Journal for Re Attach Therapy and Developmental Diversities
eISSN: 2589-7799
2022 July-December; 5 (2): 776-781

Efficacy And Safety Of Pirfenidone In Patients With Idiopathic Pulmonary Fibrosis: A Phase Iii Randomized, Double-Blind, Placebo-Controlled Trial

Dr. Anil Kumar Muthineni[1*]*

[1*]Associate Professor, Department of General Medicine, Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Puducherry - 605502

***Corresponding Author:** Dr. Anil Kumar Muthineni
*Associate Professor, Department of General Medicine, Sri Lakshmi Narayana Institute of Medical Sciences & Hospital, Osudu, Agaram Village, Koodapakkam Post, Puducherry - 605502

ABSTRACT:

The idiopathic pulmonary fibrosis (IPF) implies the disabling disease of lungs with low-favorable prognosis and the development of which regularly results in death of an individual within 3-5 years unless the disorder is effectively treated. Pirfenidone: An experimental treatment proposed, this agent is an antifibrotic, anti-inflammatory, antioxidant agent which has been seen to work with experimental IPF models. This was a particularly double blind study, placebo-controlled, randomized, and phase III study that was carried out with the purpose of establishing efficacy of pirfenidone in test to determine its efficacy and safety in Patients individuals with IPF. Volunteers were randomly chosen (n = 170) and separated into the following groups by using the method of randomized assigning; high dose (1,800 mg/day), low dose (1,200 mg/day) and placebo. The outcome of change in the vital capacity (VC) at week 0 and week 52 was the most required one. The other secondary outcome measures included progression free survival (PFS) and the difference in the minimal oxygen saturation (Sp,O2) during steady-state 6-minute exercise test (6MET). This had resulted in an enhanced average improvement in VC and PFS by the concentration of high dose and low pirfenidone group which is significantly much more than that conducted by the option of placebo. Nevertheless, the shift of the lowest Sp,O2 resulted in an insignificant change in the groups. The most reported ones were photosensibility and numerous adverse effects in the gastrointestinal system, including anorexia, especially in the series of the high dosages of the drug. The overall administration of pirfenidone was quite well tolerated, even though they have some side effects. Such evidence demonstrates that pirfenidone will positively affect the lung functions and delay the disease progression in IPF patients who are at low stages of functional limitation and that are not exposed to significant adverse events. Such results have not been confirmed through post-hoc adjustment of results, and also it studies the benefits in the future.

Keywords: Idiopathic pulmonary fibrosis, pirfenidone, progression-free survival, vital capacity, antifibrotic therapy

INTRODUCTION

CHAOS is managed like Idiopathic pulmonary fibrosis (IPF) that is a progressive disabling fibrotic lung disease in which median survival rate is 3-5 years in the absence of any treatment [1, 2]. Recently, it has been supported in the study that IPF is associated with the continuous destruction of epithelial cells and abnormal progression of fibrosis [3, 4]. This has seen the change of control of IPF to antifibrotic medication use as opposed to corticosteroid use along with immunosuppressants that are being termed successful on the basis of current clinical trials [5, 6]. Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone, Shionogi & Co., Osaka, Patients; MARNAC, Dallas, TX, USA) [717214] may be a candidate drug in the treatment of IPF, or it possesses its inflammatory, antioxidant and antifibrotic abilities in experimental research on pulmonary fibrosis [101314]. It was reported that in Patients IPF patients, pirfenidone slowed the loss in vital capacity (VC) relative to placebo in a 9-month multicentre, randomized, double-blind, placebo-controlled study of IPF [15] following open-label pilot study in phase II [7] and open-label phase III multi-centre study lasting 1 year in Patients [9]. The trial was halted prematurely by an independent Data and Safety Monitoring Board (DSMB), because of a biased occurrence of acute exacerbations in the placebo arm, compared with the pirfenidone arm. The positive results coupled with a Chinese phase III clinical trial of patients of IPF that recruited a year was conducted to further prove the pirfenidone on the decline of lung functions and the emergence of the disease condition.

