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□ ORIGINAL ARTICLE □

Health-related Quality of Life in Patients with Idiopathic Pulmonary Fibrosis —Cross-sectional and Longitudinal Study—

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Abstract

Object To validate the cross-sectional and longitudinal use of the Medical Outcome Study Short Form 36 (SF-36) for measuring health-related quality of life (HRQL) in patients with idiopathic pulmonary fibrosis (IPF).

Methods Patients were administered the SF-36 and concomitantly underwent laboratory and physiologic tests and high-resolution computed tomography (HRCT). Forty-six patients participated in the initial cross-sectional study, and 32 patients who were available more than one year later again underwent these studies under the same conditions.

Results Patients with IPF had significantly lower scores across all 8 domains of the SF-36 when compared with the general population. Significant decline of HRQL was observed in 2 physical domains. There were significant differences in within-subject changes in a few domains according to worsening of the physiologic parameters. Vital capacity as percent of predicted was significantly correlated with the results of 6 subscales and its changes were significantly correlated with those of 4 subscales. The 6-min-walk distance was correlated significantly with 3 subscales and its changes were significantly correlated with those of 4 subscales. Changes in the HRCT ground-glass score were significantly correlated with those of 3 subscales. No significant correlations between changes in 3 domains and those of any clinical parameters were observed.

Conclusion Patients with IPF had significantly impaired HRQL in both physical and psychological functions. This disease clearly decreased the physical aspects of HRQL over time. HRQL instruments should be incorporated into routine evaluations of IPF patients, since they measure dimensions not fully estimated by clinical assessment.

Key words: idiopathic pulmonary fibrosis, health-related quality of life, SF-36, 6-minute walk test, KL-6, high-resolution CT

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronically progressive interstitial lung disease that results in severe disability and death in the majority of cases. Although currently available medications, particularly corticosteroids and immunosuppressants, are prescribed with the hope of slowing progression of the disease, they are associated with significant side effects and morbidity. The primary reason why physicians intervene and treat patients with chronic disorders such as IPF when a cure is known to be impossible is to improve the length and quality of life. Thus, one of the primary goals in the current management of IPF is to improve quality of life (1, 2).

Health-related quality of life (HRQL) has been recognized as an important feature in determining goals for treatment and measuring outcome in the care of patients with chronic disabling illness. Although during the last 20 years HRQL has been studied for many chronic respiratory diseases, in-

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cluding asthma and chronic obstructive pulmonary disease (COPD), only a handful of studies have examined HRQL in IPF patients (3-9). In fact, the impact of IPF on patients' HRQL is not fully understood, and the International Consensus Statement on IPF (1) notes that measurement of quality of life in IPF patients requires additional study. Therefore, we cross-sectionally and longitudinally assessed HRQL in patients with IPF using the Medical Outcome Study Short Form 36 (SF-36), a generic HRQL instrument.

At present, pulmonary function tests and high-resolution computed tomography (HRCT) are used clinically as non-invasive means of evaluating the activity and monitoring the course of the disease. In particular, HRCT is the best non-invasive method for assessing the pattern and quantifying the extent of the disease in IPF patients (1, 10). In addition, a recently developed serum marker for interstitial lung diseases, i.e. KL-6, has appeared on the clinical stage to evaluate interstitial lung diseases, including IPF (11, 12). Since the previous investigators in this field, with one exception (8), did not use some of these modalities, their studies may have failed to detect associations between clinical variables determined by these modalities and HRQL. Furthermore, to our knowledge, no study has measured longitudinal changes in HRQL in patients with IPF. The purposes of this study were (1) to compare the HRQL of IPF patients with that of the general population as a whole, (2) to test the *a priori* hypothesis that low HRQL scores correlate with more severe clinical parameters demonstrated by KL-6, pulmonary function tests, exercise tests, and HRCT, (3) to examine longitudinal changes in HRQL and (4) to test the *a priori* hypothesis that there is a correlation between decline in HRQL and clinical parameters.

Materials and Methods

Study subjects

Forty-six Japanese patients with IPF who were referred to or followed at the outpatient pulmonary clinic of the Nishi-Kobe Medical Center, a 500-bed teaching hospital, were recruited for this study between March 2000 and November 2005. Subjects were excluded if they were 80 years of age or older or if they had an illness other than IPF that might have an impact on HRQL. In 7 patients, the diagnosis of IPF was based on the presence of usual interstitial pneumonia (UIP) by a surgical (open or thoracoscopic) lung biopsy. In the remaining 39 patients, IPF was diagnosed clinically on the basis of an international consensus statement (1). The HRCT criteria included a subpleural bilateral interstitial pulmonary process, including honeycomb changes with minimal areas of associated ground-glass opacity. In 5 of these 39 patients, a UIP pattern was confirmed on autopsy. Patients with other known possible causes of interstitial lung disease, such as drug toxicity, environmental exposure, and collagen vascular diseases, were excluded.

Methods

Pulmonary function tests consisted of determinations of vital capacity (VC) and diffusing capacity of the lung for carbon monoxide (DLco) using a CHESTAC-33 system (Chest, Tokyo, Japan). Predicted normal values for the Japanese population were derived from reference values of the Japanese Respiratory Society (13) for VC and Nishida et al (14) for DLco.

Subjects performed a modified 6-min walk test according to the method of Chang et al (3) in an enclosed level measured corridor. Supplemental oxygen was permitted at the same concentration inspired normally during daily activities at baseline. Oxygen saturation was measured continuously during the walk using a pulse oxymeter (NPB-40, Mallinckrodt Japan, Tokyo, Japan). Only one test was performed.

Either a Pro Seed or a Pro Seed Accell (GE Yokogawa Medical Systems, Tokyo, Japan) was used for computed tomography. HRCT scans were performed with a 2-mm section thickness and a 1-s scanning time during breath holding at the end of inspiration. These scans were reconstructed with a high spatial frequency algorithm and viewed at window levels appropriate for pulmonary parenchyma (window level, -700 Hounsfield units; width, 2000 Hounsfield units). One radiologist, who was unaware of clinical and functional findings, examined the HRCT scans following the method of Xaubet et al (15) with slight modifications. A semiquantitative analysis of the relative proportion (to within 10%) of both ground-glass and reticular patterns at three predetermined levels, which were the great vessels, pulmonary venous confluence, and the right diaphragm, was made. Scores of the three lung zones were then averaged to obtain one mean score. The serum concentration of KL-6 (normal value <500 U/ml) was determined by enzyme immunoassay using commercially available kits (Eisai, Tokyo, Japan).

HRQL was assessed using the SF-36 Japanese test version, which is adapted and psychometrically validated for Japanese (16, 17). In the present study, the SF-36 questionnaire was self-administered, as is the typical procedure. The questionnaire consisted of 36 questions covering 8 health concepts: physical function (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE), and mental health (MH). These 8 health components were scored separately and transformed to a 0-100 scale according to the guidelines (18) and using their methods for handling missed items. An ascending scale was used for scoring, with higher scores indicating a better HRQL and lower scores a worse quality of life.

All patients were evaluated at our outpatient clinic during a period of clinical stability. Laboratory tests, which included KL-6 measurement, HRCT, pulmonary function tests and the HRQL questionnaire were administered within one month. Those who were available more than one year later again underwent these studies under the same conditions. The same concentration of supplemental oxygen was used

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for both the baseline and repeated 6-min walk test. Informed consent was obtained from all participants, and the study protocol had the approval of the local ethics committee. Some data that we used had been collected as part of a prospective study of aerosolized N-acetylcysteine for IPF (19).

Statistical Analysis

In the cross-sectional study, deviation values for the 8 health components against Japanese reference values were calculated according to the guidelines (18), and differences between patients' scores and the general population mean, i.e. 50, were tested with the Student's *t*-test or Wilcoxon rank-sum test. Then Spearman's rank correlation was used to examine the correlation between the transformed subscales of the SF-36 and clinical parameters measured.

In the longitudinal study, changes in parameters were expressed as an absolute value from the initial study. Changes in the SF-36 transformed subscales and clinical parameters were analyzed with a paired *t* test or Wilcoxon signed-rank test. Then Spearman's rank correlation was used to examine the correlation between the changes of transformed subscales and those of clinical parameters. Furthermore, for each clinical parameter the examined patients were divided into 2 groups (i.e., subjects whose VC decreased by $\geqq 10\%$ and subjects whose VC did not, subjects whose DLco decreased by $\geqq 15\%$ and subjects whose DLco did not, subjects whose lowest oxygen saturation during the 6-min walk test decreased by $\geqq 4$ percentage points and subjects whose lowest oxygen saturation did not, and subjects who developed the need for supplemental oxygen during the follow-up and subjects who did not). Then comparisons were made between each group and within-subject changes in each SF-36 domain using the Student's *t*-test or Wilcoxon signed-rank test. Regarding VC, DLco and oxygen desaturation, the basis for the division was in accordance with the assessment of pulmonary function tests recommended in the guidelines (1). Significance was defined as $p< 0.05$. All analyses were performed using JMP statistical software (SAS Institute, Inc., Cary, NC).

