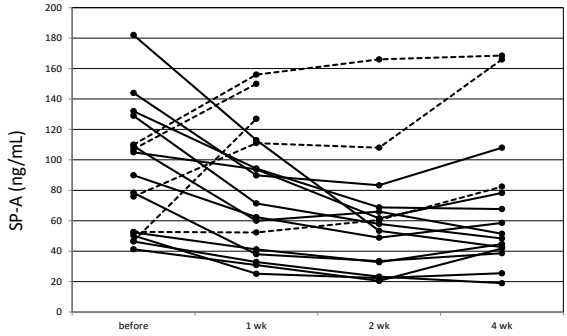

Figure 2B

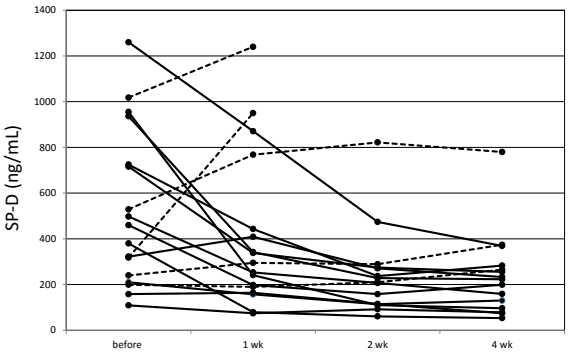

Figure 2C

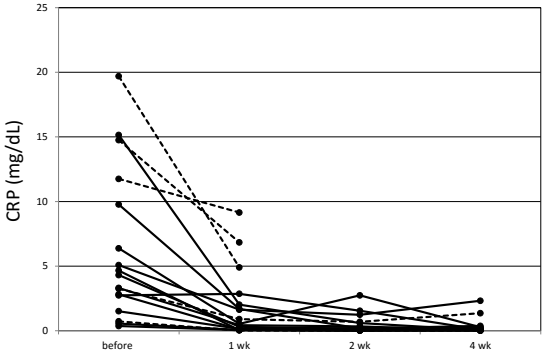

Figure 2D

Figure 2. Serum levels of biomarkers (KL-6: 2A, SP-A: 2B, SP-D: 2C, and CRP: 2D) in each patient before treatment and at 1, 2 and 4 weeks after the start of treatment. Dotted lines show changes of levels in the non-responders.

Discussion

Alveolar epithelial type Ⅱ cells are responsible for producing and secreting surfactant proteins into the alveolar lining fluid. SP-A and SP-D are both hydrophilic glycoproteins. Serum levels of SP-A in patients with IPF and pulmonary alveolar proteinosis (PAP) were shown to be higher than those in other interstitial lung diseases including non-specific interstitial pneumonia [8]. Serum levels of SP-D in patients with IPF, PAP and interstitial pneumonia due to collagen diseases (IPCD) were higher than those in other non-interstitial lung diseases [9]. Furthermore, serum levels of SP-A and SP-D were found to indicate activity and prognosis for IPF patients [4,10]. KL-6 is a mucin-like high-molecular-weight glycoprotein preferentially expressed in regenerating alveolar epithelial type Ⅱ cells and was reported to be a sensitive biomarker for interstitial lung diseases, such as IPF, IPCD, radiation pneumonitis, hypersensi-

tivity pneumonitis, pulmonary sarcoidosis and PAP. Although, in patients with IPF, the range of levels of circulating KL-6 was shown to be wide, from normal to extremely high, it was suggested that serum levels of KL-6 could predict disease activity and prognosis in patients with IPF [3]. The mechanisms behind the increases of these serum biomarkers have been postulated [4,6]. Lung injury causes type II cells to increase secretion of KL-6, SP-D and SP-A to lose cell polarity, and promote the differentiation of type Ⅱ cells into type Ⅰ cells to repair the injured epithelium. The increased basement membrane permeability, which results in increased leakage of the biomarkers from alveolar space to the interstitium, is thought to be the essential mechanism [11]. Secretion of KL-6, SP-A and SP-D can decrease as a result of inhibition of proinflammatory cytokine product with corticosteroid treatment, and corticosteroid therapy may decrease permeability caused by inflammation.

The present study showed that serum levels of KL-6, SP-A, SP-D and CRP in the patients who responded to corticosteroid therapy significantly decreased at 1 week, 2 weeks and 4 weeks after the start of treatment compared with those before treatment, but KL-6, SP-A and SP-D levels in the patients who did not respond to treatment tended to increase. However, CRP levels in the patients not responsive to treatment also decreased at 1 week. The reduction rates of KL-6 gradually increased from 4.5±4.2% at 1 week to 14.7±15.2% at 4 weeks after the start of treatment and KL-6 level in one responsive patient increased at 1 week after treatment, but those of SP-A and SP-D were 34.4±12.3% and 39.4±31.0% even at 1 week after the start of treatment. The reduction rates of serum levels of SP-A and SP-D were significantly higher than that of KL-6 at each point after the start of treatment, but the reduction rates of SP-A and SP-D did not differ from each other at every time point. The mechanism behind the difference of reduction rates is unclear at present. The higher molecular weight of KL-6 (>200 kDa) than those of SP-A (28-36 kDa) and SP-D (43 kDa) and the property of KL-6 of being relatively resistant to protease as a mucin might be related to the findings. However, the levels of SP-D in two patients responded to treatment increased at 1 week after treatment. On the other hand, SP-A levels in all patients responded decreased at 1 week. These findings suggest that monitoring of serum levels of biomarkers (Kl-6, SP-A and SP-D) before and 1 week after the start of treatment, especially SP-A concerning its reduction rate and the sensitivity, may be effective to evaluate the early therapeutic effects of treatment and management in AE of IPF.

In the present study, the pretreatment levels of KL-6 in the responsive patients were significantly higher than those of KL-6 in the patients who did not respond to treatment, and the pretreatment levels of SP-A and SP-D in the responsive patients tended to be higher than those in the patients who did not respond to treatment. To elucidate these findings is difficult. Severe lung injury might delay alveolar type Ⅱ cells to regenerate and/or to produce and secrete these serum biomarkers.

The prognosis of AE of IPF in early reports was very poor [12,13]. However, more recent studies reported better outcomes; the overall survival rate was 67% at 30 days, 43% at 60 days and 40% at 90 days after admission and the in-hospital and 90-day mortalities were shown to be 50% and 60%, respectively [2]. Moreover, in a recent placebo-controlled trial of pirfenidone, AE of IPF was manifested in 14% of the placebo group (5/35) and 1 of these 5 patients died after its onset [14]. However, the prognosis of patients with AE of IPF requiring invasive MV is as poor as ever [15]. Invasive MV is associated with risks, such as aspiration, ventilator-associated pneumonia and ventilator-associated lung injury. The distinct advantage of NIV is avoidance of these risks, but the data on the effects of NIV in patients with AE of IPF compared with invasive MV are still lacking [16]. In the present study, 11 of 17 patients underwent NIV use and the 6-month survival was 57% and the median survival time after the initial onset of AE of IPF was 9 months.

The main limitation of this study was the number of patients enrolled. Because AE of IPF is not common, the patient number in the present study was not thoroughly for an appropriate statistical analysis. Further examination including larger patients with AE of IPF must be done to confirm these results.

In conclusion, even at 1 week after the start of treatment, serum levels of biomarkers (KL-6, SP-A and SP-D) decreased significantly in patients responsive to treatment in compared with those of before treatment, and monitoring of SP-A level might be more effective in comparison with KL-6 and SP-D to predict the outcome of treatment concerning the reduction rates and sensitivity.

Conflict Interest

None of the authors have potential conflict of interest.

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