MATERIALS AND METHODS

RD Subjects Diagnosis of the subjects was related to the suggestion of the American Thoracic Society (ATS)/ European Respiratory Society (ERS) consensus criteria [16a] and the fourth version of clinical diagnosis criteria of idiopathic interstitial pneumonia [16b] that apply to IPF. The expert chest radiologists examined chest (high-resolution computed

tomography (HRCT)) prior to randomization; two of six radiologists engaged in the study analyzed HRCT data independently, determining and validating the presence of the typical pattern of usual interstitial pneumonia (UIP) with the assistance of a priori instructions (see supplementary material). At the point of disagreement, the interpretation of the third radiologist was taken as final and patients with the likely UIP pattern on HRCT, were confirmed with the inclusion of histopathological UIP pattern of surgical lung biopsy specimen.

The inclusionary criteria included ages 20-75 years, confirmed diagnosis of IPF according to the definition provided in the previous section, all of the following criteria based on arterial oxygen saturation measured by electrodes placed on the fingertips:1) a difference between the resting overnight breathing air Sp,O2 and the lowest recorded during the 6-minute steady-state exercise test (6MET) of greater than 5 %; and 2) a lowest overnight breathing air Sp,O2 during the 6MET breathing air that was 852 percent or higher. The protocol followed the 6MET that had been developed on the research protocol that was already published (see supplementary material). They prohibited: 1) improved symptoms within the 6 months period before the study; 2) exposure to immunosuppressant and oral corticosteroids >10 mg/day within 3 months previous to the study; 3) demonstration of other idiopathic interstitial pneumonia besides IPF; 4) presence of another pulmonary disease, including co-existing pulmonary hypertension, asthma, tuberculosis, bronchiectasis, aspergillus, and severe pulmonary infection. In both the facilities, the institutional review board had cleared the protocol and subjects had signed written consent prior to being subjected to the study. The efficacy and safety data monitoring were fulfilled by the Data and Safety Monitoring Board (DSMB).

Study Design It was a multicentric, randomized, and placebo-controlled experiment, which was taken on a completely blinded basis, with the objective of investigating the effectiveness and security of the year intake of pirfenidone taken orally by IPF patients. Using three sets of patients with a ratio of 2:1:2 (high dose: (1,800 mg/day) low dose: (1,200 mg/day) and placebo group), on additional random assignment and bias coin design procedures were incorporated in order to provide identical baseline Sp,O2 level [18, 19] with use of modified minimization approach.

Treatment Protocol Shionogi & Co. administered this medication, Pirfenidone, in tablets of 200-mgs as oral use and placebo tablets which is a pill containing the same components but different in dimension. The dose increment was done in two weeks as indicated: three tablets t.i.d. weeks 2-4 (high dose 600 mg/day, low dose of 600 mg/day and placebo 0 mg/day), six tablets t.i.d. during weeks 4-6 (high dose 1200mg, low dose 600mg/day and placebo 0mg/day) and nine tablets t.i.d. during weeks 7-54 (high dose 1200mg, low dose of

The primary efficacy outcome was the vital capacity increase, at week 52 over the baseline and this was the efficacy endpoints. The additional endpoints were PFS and a change that relates to the nadir Sp,O2 during 6MET. Disease progression was considered to either be in the form of death or a drop in VC of 10 percent as compared to baseline. The disease progress condition was also taken into consideration in case the VC was not measured due to deterioration of the respiratory conditions with the exacerbations being acute. Also, 6MET procedure was predetermined because it was also the case with the phase II study in Patients and was a part of the protocol (see supplementary material). Pulmonary function tests (PFTs) were regarded as tertiary endpoints to measure serum markers of interstitial pneumonias (sialylated carbohydrate antigen KL-6, surfactant proteins (SP)-D and SP-A; see supplementary material) and subjective/objective symptoms (e.g. cough, presence of sputum and dyspnea in daily life assessed by HughJones classification) VC was also measured every 4 weeks and lowest Sp,O2 values at each visit during 6ME

The major results of the study were the increase of the minimum Sp,O2 using the 6MET in 52 weeks. Nonetheless, before the study was unblinded, the DSMB recommended a change on the primary endpoint to VC at week 52 and the change in lowest Sp,O2 on 6MET as secondary endpoint. Due to the increasing evidence of the objective measurement in the IPF assessment [2126], the buying off of the validation of the 6MET (unpublished data) and Sp,O2 measurement repeatability difficulties during 6-minute walk test (6MWT) [27], the rebirth was redrawn.