Results

Cross-sectional Study

Baseline characteristics of the patients (32 males, 14 females; age 55 to 79 year) are shown in Table 1. Of the 46 subjects, at the time of the initial study, 7 were dependent on supplemental oxygen and 2 were treated with prednisolone (25 mg/day and 2.5 mg/day, respectively). Thirteen patients were current smokers (they had smoked cigarettes regularly within the previous year), 19 were former smokers (they had not smoked cigarettes in the previous year but had smoked in the past), and 14 were never smokers. The KL-6 value was elevated (mean, 1,198±952 U/ml; range 268 to 4,330 U/ml). DLco was not performed in 2 patients because of a severe reduction in lung volume.

Table 1. Baseline Characteristics of Patients (n=46)

Gender, Female / Male	14 / 32
Age (years)	69.9 ± 5.8
Duration of symptoms (months)	31.8 ± 29.5
Serum KL-6 (U/ml)	1198 ± 952
Pulmonary function tests	
VC (% of predicted)	71.0 ± 17.5
DLco (% of predicted) *	58.3 ± 18.2
Six-min walk test	
Distance (m)	395 ± 105
Lowest oxygen saturation (%)	90.2 ± 6.7
High-resolution CT score	
Ground-glass score	11.0 ± 9.9
Reticular score	25.4 ± 14.8

Plus-minus values are means ± SD.

VC, Vital capacity; DLco, carbon monoxide diffusing capacity

* DLco was not performed in 2 patients because of a severe reduction in lung volume.

Figure 1 presents the profile of the deviation values of the 8 health components of the SF-36. All of the mean deviation values were significantly below the national reference values, i.e. 50. In particular, the mean deviation values of PF and RP were 37.2 (95% confidence interval, 33.5 to 41.0), and 34.3 (29.8 to 38.7), respectively, which were markedly low.

Spearman correlation coefficients between each SF-36 domain and the clinical parameters are presented in Table 2. The serum level of KL-6 was not significantly correlated with scores for any domain. With respect to physiological parameters, VC as a percent of predicted was significantly correlated with 6 items; the exceptions were BP and VT. However, there were no significant correlations with DLco as a percent of predicted. The 6-min-walk distance was significantly correlated with PF, RP and VT. The strongest correlation was observed between PF and the 6-min-walk distance ($\rho=0.68$, $p<0.01$). The lowest oxygen saturation during the 6-min walk significantly correlated with GH, SF, and MH. With regard to HRCT scores, the reticular score was significantly correlated with only PF. When the relation between pulmonary function tests and HRCT scan scores was examined, the following significant correlations were found: VC as a percent of predicted versus ground-glass score ($\rho=-0.33$, $p<0.05$) and reticular score ($\rho=-0.50$, $p<0.001$) and DLco as a percent of predicted versus reticular score

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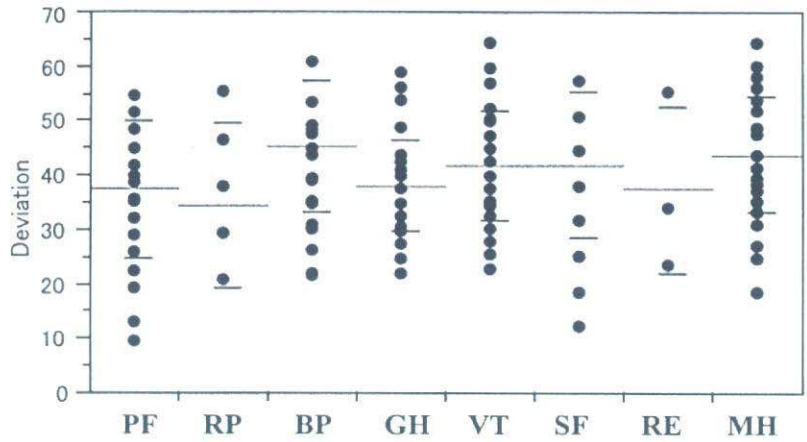

Figure 1. Deviation values against the national reference values of the 8 health components of the SF-36. All of the mean deviation values were significantly below the national reference values, i.e. 50: PF, RP, RE and MH ($p<0.001$), BP and SF ($p<0.01$), GH and VT ($p<0.0001$). Mean ± SD is shown. PF, physical function; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health.

Table 2. Spearman Correlation Coefficients (ρ) between Each SF-36 Domain and Clinical Parameters (n=46)

	PF	RP	BP	GH	VT	SF	RE	MH
Serum KL-6 (U/ml)	-0.06	-0.02	0.27	0.08	0.09	-0.16	-0.12	-0.12
Pulmonary function tests								
VC (% predicted)	0.45 †	0.31*	0.26	0.52 †	0.21	0.41 †	0.39 †	0.39 †
DLco (% predicted)	0.23	0.10	0.03	0.09	0.12	0.02	0.18	0.14
Six-min-walk test								
Distance (m)	0.68 †	0.32*	0.10	0.22	0.36*	0.18	0.17	0.20
Lowest oxygen saturation (%)	0.21	0.09	0.04	0.35*	-0.01	0.30*	0.25	0.31*
High-resolution CT score								
Ground-glass score	-0.01	-0.06	-0.09	-0.04	0.03	-0.15	-0.20	-0.18
Reticular score	-0.34*	-0.17	-0.11	-0.22	-0.07	-0.23	-0.30	-0.22

VC, Vital capacity; DLco, carbon monoxide diffusing capacity

See Figure 1 for abbreviations.

*$p < 0.05$. †$p < 0.01$.

(ρ=-0.48, $p<0.01$).

Longitudinal study

Out of the 46 subjects who participated in the initial cross-sectional study, 32 patients (21 males) completed the follow-up study. In 2 patients, the observation period from the initial study was less than one year. Follow-up data were not available for the remaining 12 patients because of death

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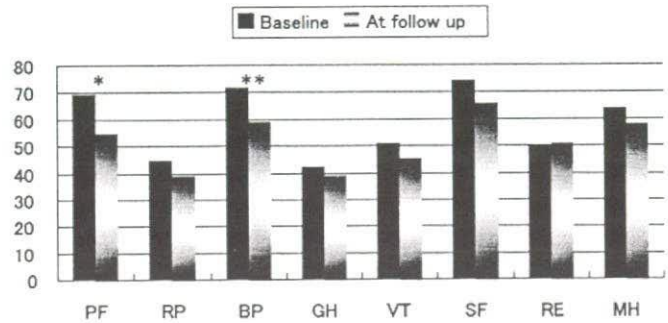

Figure 2. Mean SF-36 scores at baseline and at follow up. There was a significant decline in health-related quality of life in 2 subscales: *PF ($p<0.001$) and **BP ($p<0.05$). See Figure 1 for abbreviations.

due to respiratory failure (n=5) or gastrointestinal bleeding (n=1), being lost to follow-up (n=3) or the occurrence of other disorders (lung cancer, gastric cancer, and thrombocytopenic purpura, n=1, respectively). Periods from the initial study to the follow-up study were 12 to 31 months (median 14 months). Newly begun treatment during the follow-up period was as follows: corticosteroid n=4 and aerosolized N-acetylcysteine n=11. Although 4 patients developed the need for supplemental oxygen during the follow-up, all 4 underwent the 6-min-walk test without supplemental oxygen at the follow-up study.

Figure 2 presents mean SF-36 scores at baseline and at follow up. There was a significant decline of HRQL in 2 subscales: PF ($p<0.001$) and BP ($p<0.05$). The decrease in the PF score was particularly noteworthy (mean, -14.6; 95% confidence interval, -7.1 to -22.0). Although there were declines in SF and MH that were almost significant (mean, -8.2; 95% confidence interval, 0.26 to -16.7, $p=0.057$, mean, -5.9; 95% confidence interval, 0.37 to -12.1, $p=0.064$), no significant changes in the other 4 health components were shown over time. When within-subject changes in each SF-36 domain were compared between two subgroups divided according to the follow-up period, declines did not differ significantly in each SF-36 score between subjects whose follow-up period was within 15 months (n=20) and those whose follow-up period was more than 15 months (n=12) (data not shown).

Some of the clinical parameters in the 32 patients changed significantly. Examples of changes included ΔKL-6 in serum = -53.6±656.1 U/ml ($p=0.75$), ΔVC = -5.8±13.6% of predicted ($p<0.05$), ΔDLco = -10.0±18.4% of predicted ($p<0.005$), Δ6-min-walk distance = -37.3±120.9 m ($p=0.20$), Δlowest saturation during 6-min walk test = -4.0±6.5% ($p<0.005$), Δground-glass score on HRCT = 2.6±11.2 ($p<0.05$), and Δreticular score on HRCT = 6.4±8.0 ($p<0.0001$). When correlations between changes in HRCT scores and those in pulmonary function tests, including VC and DLco, were examined, no significant correlations were found (data not shown).

Correlations between changes in clinical variables and those in each SF-36 domain are presented in Table 3. Changes in the serum level of KL-6 did not significantly correlate with changes in any domain. With respect to physiological parameters, changes in VC as a percent of predicted were significantly correlated with those of PF, BP, GH and VT, and changes in DLco as a percent of predicted were significantly correlated with those of PF, BP and GH. Within-subject changes in distance in the 6-min-walk were significantly correlated with changes in 4 items, i.e., BP, GH, VT and MH; these were most highly correlated with changes in GH ($\rho=0.61$, $p<0.01$). Change in the lowest oxygen saturation during the 6-min-walk was significantly correlated with changes in PF and GH. With regard to HRCT scores, changes in the ground-glass score were significantly correlated with changes in BP, GH and MH, and changes in the reticular score were significantly correlated with those of GH. There were no significant correlations between changes in 3 domains (RP, SF and RE) and those of any of the clinical parameters examined.

When within-subject changes in each SF-36 domain were compared between two subgroups divided according to clinical parameters, the following results were obtained. First, declines in PF, BP and VT were significantly more severe in subjects whose VC decreased by ≧10% (worsening of VC) than in subjects whose VC did not (stable or improved VC) ($p<0.05$, respectively) (Table 4). Second, declines in PF ($p<0.005$), BP ($p<0.05$), GH ($p<0.05$) and VT ($p<0.05$) were significantly more severe in subjects whose DLco decreased by ≧15% (worsening of DLco) than in those without such a decrease (stable or improved DLco) (Table 5). Third, deterioration in PF and GH ($p<0.05$, respectively) were significantly more severe in subjects whose lowest oxygen saturation during the 6-min walk test decreased by ≧4 percentage points than in subjects without such a decrease (Table 6). Finally, deterioration in PF ($p<0.05$), GH ($p<0.05$), VT ($p<0.005$), SF ($p<0.01$) and MH ($p<0.05$) was significantly more severe in subjects who developed the need for supplemental oxygen during the follow-up than in subjects who did not (Table 7). When scores for each SF-36 subscale before and after introduction of home oxygen therapy in these 4 patients were compared, significant declines were found as follows: ΔPF=-36.1±18.8 (p<

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Table 3. Spearman Correlation Coefficients (ρ) between Within-subject Changes in SF-36 Domains and Changes in Clinical Parameters (n=32)

	ΔPF	ΔRP	ΔBP	ΔGH	ΔVT	ΔSF	ΔRE	ΔMH
Δ Serum KL-6 (U/ml)	0.01	0.03	0.04	0.08	0.14	-0.03	-0.19	-0.17
Pulmonary function tests								
Δ VC (% predicted)	0.37*	0.09	0.44*	0.45 †	0.51 †	0.26	0.23	0.22
Δ DLco (% predicted)	0.59 †	0.26	0.56 †	0.48 †	0.16	0.23	0.31	0.22
Six-min-walk test								
Δ Distance (m)	0.35	0.14	0.49 †	0.61 †	0.42*	0.28	0.30	0.52 †
Δ Lowest oxygen saturation (%)	0.45*	-0.19	0.16	0.47 †	0.14	0.32	-0.01	0.25
High-resolution CT score								
Δ Ground-glass score	-0.13	-0.03	-0.42*	-0.46 †	-0.17	-0.24	-0.29	-0.39*
Δ Reticular score	-0.02	-0.02	-0.02	-0.38*	0.05	-0.09	0.23	-0.25

VC, Vital capacity; DLco, carbon monoxide diffusing capacity

See Figure 1 for abbreviations.

*$p < 0.05$. †$p < 0.01$.

Table 4. Comparison of Within-subject Changes (mean±SEM) in SF-36 Domains between Subjects Whose VC Decreased by ≧ 10% (Worsening of VC) and Subjects Whose VC Did Not Decrease by ≧ 10% (Stable or improved VC)

	Worsening of VC (n=13)	Stable or improved VC (n=19)	P value
ΔPF	-24.9±5.3	-7.5±4.4	0.02
ΔRP	-15.4±12.1	1.3±10.0	0.30
ΔBP	-27.5±8.0	-2.8±6.7	0.02
ΔGH	-9.3±4.2	1.3±3.5	0.06
ΔVT	-16.4±5.5	1.8±4.6	0.02
ΔSF	-14.4±6.4	-3.9±5.3	0.22
ΔRE	-12.8±15.8	10.5±13.0	0.26
ΔMH	-9.1±4.8	-3.7±4.0	0.40

VC, Vital capacity

See Figure 1 for abbreviations.

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Table 5. Comparison of Within-subject Changes (mean±SEM) in SF-36 Domains between Subjects Whose DLco Decreased by ≧ 15% (Worsening of DLco) and Subjects Whose DLco Did Not Decrease by ≧ 15% (Stable or improved DLco)

	Worsening of DLco (n=11)	Stable or improved DLco (n=21)	P value
ΔPF	-29.9±5.3	-6.5±3.8	0.001
ΔRP	-4.5±13.4	-6.0±9.7	0.93
ΔBP	-29.9±8.7	-4.0±6.3	0.02
ΔGH	-12.6±4.3	2.0±3.1	0.01
ΔVT	-16.7±6.1	0.24±4.4	0.03
ΔSF	-13.6±7.1	-5.4±5.1	0.35
ΔRE	-9.1±17.4	6.3±12.6	0.48
ΔMH	-12.9±5.1	-2.2±3.7	0.10

DLco, carbon monoxide diffusing capacity

See Figure 1 for abbreviations.

Table 6. Comparison of Within-subject Changes (mean±SEM) in SF-36 Domains between Subjects Whose Lowest Oxygen Saturation during 6-min Walking Test Decreased by ≧ 4 Percentage Points (Worsening of Oxygen Saturation) and Subjects without such a Decrease (Stable or Improved Oxygen Saturation)

	Worsening of oxygen saturation (n=13)	Stable or improved oxygen saturation (n=19)	P value
ΔPF	-24.5±5.3	-7.7±4.4	0.02
ΔRP	-3.9±12.4	-6.6±10.2	0.87
ΔBP	-18.6±8.7	-8.9±7.2	0.40
ΔGH	-10.5±4.1	2.1±3.4	0.02
ΔVT	-10.5±6.0	-2.18±4.9	0.29
ΔSF	-15.4±6.4	-3.3±5.3	0.16
ΔRE	-15.4±15.6	12.3±12.9	0.18
ΔMH	-12.0±4.7	-1.7±3.9	0.10

See Figure 1 for abbreviations.

0.05), ΔVT=-35.0±10.8 ($p<0.01$), and ΔSF=-37.5±20.4 ($p<0.05$).

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Table 7. Comparison of Within-subject Changes (mean±SEM) in SF-36 Domains between Subjects Who Developed the Need for Supplemental Oxygen During the Follow Up and Subjects Who Did Not

	Subjects who developed the need for supplemental oxygen (n=4)	Subjects who did not develop the need for supplemental oxygen (n=28)	P value
ΔPF	-36.1±9.6	-11.5±3.6	0.02
ΔRP	-18.8±22.1	-3.6±8.4	0.53
ΔBP	-37.0±15.1	-9.4±5.7	0.10
ΔGH	-18.5±7.4	-0.8±2.8	0.03
ΔVT	-35.0±9.3	-1.4±3.5	0.002
ΔSF	-37.5±10.5	-4.0±4.0	0.006
ΔRE	-25.0±28.6	4.8±10.8	0.34
ΔMH	-23.0±8.1	-3.4±3.1	0.03

See Figure 1 for abbreviations.

Discussion

This is the first longitudinal study of HRQL in IPF patients showing impaired HRQL in both physical and psychological functions when compared with the general population and that scores in a few physical domains worsened significantly over time. Some clinical parameters were significantly related to the HRQL scores in the cross-sectional study and changes in scores in the longitudinal study; however, the HRQL and its longitudinal changes were incompletely predicted by these clinical parameters.

When evaluating HRQL for a specific disease, both generic questionnaires and disease-specific questionnaires are available. In the present study, we chose the SF-36, a generic HRQL instrument, due to its relative simplicity, wide use in chronic pulmonary disease, and availability of a validated version for the Japanese population. Although disease-specific questionnaires are likely to be more sensitive to particular symptoms and to slight responses to therapeutic interventions than are generic measures, the advantage of disease-specific measures is not frequently proven (3, 20, 21). However, there is no disease-specific instrument for use in patients with IPF. Investigators have noted problems with some of the existing non-IPF respiratory disease-specific instruments when applied to patients with IPF. Developing an IPF-specific instrument that includes items most relevant to IPF patients would be ideal for evaluating the real HRQL in IPF (2).