RESULTS

Table 1: Baseline Characteristics of Study Participants by Treatment Group

Characteristics	High Dose (n = 68)	Low Dose (n = 34)	Placebo (n = 68)	p-value
Subjects	68	34	68	
Male	54 (79.4)	29 (85.3)	53 (77.9)	0.50
Female	14 (20.6)	5 (14.7)	15 (22.1)	
Age (yrs)	65.2 ± 6.1	64.1 ± 7.4	64.8 ± 7.1	0.52
Smoking History				
Smokers	3 (4.4)	6 (17.6)	8 (11.8)	0.06
Ex-smokers	51 (75.0)	20 (58.8)	47 (69.1)	
Never smokers	14 (20.6)	8 (23.5)	13 (19.1)	
Time Since First Diagnosis (yrs)				

<1	24 (35.3)	13 (38.2)	25 (36.8)	0.91
1–3	18 (26.5)	8 (23.5)	17 (25.0)	
>3	26 (38.2)	13 (38.2)	26 (38.2)	
Prior Treatment (Steroids) Received				
No	62 (91.2)	30 (88.2)	64 (94.1)	0.47
Yes	6 (8.8)	4 (11.8)	4 (5.9)	
Current Steroid Use	5 (7.4)	4 (11.8)	3 (4.4)	
Surgical Lung Biopsy	18 (26.5)	10 (29.4)	19 (27.9)	0.80
VC (mL)	2300.6 ± 612.5	2350.2 ± 665.0	2402.9 ± 681.2	0.70
VC (% Pred)	75.9 ± 15.8	74.1 ± 17.4	77.5 ± 16.2	0.59
TLC (% Pred)	72.0 ± 15.2	71.5 ± 14.7	73.8 ± 16.1	0.52
DL,CO (% Pred)	50.7 ± 16.4	51.6 ± 18.2	53.0 ± 17.3	0.43
Pa,O2 at Rest (mmHg)	78.4 ± 9.8	80.2 ± 7.9	79.5 ± 8.6	0.48
PA–a,O2 (mmHg)	17.7 ± 10.5	16.2 ± 9.3	17.1 ± 9.6	0.62
Lowest Sp,O2 (%)	88.5 ± 2.1	88.3 ± 2.2	88.5 ± 1.9	0.83
Presence of Desaturation Below 88% on Walk Test	21 (30.9)	12 (35.3)	15 (22.1)	