There are a few cross-sectional studies (3, 5-8) of IPF patients that used the SF-36, although one study (3) included interstitial lung diseases other than IPF such as nonspecific interstitial pneumonia, sarcoidosis, or asbestosis. As did these studies, we also demonstrated that using national-norm characteristics our patients with IPF had significantly impaired HRQL in both physical and psychological functioning. Although Martinez et al (5) and Ohno et al (8) reported that IPF patients and control subjects had similar scores only for the BP component, all of the 8 domains, including BP, were significantly below the national reference values in our patients.

Although longitudinal assessments are needed to map the trajectory of HRQL in relation to disease progression and to reveal whether different aspects of HRQL become impaired over time (2), such assessments in IPF patients have yet to be performed. In our longitudinal study, we found clear evidence of a measurable and progressive deterioration in the physical aspects of quality of life of this population. Particularly, PF showed remarkable aggravation, so it is possible that the PF domain is the initial health component to decline in patients with IPF, as in patients with COPD (22). Furthermore, there were significant differences in within-subject changes in a few SF-36 domains when subjects were divided according to changes in physiologic parameters. Our results showed that PF was very sensitive to the deterioration of physiologic clinical parameters assessed by VC, DLco and desaturation during exercise. As the SF-36 has been reported to be responsive to changes in quality of life in COPD (23, 24) or asthma (25), it also demonstrated sensitivity to changes in IPF in the present study.

Longitudinal studies also provide a platform for evaluating how IPF patients adapt to disease (2). From the present

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longitudinal study showing that all of the psychosocial domains revealed no significant aggravation over time despite results of the cross-sectional study that showed significantly lower scores than the national norm, it is indicated that an individual's assessment of HRQL might change over time.

The present results showed that not only the physical function domains (PF and GH) but also the psychosocial domains (VT, SF, and MH) deteriorated more severely in subjects who developed the need for supplemental oxygen compared with those in subjects who did not (Table 7). Of course, these patients started long-term oxygen therapy due to the progression of the disease. Although further examination is necessary as to the usefulness of long-term oxygen therapy in IPF, it is possible that supplemental oxygen use does not attenuate the decline of HRQL in patients with IPF. It is reported that long-term oxygen therapy does not affect quality of life in patients with COPD (26).

Since HRQL is an important outcome in IPF management, we examined various clinical parameters to identify factors that were correlated with HRQL and its longitudinal changes. The cross-sectional correlations between clinical parameters and HRQL observed in this study are similar to those reported in the literature (3, 5, 7, 8). In the present study, VC as percent of predicted showed a significant correlation with 6 subscales and its changes were significantly correlated with those of 4 subscales. It appears as if VC covers a significant part of the HRQL of IPF patients in both cross-sectional and longitudinal assessments. The analyses of efficacy endpoints in the large multicenter controlled trial of interferon-γ1b for IPF revealed that a decrement in the percentage of predicted forced vital capacity represents a valid measure of disease progression (27). Therefore, these longitudinal measurements are important from the viewpoint of both length and quality of life in IPF patients.

The 6-min-walk distance was significantly correlated with 3 subscales, with the correlation greatest with the PF domain. In addition, its changes were significantly correlated with those in 4 subscales, suggesting that this measurement reflected a change of those HRQL domains comparatively well. In the same way, the lowest oxygen saturation showed a significant correlation with 3 subscales and its changes were significantly correlated with those of 2 subscales. To our knowledge, there has been no report on the relationship between desaturation during the 6-min-walk test and HRQL in IPF patients. Interestingly, the lowest oxygen saturation was significantly correlated with psychological functions such as SF or MH, and in contrast, the 6-min-walk distance was significantly correlated with physical functions such as PF or RP. Desaturation during the 6-min-walk might be related to the psychological aspects of HRQL. Nishiyama and coworkers (9) also reported a significant relationship between the lowest saturation during a cycle ergometer exercise test and the St. George Respiratory Questionnaire scores. It is possible that desaturation during exercise affects the HRQL of patients with IPF. Exercise physiology measurements are important to predict the impairment of HRQL of IPF patients, as with COPD (20).

Although HRCT scanning has come to play a central role in the diagnosis and assessment of the clinical course of IPF, previous studies in this field did not use this modality. Semiquantitative assessment of disease extent by HRCT following the method of Xaubet et al (15), which correlates with the evidence of physiological impairment, including forced vital capacity and DLco, was performed to evaluate the impact of the HRCT findings on HRQL of IPF patients. However, the present results suggested that HRCT scanning was not so useful in predicting impairment and longitudinal changes in HRQL of IPF patients because it showed only correlations with a few SF-36 domains, and the magnitude of those correlations was weak in comparison with physiological parameters.

In addition to the above-mentioned clinical variables, we examined KL-6, the recently developed serum marker for interstitial lung diseases. However, the present results suggested that KL-6 was not useful in predicting impairment of HRQL or its longitudinal changes in IPF patients. Ohno and coworkers (8) also reported no correlation between SF-36 scores and KL-6 values.

From these observations, although some conventional clinical parameters correlated with HRQL and its change, the magnitude of these correlations was moderate to weak. Therefore, these clinical parameters, even when HRCT scanning is included, should not be used in place of measuring HRQL directly. HRQL has come to be recognized as an important parameter for measuring the impact and progression of chronic diseases, including IPF (2-9). Therefore, these results indicate that HRQL instruments should be incorporated into routine evaluations of IPF patients.

The present study has some limitations. First, the study was limited to one medical center, so the small sample size weakens the power of the study. Second, in this longitudinal study the management of patients varied, so we could not address the impact of drug therapy on HRQL. Limited attempts have been made to evaluate HRQL as an outcome measure in clinical trials of IPF. Investigators using The St. George Respiratory Questionnaire (28), Chronic Respiratory Disease Questionnaire (29) and the SF-36 (18) found no difference in HRQL between control and treatment groups. Any of the following 3 possibilities could explain the lack of a significant change in HRQL scores: (1) the investigational drug truly had no effect on HRQL; (2) the study was not adequately powered to detect a significant change in HRQL; or (3) the instrument was not sensitive to detect a true change in HRQL (2). The present study showed that the SF-36 was responsive to changes in HRQL in IPF, so a major focus of future research should include improvement of the SF-36 score as a study endpoint. Third, our study lacked an evaluation of dyspnea, which may be more useful to predict the impairment of HRQL in IPF patients than the clinical parameters mentioned above. Across the 4 studies (3, 5, 6, 9) that examined IPF, dyspnea correlated better with

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HRQL than any other disease symptom or measure of clinical severity.

In conclusion, patients with IPF had significantly impaired HRQL in both physical and psychological functions. This disease clearly decreased the physical aspects of quality of life over time. HRQL instruments should be incorporated into routine evaluations of IPF patients, since they measure dimensions not fully estimated by clinical assessment even when HRCT is used.

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ORIGINAL ARTICLE

Acute exacerbation of idiopathic pulmonary fibrosis: Role of *Chlamydophila pneumoniae* infection

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Acute exacerbation of idiopathic pulmonary fibrosis: Role of *Chlamydophila pneumoniae* infection

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Background and objectives: Patients with idiopathic pulmonary fibrosis (IPF) may experience acute exacerbations of their illness. The actual trigger(s) of such exacerbations is unknown. *Chlamydophila pneumoniae* infection can cause exacerbation of asthma and COPD. A prospective study was conducted to investigate the possible role of *C. pneumoniae* infection in triggering acute exacerbations of IPF.

Methods: A prospective observational study over 5 years of consecutive IPF patients who fulfilled the criteria for acute exacerbation. Sputum, blood cultures and acute and convalescent serology for *C. pneumoniae* IgG and IgA (ELISA) were performed.

Results: Previous infection with *C. pneumoniae* is common. Of the 27 study patients, 15 had a *C. pneumoniae* IgG index of 1.10–2.99 (positive) and 3 had a *C. pneumoniae* IgG index of >2.99 (strongly positive) at the time of presentation with an acute exacerbation. In addition, 15 subjects had a *C. pneumoniae* IgA index of 1.10–2.99 (positive) and 6 subjects had a *C. pneumoniae* IgA index of >2.99 (strongly positive). However, only two of the 15 subjects (13%) for whom paired sera were tested exhibited a significant rise in antibody response (change in index of 1.90 for *C. pneumoniae* IgG and 1.54 for IgA, respectively) indicating either acute or reactivated infection with *C. pneumoniae*. There were 15 deaths (56%) despite supportive care that included high-dose corticosteroid therapy and oxygen supplementation.

Conclusions: Mortality is high with acute exacerbation of IPF. Acute infection with *C. pneumoniae* is uncommon at the time of presentation with acute exacerbation of IPF.

Key words: acute exacerbation, *Chlamydia pneumoniae*, *Chlamydophila pneumoniae*, idiopathic pulmonary fibrosis.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial lung disease of unknown aetiology, resulting in severe morbidity and death due to progressive respiratory failure.[1] The natural history is invariably one of gradual and progressive deterioration, with the median length of survival from the time of diagnosis being 2.5–3.5 years. Although IPF is a slowly progressive disease in nature, acute exacerbation of IPF, also known as the accelerated form of IPF, has been described.[2,3] This syndrome is characterized by acute progression of dyspnoea over 1 month or less, accompanied by new, diffuse opacities on CXR, worsening hypoxaemia, and the rapid development of respiratory failure in the absence of infection or an alternative diagnosis.[2,3] Recent reports have indicated significant episodes of acute respiratory decompensation preceding death.[4–12] An acute exacerbation of IPF can occasionally occur without a known precipitating event and the actual trigger of these exacerbations is unknown, despite extensive studies on tissues and fluid from BAL and thoracoscopic or open lung biopsy.[2,4–6,11]

The atypical bacteria *Chlamydophila* (previously *Chlamydia*) *pneumoniae* was classified as a new

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Chlamydial species by Grayston *et al.*[13,14] in 1989. *C. pneumoniae* is an important cause of both lower and upper respiratory tract infections, including pneumonia, bronchitis, pharyngitis and sinusitis.[13–15] There is an increasing body of literature concerning the association between *C. pneumoniae* infection and exacerbation of asthma[16–19] and COPD.[20–22] The association of *C. pneumoniae* infection with acute exacerbations of IPF has not been examined. A prospective study was conducted to investigate the possible role of *C. pneumoniae* infection in triggering acute exacerbations of IPF.

METHODS

Subjects

The study population consisted of 27 consecutive IPF patients treated between January 1999 and March 2006 who fulfilled the following criteria for acute exacerbation of IPF (modified from Kondoh[2] *et al.* and Akira *et al.*[3]): exacerbation of dyspnoea within the preceding month, new diffuse pulmonary infiltrates on CXR, deterioration of hypoxaemia and the absence of apparent infectious agents and heart failure. Subjects were excluded if the aggravation occurred after surgery or bronchoscopic examination. In three patients, the diagnosis of IPF was based on the presence of usual interstitial pneumonia (UIP) diagnosed by surgical lung biopsy. In the remaining 24 patients, IPF was diagnosed clinically according to an international consensus statement.[1] The high-resolution CT (HRCT) criteria included a symmetrical and subpleural bilateral interstitial pulmonary process, including honeycomb changes with minimal areas of associated ground-glass opacity. In 12 of these 24 patients, a UIP pattern was confirmed on autopsy. Other known causes of interstitial lung disease, such as drug toxicity, environmental toxins and collagen vascular diseases, were excluded. Of the 27 study patients, 25 required hospital admission for treatment of worsening dyspnoea; the remaining two patients were already hospitalized for evaluation of IPF and management of pulmonary TB complicated with IPF, respectively.

Serology

Acute and convalescent sera were tested for *C. pneumoniae* IgG and IgA. The presence of antibodies against the *C. pneumoniae* outer membrane complex in serum was investigated using ELISA (Hitachi Chemical Company, Ltd, Tokyo, Japan). A test index was calculated from the optical density relative to that of control material; an index of <0.9 was negative, 0.9–1.09 was equivocal, 1.10–2.99 was positive and >2.99 was strongly positive. A rise in antibody response was defined as a change in the index of ≥1.35 for *C. pneumoniae* IgG and ≥1.0 for IgA, which corresponds to a fourfold rise in titre by microimmunofluorescent assay.[23] A specific rise in *C. pneumoniae* IgG or IgA between the first and second test was regarded as serological evidence of either acute or reactivated infection with *C. pneumoniae*.

Design

At the time of presentation with the acute exacerbation, blood cultures were done for patients who had fever, and sputum culture and blood tests, including acute serology for *C. pneumoniae*, were performed in all patients. Appropriate cultures were all negative. The serum concentration of KL-6 (normal value <500 U/mL) was determined by enzyme immunoassay using commercially available kits (Eisai, Tokyo, Japan) after June 2000 when this methodology became available. Sixteen subjects underwent an HRCT scan of the chest at presentation. HRCT scans using either a Pro Seed or a Pro Seed Accell (GE Yokogawa Medical Systems, Tokyo, Japan) were performed with a 2-mm section thickness and a 1-s scanning time during breath holding at the end of inspiration. Convalescent sera for *C. pneumoniae* were collected 3–4 weeks after the initial serological test. Additional data collected included information on tobacco smoke exposure, symptoms and clinical evaluation at presentation, laboratory findings, treatment before admission, need for mechanical ventilation, survival days in hospital and follow up. Informed consent was obtained from all subjects and the study protocol had the approval of the local ethics committee.

Analysis

Group comparisons were made using the Student's *t*-test or Wilcoxon signed-rank test. Significance was defined as $P < 0.05$. All analyses were performed using JMP statistical software (SAS Institute, Inc., Cary, NC, USA). Results are presented as mean ± SD.

RESULTS

Clinical data at presentation for the 27 patients studied, who had a mean age of 71 years are shown in Table 1. Seven patients were current smokers (they had smoked cigarettes regularly within the previous year), 13 were former smokers (they had not smoked cigarettes in the previous year but had smoked in the past), and seven were never smokers. Five patients were receiving systemic corticosteroids (7.5–25 mg per day). One patient received cyclosporine A in addition to corticosteroid therapy. Three cases were being administered aerosolized N-acetylcysteine,[24] an antioxidant. Nineteen patients were not receiving any pharmacologic therapy for IPF. The time from onset of the acute exacerbation to presentation ranged from 0 to 11 days (median 3 days).

Laboratory studies revealed leucocytosis (11 926 ± 4616/mm^3; range 6000–24 500/mm^3) and elevation of CRP (6.9 ± 5.7 mg/dL; range 0.4–20.4 mg/dL), LDH (390 ± 145 IU/L; range 179–740 IU/L), and KL-6

Table 1 Demographic and clinical data at presentation of patients with acute exacerbation of idiopathic pulmonary fibrosis ($n = 27$)

	n
Gender (women/men)	9/18
Age range (year)	60–85
Smoking status	
Current	7
Former	13
Never	7
Symptoms	
Dyspnoea	27
Cough	25
Bloody sputum	3
Fever (≥37°C)	18
Inspiratory crackles	27
Clubbing	7
Previous steroid therapy	5†
Oxygen therapy	11
Duration (months) from IPF diagnosis (range)	1–84

†One case received cyclosporine A in addition to steroid.

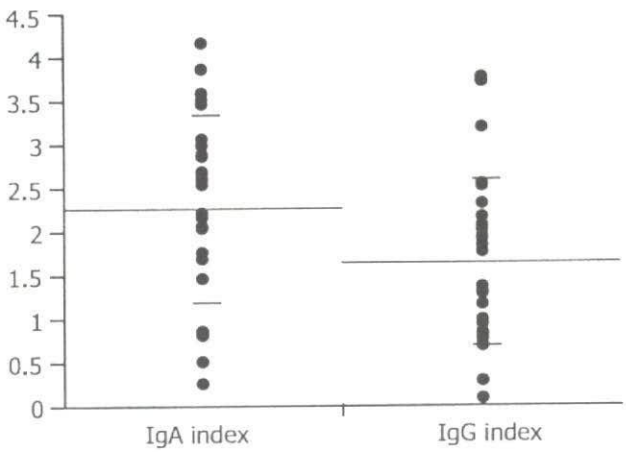

Figure 1 *Chlamydophila pneumoniae* IgG and IgA index at the time of presentation of acute exacerbation of idiopathic pulmonary fibrosis ($n = 27$). A test index was calculated from optical densities relative to that of control material, where an index of <0.9 is negative, 0.9–1.09 is equivocal, 1.10–2.99 is positive and >2.99 is strongly positive. The mean ± SD are shown.

(2138 ± 1187 U/mL; range 378–4920 U/mL, $n = 22$). The respiratory index, calculated as PaO_2/FiO_2, ranged from 33.6 to 374.3 mm Hg (168.3 ± 97.3 mm Hg).

Chest CT at presentation in 16 patients demonstrated diffuse ground-glass opacities and air space consolidation together with pre-existing subpleural honeycombing predominantly in both lung bases.