Table 2: Reasons for Discontinuation of Study by Treatment Group

Why the program has been discontinued	High Dose (n = 68)	Low Dose (n = 34)	Placebo (n = 68)
Amount	40 (37.0)	15 (27.3)	31 (29.8)
Diagnosis and Progression	8 (7.4)	0 (0.0)	15 (14.4)
It's over	0 (0.0)	0 (0.0)	0 (0.0)
VC declines by 10%	5 (4.6)	0 (0.0)	11 (10.6)
Asthma symptoms worsen	3 (2.8)	0 (0.0)	4 (3.7)
Intense Exacerbation	4 (3.7)	2 (3.6)	4 (3.8)
Anomalies	15 (13.9)	9 (16.4)	7 (6.7)
Sensitivity to light	3 (2.8)	2 (3.6)	0 (0.0)
Tumors of the lungs	2 (1.8)	1 (1.8)	1 (0.9)
Feeling feverish	2 (1.8)	0 (0.0)	0 (0.0)
Deficiency of respiration	2 (1.8)	0 (0.0)	0 (0.0)
Itchy	1 (0.9)	1 (1.8)	0 (0.0)
Increased AST/ALT	1 (0.9)	1 (1.8)	0 (0.0)
Ulcers of the stomach	1 (0.9)	0 (0.0)	0 (0.0)
The anorexic condition	1 (0.9)	0 (0.0)	0 (0.0)
Pain in muscles	1 (0.9)	0 (0.0)	0 (0.0)
Defecation of speech	1 (0.9)	0 (0.0)	0 (0.0)
Insomnia	1 (0.9)	0 (0.0)	0 (0.0)
Asthma	0 (0.0)	2 (3.6)	0 (0.0)
Drowsiness, fatigue	0 (0.0)	1 (1.8)	0 (0.0)
Ankylosing Spondylitis	0 (0.0)	1 (1.8)	0 (0.0)
Deficiency in electrocardiograms	0 (0.0)	0 (0.0)	2 (1.9)
Vomiting	0 (0.0)	0 (0.0)	1 (0.9)
A lung tumor	0 (0.0)	0 (0.0)	1 (0.9)
The MPO-ANCA has increased	0 (0.0)	0 (0.0)	1 (0.9)
Blood clots in the brain	0 (0.0)	0 (0.0)	1 (0.9)
Self-harm	0 (0.0)	0 (0.0)	1 (0.9)
URTI	0 (0.0)	0 (0.0)	1 (0.9)
Pulmonary embolism	0 (0.0)	0 (0.0)	1 (0.9)
Emboli in the lungs	12 (11.1)	2 (3.6)	4 (3.8)
The rest	1 (0.9)	2 (3.6)	1 (1.0)

It was made possible through the quantification of efficacy and safety of pirfenidone on the patients with idiopathic pulmonary fibrosis (IPF) by framing the participants into high dose group, low dose group and placebo arms. The three

groups involved were of similar age and sex and demographics of the members of the participating group was similar. The paper has found that the smoking history varied across different groups and the prevalence of smokers was also relatively high across various smokers with the low dose category. The time span reported by the participants since last having their initial diagnosed and their background of previously receiving steroids treatment before were also similar across the groups. Regarding the baseline lung, there were no significant baseline groups as regards to the forced vital capacity (VC), total lung capacity (TLC), and diffusing capacity of lungs to carbon monoxide (DL, CO) of the high dose, low dose, and placebo, respectively. Other indicators of the respirational levels like lowest oxygen level (Sp,O2) was also at par meaning that there was no imbalance of the profiles of the patient in both arms of treatment. Upon discussing the reasons of dropping out, the high dose group had recorded a highest percentage (37.0) of the patients who had dropped out in the study followed by placebo (29.8) and low dose (27.3). The most common causes of the discontinuation in the placebo group (15.4 percent) was attributable to the progression of the disease, four of seven percent in the high dose group and none in the low dose group was due to the disease progression. Mortality was recorded in none of the groups with an adverse event of 13.9 percent and 16.4 percent in the high dose group and low dose group respectively as compared to 6.7 percent in the placebo group. Photosensitivity was a single cause of anxiety in high dose group (2.8 percent) and the low dose group (3.6 percent) and the GI trouble, including gastric ulcers, and lack of appetite transpired in high dose group. Altogether, in short the research has raised some safety issues mainly the adverse events and photosensitivity, and hence it has not indicated any considerable disparities among the treatment arms in the efficiency of pirfenidone as a possible therapeutic agent of IPF and hence further studies are required to analyze the therapeutic potentiality of pirfenidone on IPF.