Figure 1 shows the *C. pneumoniae* IgG and IgA index at the time of the acute exacerbation. The overall prevalence of antibody (*C. pneumoniae* IgG or IgA index of ≥1.1) was 89%, and seven individuals (26%) had a *C. pneumoniae* IgG or IgA index of >2.99 (strongly positive). Convalescent sera were obtained in 15 of the 27 subjects for whom acute serology for *C. pneumoniae* was obtained. In the remaining 12 patients, convalescent sera were not available because of death owing to respiratory failure ($n = 11$) or transfer to another hospital ($n = 1$) within three weeks of the initial serological test. Figure 2 shows changes in the *C. pneumoniae* IgA index (a) and IgG index (b). The antibody response rose in two subjects (change in index of 1.54 for *C. pneumoniae* IgA and 1.90 for *C. pneumoniae* IgG, respectively).

All patients were treated with high doses of methylprednisolone (500–1000 mg per day for 3 days) followed by oral or i.v. prednisolone. Other immunosuppressive drugs including cyclophosphamide ($n = 2$), cyclosporine A ($n = 2$) and azathioprine ($n = 1$) were administered, as well as ulinastatin ($n = 11$), sivelstat ($n = 5$) and aerosolized N-acetylcysteine ($n = 1$). Oxygen therapy and empirical antibiotic therapy were instituted in all cases. Mechanical ventilation was required in eight patients (non-invasive mechanical ventilation $n = 6$, invasive mechanical ventilation $n = 1$, non-invasive and invasive mechanical ventilation $n = 1$).

In total, 12 patients survived to hospital discharge and the remaining 15 died during their hospitalization (mortality 56%). The mean time from the onset of the acute exacerbation to death was 23 days (range 3–65). Autopsy was performed in 11 of the 15 patients who died. In all cases, autopsy revealed various combinations of typical UIP and areas of diffuse alveolar damage. Neutrophil infiltration was also seen, suggesting focal bacterial infection in two cases, focal bleeding in one case, and tuberculous cavitary changes in one patient who had been treated with antituberculous drugs. When the laboratory data at presentation were compared between survivors and non-survivors, the respiratory index, calculated as PaO_2/FiO_2, in non-survivors was significantly lower than in survivors (131 ± 23.0 vs 215 ± 25.7, respectively, $P < 0.05$) (Table 2). The analysis did not control for the treatment regimen used. Antibiotics that are thought to be effective for *C. pneumoniae* infection were instituted in two cases among the survivors (telithromycin, minocycline) and two cases among non-survivors (clarithromycin, minocycline). With regard to the outcome of the two cases having a rise in antibody response, one case (72-year-old man, change in index of 1.90 for *C. pneumoniae* IgG) survived and was discharged home with a new prescription of supplemental oxygen. Figure 3 shows changes in this patient's HRCT findings. He received pulse therapy with methylprednisolone and antibiotic therapy including biapenum and telithromycin, which is thought to be effective for *C. pneumoniae* infection. The other case (63-year-old man, change in index of 1.54 for *C. pneumoniae* IgA) did not respond to the initial therapy, including high doses of methylprednisolone and antibiotics with ampicillin/sultamicillin and cefditoren pivoxil, and died 1 month after hospital admission from cytomegalovirus superinfection.

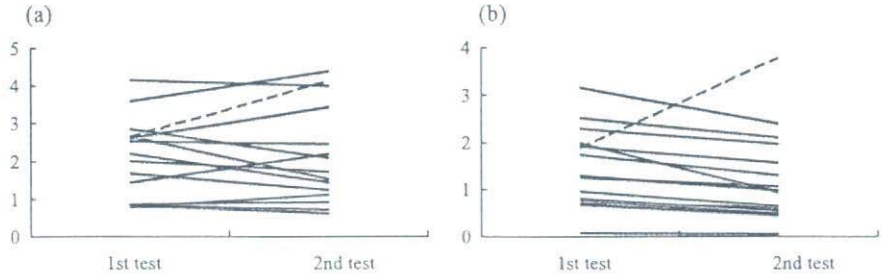

Figure 2 Changes in *Chlamydophila pneumoniae* IgA index (a) and IgG index (b). Two (dotted line) out of 15 subjects with idiopathic pulmonary fibrosis and acute exacerbation in whom both acute and convalescent sera were tested showed a rise in antibody response (change in index of 1.54 for *C. pneumoniae* IgA and 1.90 for *C. pneumoniae* IgG, respectively).

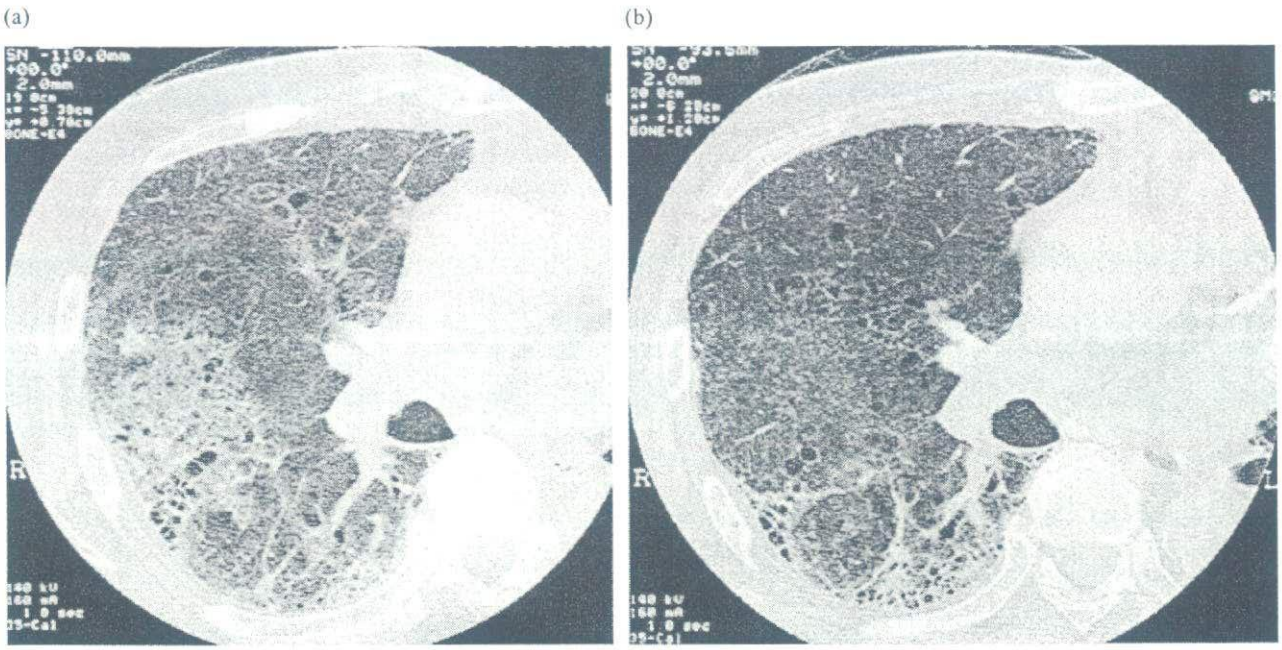

Figure 3 A 72-year-old man with idiopathic pulmonary fibrosis and acute exacerbation. (a) High-resolution CT scans taken on admission owing to acute exacerbation show ground-glass opacities with subpleural honeycomb appearance. (b) In follow-up CT after 1 month, ground-glass opacities decreased. The patient with a rise in *Chlamydophila pneumoniae* antibody response (change in index of 1.90 for *C. pneumoniae* IgG) received pulse therapy with methylprednisolone and antibiotic therapy including biapenum and telithromycin, which is thought to be effective for *C. pneumoniae* infection. He was discharged home on supplemental oxygen.

Table 2 Comparison of laboratory data at presentation for survivors and non-survivors of acute exacerbation of idiopathic pulmonary fibrosis ($n = 27$)

	Survivors ($n = 12$)	Non-survivors ($n = 15$)	*P*-value
WBC ($\times 10^3/mm^3$)	11 517 ± 1 355	12 253 ± 1 211	0.689
CRP (mg/dL)	5.2 ± 1.6	8.3 ± 1.4	0.173
LDH (IU/L)	345 ± 41	426 ± 37	0.156
KL-6 (U/mL)	2 246 ± 404†	2 063 ± 336‡	0.732
Chlamydophila pneumoniae			
IgG index	1.5 ± 0.3	1.8 ± 0.2	0.480
IgA index	2.3 ± 0.3	2.2 ± 0.3	0.755
PaO_2/FiO_2 (mm Hg)	215 ± 25.7	131 ± 23.0	0.022

†$n = 9$, ‡$n = 13$. Values are mean ± SEM.

DISCUSSION

This is the first study to investigate the serologic markers of *C. pneumoniae* infection in patients with an acute exacerbation of IPF. Previous studies have examined the use of serologic tests for *Mycoplasma pneumoniae*,[2,3,11] *Chlamydia psittaci*,[2,3] legionella[3,5,11] and various viruses[2,3,5,11] to exclude an aetiological associated between these organisms and acute exacerbations of IPF. Jeon *et al.*[12] performed serologic tests for *C. pneumoniae* in patients with suspected pneumonia and acute exacerbation of IPF, but results of those tests were not reported. The present study showed that only two of the 15 patients (13%) had serological evidence of either acute or reactivated infection with *C. pneumoniae*, suggesting the latter is uncommon for acute exacerbations of IPF.

This study has several limitations. First, the number of cases with paired sera was limited. More than half of the patients died before a second sample could be collected. It is not possible to predict whether the incidence of acute *C. pneumoniae* infection may be different in those who died. If *C. pneumoniae* infection plays a key role in acute exacerbation, it is possible the acute infection rate might have been significantly higher in those who died. However, the post-mortem results did not favour this hypothesis.

Second, we cannot ascribe causality to the finding of an association between an acute exacerbation of IPF and an elevation in the titre of antibody to *C. pneumoniae*. Of the two patients with increased serological titres in paired sera, one received antibiotic therapy covering *C. pneumoniae* infection in addition to high doses of methylprednisolone survived hospitalization. The other patient, whose initial therapy did not include antibiotics covering *C. pneumoniae*, died. However, no conclusion can be drawn based on this evidence on whether treatment of *C. pneumoniae* might have influenced the clinical outcome.

Third, there was no control group of patient in the present study to help determine if the high prevalence of antibodies to *C. pneumoniae* (89%) in the IPF patients was significant. Epidemiologic studies have demonstrated that up to 70% of adults have antibodies to *C. pneumoniae*, and most subjects experience at least one *C. pneumoniae* infection over the course of a lifetime.[15] This study took place in an area known to have high prevalence of antibodies against *C. pneumoniae* even among healthy persons.[17,22] The high percentage of patients with positive serology to *C. pneumoniae* in the present study may merely reflect the high prevalence of background past infection in an elderly population.

A prospective study on community-acquired *C. pneumoniae* pneumonia in Japan[25] indicated that pneumonia with *C. pneumoniae* as a single aetiologic agent is mild. However, *C. pneumoniae* can cause severe pneumonia in patients with underlying diseases[26] and acute respiratory failure caused by *C. pneumoniae* has been reported.[27–29] A study on the spectrum of radiographic findings associated with *C. pneumoniae*, [30] reported that bilateral interstitial changes were seen in recurrent infection of *C. pneumoniae* and sometimes the appearance of recurrent *C. pneumoniae* infection radiographically mimicked non-cardiogenic pulmonary oedema. The same authors also reported four cases of *C. pneumoniae* infection in which there was evidence of interstitial fibrosis in past radiographs. As *C. pneumoniae* is difficult to culture, concerns have been raised whether patients with an acute exacerbation of IPF should be covered with antibiotics against atypical pathogens including *C. pneumoniae*. Based on this study, such concern may not be justified as acute infection with *C. pneumoniae* appeared uncommon in this setting.

The present study also addresses important aspects of an acute exacerbation of IPF. Although acute exacerbations seem to be a major problem in IPF, their incidence, clinical profile, morphological pattern, laboratory data, relevance and relationship to outcome measures and mortality are not well known. Martinez *et al.*[8] reported that out of 168 patients in the placebo group of a randomized, controlled trial evaluating interferon-γ1b, 36 patients died, and six of those who died of an IPF-related cause appeared to fall into the category of acute exacerbation. Azuma *et al.*[9] found that out of 35 patients in the placebo group of a randomized, controlled trial evaluating pirfenidone, acute exacerbation was manifested in five patients. According to a report by Kim *et al.*[11] the 2-year frequency of acute exacerbation was 9.6% after the diagnosis of IPF. Jeon *et al.*[12] examined the causes of death in IPF patients and reported that 23 out of 50 deaths occurred in patients who experienced acute exacerbations. Mortality rates have been reported as 0%,[2] 20%,[9] 53%,[3] 69%,[7] 80%[5] and 82%.[11] In the present study population the hospital mortality rate was 56% and the time from the onset of the acute exacerbation to death averaged 23 days.

Comparison between survivors and non-survivors of laboratory data at presentation showed that the respiratory index significantly differed between the two groups. The respiratory index at the time of the acute exacerbation may have significant prognostic value, so early intervention would be important. However, it should be noted that the present study did not take into account the severity of the acute exacerbation. The definition of an acute exacerbation varies among authors. Kim *et al.*[11] reported 11 patients who satisfied the strict criteria of Kondoh *et al.*[2] for acute exacerbation (e.g. $PaO_2/FiO_2 < 225$). They mentioned that another five patients who did not strictly satisfy all of Kondoh's criteria did in fact have clinical and surgical lung biopsy pathology features that strongly suggested acute exacerbation. Therefore, the degree of severity should not necessarily be included in making the diagnosis of this acute syndrome and therapy should be commenced early. In this report the relevance of HRCT findings to the prognosis of acute exacerbation were not analyzed. Other reports have shown that the HRCT pattern at the time of acute exacerbation has significant prognostic value, with patients with multifocal and diffuse parenchymal opacification having a poorer prognosis than those with peripheral parenchymal opacification.[3,11]

There are no perfect serological methods for the diagnosis of *C. pneumoniae* infection and standardized testing methods are lacking.[31] However, the ELISA used in the present study, which detects the antibody response to an outer membrane protein complex, has been shown to be highly sensitive and specific when compared with Western blot analysis and has very high concordance with the results obtained by microimmunofluorescence[23] which is the method currently recommended for routine diagnosis of *C. pneumoniae*.[31] The ELISA method could not detect IgM antibody to *C. pneumoniae*. This may not be crucial as adult infections are thought to be mainly reinfections characterized by specific IgG and IgA antibody responses without changes in IgM.[13] All patients from whom paired sera were obtained had received high doses of methylprednisolone—the effect of which on the serologic testing of *C. pneumoniae* is unknown. It is possible steroid therapy can inhibit a rise in antibody titre, thus causing an underestimation of the acute or reactivated infection with *C. pneumoniae*. Serology cannot determine the precise location of infection (e.g. upper or lower airways) and cross-reactivity with other *Chlamydia* spp. may also occur.

This study has not demonstrated any significant relationship between *C. pneumoniae* infection and acute exacerbation of IPF, based on serological testing. Future studies using alternative methodology (e.g. histopathological examinations or PCR) of detection of *C. pneumoniae* may be required to further exclude any association of *C. pneumoniae* infection with acute exacerbations of IPF.

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特集 特発性間質性肺炎

最新の治療薬開発*
—生命予後の改善を目指して—

冨岡洋海**

Key Words：IPF, pirfenidone, NAC, Bosentan

はじめに

特発性間質性肺炎は，原因を特定しえない種々の間質性肺炎の総称であり，わが国においても「難病対策要綱」に基づいた「特定疾患」に指定され，国をあげて原因究明や治療方法の確立に取り組まれている．なかでももっとも頻度が高く，また，もっとも予後不良な特発性肺線維症(IPF)については，現行のガイドラインにおいて経験的に推奨されているステロイド，免疫抑制剤などの効果は乏しく，新たな治療薬の開発が急務である．本稿では，このIPFを中心に最新の治療薬開発の現況について解説する．

IPFの病態からの治療戦略

かって，1980～1990年代，IPFには，ステロイド治療に反応する剥離性間質性肺炎(desquamative interstitial pneumonia：DIP)や非特異性間質性肺炎(nonspecific interstitial pneumonia：NSIP)などの間質性肺炎が含まれて検討されてきた経緯があり，その病態は慢性炎症により直接ひき起こされる間質の線維化であると考えられていた．この慢性炎症のカスケードを止める目的で，ステロイド，免疫抑制剤による治療が経験的に行われてきたが，現在の独立した疾患概念であるIPFに対しては，その効果は乏しく，予後をかえるものではないことが検証されている[1]．現在，IPFの病態としては，繰り返される肺胞上皮障害によって肺胞上皮細胞の障害と，線維芽細胞/筋線維芽細胞の増生，細胞外基質の沈着という異常な修復をひき起こし，結果として線維化，肺の構造破壊が進行すると考えられている[2][3]．このようなIPFの病態についてのパラダイムシフトを受けて，現在の治療戦略は，肺胞上皮障害を制御し，線維芽細胞の増殖を修正し，細胞外基質の吸収を促すことが提案されている．

ガイドラインと臨床試験

ガイドラインは科学的根拠に基づく医学(EBM)思想が定着，普及するとともに多くの疾患で制定されるようになり，特発性間質性肺炎についても，米国胸部学会/ヨーロッパ呼吸器学会(ATS/ERS)や日本呼吸器学会によるものが発表されている(2．診断と治療のガイドライン—現行の問題点と改善点—参照)．これらのガイドラインは，特発性間質性肺炎に関する疾患概念の共通認識により，同一の診断基準を用いた臨床試験の活発化に果たした役割は大きい．さらに，EBMの精度をより高めるためにも，無作為化比較対照試験(RCT)が重要であり，これまでに論文として発表されたIPFの治療薬に関するRCT[4]～[12]を表1に示す．

* The latest drug development to improve the prognosis of IPF.

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表1　特発性肺線維症(IPF)治療薬に関する無作為化比較対照試験

文献報告年	総症例数	実薬治療	対照治療	結果
4) 1998	26	コルヒチン	PSL	無増悪生存期間で有意差なし
5) 1999	18	IFNγ+PSL	PSL	TLC，安静・運動時のPaO_2の悪化が有意に抑制
6) 2004	330	IFNγ	プラセボ	無増悪生存期間で有意差なし
7) 2005	182	NAC+PSL+AZP	プラセボ+PSL+AZP	VC，DLcoの悪化が有意に抑制
8) 2005	30	NAC吸入	塩酸ブロムヘキシン吸入	6分間歩行中最低SpO_2，血清KL-6値，HRCTすりガラススコアの悪化が有意に抑制
9) 2005	56	ワーファリン+PSL	PSL	生存期間，急性増悪による死亡率に有意差
10) 2005	107	ピルフェニドン+PSL	プラセボ+PSL	6分間歩行中SpO_2低下面積，VCの悪化，急性増悪の頻度が有意に抑制
11) 2006	50	IFNγ+PSL	コルヒチン+PSL	生存期間に有意差
12) 2008	158	ボセンタン	プラセボ	6分間歩行距離で有意差なし

PSL：プレドニゾロン，AZP：アザチオプリン，NAC：N-アセチルシステイン
TLC：全肺気量，VC：肺活量，DLco：一酸化炭素肺拡散能

新規治療薬の現況

1．インターフェロン(IFN)γ

IFNγは活性化されたTh1細胞より産生される細胞性免疫の活性化因子であり，線維芽細胞の増殖を促進するTh2サイトカインや形質転換増殖因子β(transforming growth factor-β：TGF-β)遺伝子の転写を抑制する．小規模非盲検の臨床試験[5]で，IFNγ-1bとステロイド併用治療群が，ステロイド単独群に比べて全肺気量と動脈血酸素分圧の有意な改善を認めた報告を検証する目的で，北米においてIPF 330例を対象にRCT(INSPIRE1)が行われた[6]．その結果，主要評価項目である無増悪生存期間や全体の死亡率について有意差は認められなかったが，%努力肺活量(FVC)>55%のより軽症のIPFでは，予後を改善する可能性が示唆された．この後解析の結果を受け，%FVC>55%を826例エントリーしたINSPIRE2試験が展開されたが，2007年3月に発表された結果では有意差はなく，IFNγの有効性は否定されている．

2．ピルフェニドン

ピルフェニドンは，米国で開発された経口投与のピリドン誘導体であるが，線維芽細胞のコラーゲン産生抑制や線維化にかかわるTGF-βや血小板由来増殖因子(platelet-derived growth factor：PDGF)といったサイトカイン発現抑制が見出された．米国において，IPF 54例を対象とした非盲検オープンラベル試験[13]の結果を受け，わが国においてIPF 107例を対象に無作為化二重盲検比較試験が行われた[10]が，6か月の時点で中間解析が行われ，急性増悪例がすべてプラセボ群に偏っていたことから，効果・安全性評価委員会の答申を受け，試験開始9か月で開鍵し，解析が行われた．その結果，主要評価項目である6分間定速歩行試験の歩行完遂例では，投与開始6か月後のSpO_2低下面積において，ピルフェニドン群がプラセボ群と比較し有意な改善を示し，また，肺活量の変化や急性増悪の頻度にも有意差を認めた(表2)．有害事象としては，約半数に光線過敏症を認め，本剤の服用に関しては日光曝露に対して十分な注意が必要とされた．さらにその再現性を検証するため，肺活量の変化量を主要評価項目とし，低用量投与群も含めた3群間での第III相試験が実施された．高用量，低用量投与群とも，プラセボ群に比べ肺活量低下が有意に抑制された結果が2008年5月にATSで発表され，大きな反響を呼んだ．このようにピルフェニドンは，わが国のIPFに対する有効性のエビデンスをもつ初めての薬剤であり，上市(塩野義製薬株式会社)が予定されている．なお，肺線維症を合併する遺伝性疾患であるHemansky-Pudlak症候群に対しても，二重盲検試験による本剤の有効性が示されている．

3．N-アセチルシステイン(NAC)

IPFではオキシダントによる肺胞上皮障害の関与が報告されており，抗酸化作用を有する薬剤の有効性が検討されている．還元型グルタチオン(GSH)とこれに関連する酸化還元酵素は，肺

表2 ピルフェニドン第II相無作為化二重盲検比較試験

	ピルフェニドン(n=72)	プラセボ(n=35)	P value
Δ6分間歩行中最低SpO_2(%)	0.47±3.88	−0.94±3.36	0.072
ΔVC(*l*)	−0.03±0.22	−0.13±0.19	0.037
Δ DLco(ml/min/mmHg)	−0.57±2.15	−1.19±2.30	0.212
Δ安静時 PaO_2(Torr)	−2.48±10.30	−3.66±10.43	0.598
有害事象による治療中止	11(15.1%)	2(5.6%)	0.213
IPF急性増悪	0(0.0%)	5(13.9%)	0.003

VC：肺活量，DLco：一酸化炭素肺拡散能 （文献[10]より）

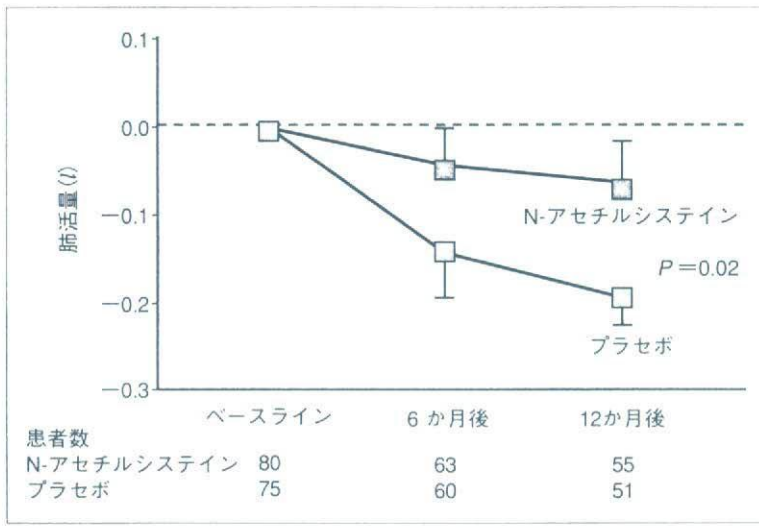

図1 高用量経口N-アセチルシステイン無作為化比較対照試験（文献[7]より）

における主要な抗酸化機構であり，GSHはIPF患者の肺において有意に低下していることが示されている[14]．NACはGSH合成の前駆体であり，抗酸化作用を有する．IPF患者を対象に，高用量経口NAC投与により，気管支肺胞洗浄液中および気道上皮被覆液中のGSHの有意な上昇が確認され[15]，無作為化大規模臨床試験が行われた[7]．IPF患者182例をNAC投与群(1,800mg/day)とプラセボ群に分け，現行のガイドライン推奨治療であるステロイドと免疫抑制剤(PSL 0.5mg/kg/dayより開始し漸減＋アザチオプリン2 mg/kg/day)に併用した．生命予後の改善にはいたらなかったが，12か月後にNAC投与群で肺活量，一酸化炭素肺拡散能の低下が有意に抑制された(図1)．

一方，わが国では，NACの経口剤はなく，吸入去痰剤(ムコフィリン®)として長年使用されてきた経緯があり，抗酸化作用が期待される肺局所へのdrug deliveryの利点からもNAC吸入療法が検討されている．30例のIPF患者を対象に行われたRCT[8]では，NAC群(NAC 352mg/day吸入)と対照群(塩酸ブロムヘキシン4 mg/day吸入)との比較で，6分間歩行中のSpO_2最低値，血清KL-6, HRCTすりガラス状陰影スコアの各変化量について有意差を認め，NAC吸入療法はIPFの進行を遅らせる可能性が示唆された．現在，厚生労働科学研究として早期IPF(重症度がI度～II度，かつ6分間歩行時SpO_2が90%以上)を対象としたNAC吸入療法の多施設共同試験が実施され解析がなされている．ただし，この試験では，無治療群を対照としている点がデザイン上問題視されるであろう．

4．ボセンタン(トラクリア®)

エンドセリン-1(ET-1)は，肺動脈の血管を収縮し，肺動脈平滑筋細胞の増殖を促進することが知られている．さらに，ET-1はマトリックスの