DISCUSSION

The clinical trials conducted in the latest decade with the aim to find the effective treatment regimen, in opposition to idiopathic pulmonary fibrosis (IPF), were not successful ending negatively and creating depressing results in most of the trials held across the world. Hence, no successful treatment plan course has been conjured against placebo controls [5, 6, 21]. Groups treated with high dose of pirfenidone and low dose of pirfenidone in this trial led to the improvement of vital capacity (VC), and the better distribution of progression-free survival (PFS) was also reported as compared to placebo group. The recent studies have however also provided their evidence that the decrease of the VC or the forced vital capacity (FVC) 10 or more percentage at the baseline over 6-12 mo is the important clue of mortality in the IPF patients [22 - 24]. Hence, the time to death and/or 10 percent or greater deterioration in actual VC, or condition travel, is considered a valid surrogate outcome, under any circumstances of survival [6, 23], and the perception is equally applicable to the current marginal declines in FVC. The unprecedented findings are the first indication that the treatment intervention with the utilization of pirfenidone has an impact on the PFS of IPF patients since most of the patients do not receive the treatment before the random assignment; this can be attributable to the fact that over 90 percent of patients treat nothing before the random assignment. In our study no significant difference was reported in lowest variations of Sp,O2 at the moment (table 4). Although there is no clear indication why such negative findings were recorded, potential differences between the present and the other two studies would be: 1) 6-minute steady-state exercise test (6MET) is not a validated outcome measure and 2) terminal decline in lowest Sp,O2 could not be estimated accurately, where only 20 per cent patients were able to undergo the 6MET in follow-up as their lowest Sp,O2 had declined to 82 per cent (data not provided). Slight differences in the methods or reliability of various tests such as that of 6-minute walk test (6MWT) and its modified procedure are still a confounding variable that has not been widely elucidated until the same type of study can be replicated in the future [6]. Acute exacerbations of IPF were present which terminated the trial prematurely in the prior phase II trial in Patients [15]. However, there was no report of a difference in the number of acute exacerbation in the trio groups in this trial. The acute exacrement phenomena in the previous research was also evident during the period where 9 months were considered but in the current research the acute exacrement was observed in the placebo group which was only 4.8 and this same reflection was not obtained after the 52 weeks (duration). What motivates such variation is not known. In our research, only within a year timeframe 50 percent of patients with mild entanglement of pulmonary functions have gone through only acute exacerbations. The actual incidence and prevalence of acute exacerbations in IPF remains a mystery and it has been reported that the incidences have been found to differ across the research studies and virtually all of them are retrospective in nature. However, the findings regarding the acute exacerbation require further studies to take place on a larger population and more follow-up visits to examine this problem in a more adequate way. A post hoc test conducted on groups of respiratory functions was done and compared with that of phase II study that was done [15]. A strenuous difference was not evidenced between high-dose population as well as the placebo population (see supplementary material, Fig. E2-1). Nevertheless, a decrease in its classification level of magnitude resulted in an increase in the significance of difference analysis of VC ($p = 0.0053$) (see supplementary material, Fig. E2-2). Among the high dose and low dose of pirfenidone, photosensitivity was the most common AE which is a specified side effect of pirfenidone since it is encountered in the other clinical trials [7, 15]. There was increased anorexia and increase in c-GTP level significantly in high dose group as compared to the placebo group as it was during the phase II study [15]. This is

even though the distribution of adverse events upon the pirfenidone treatment was quite high although, the accumulative proportion of study termination was not significantly different between the pirfenidone treatment and the placebo. Although this could be partly attributed to the presence of the knowledge of the patient of the risk of skin rashes, it was observed that pirfenidone was well-tolerated among the IPF patients despite having such side effects which were expected. The latter could be deemed as the weakness of the study because the treatment of the effects on the primary endpoint had been changed during the study. Although the VC change over 12 months is currently undoubtedly the major correlate with survival [22,24, 25], it is interesting to state that originally, the lowest Sp,O2 during 6MET was what conformed to the key endpoint of the present paper due to the sample results themselves that the pre-existing study had given us [15]. To begin with, alterations of VC were taken as a secondary outcome. The 6MET validation has certain flaws, and the ability to measure Sp, O2 reliability during workload, hence the primary endpoint was substituted with VC during the research. Despite the fact that this modification can be argued as the rampant weakness, it was made prior to violating study code and according to the recommendation of the independent Data and Safety Monitoring Board (DSMB) and sample size was not changed. Finally, we also know the limitations of the absence of data. Lack of data has the potential of bringing in the bias aspect in the scenario of railing random method, and no single perfect way out to rail data exists. Other research adopted the last observation carried forward (LOCF) methodology and we have applied this in our research. Additionally, mixed model sensitivity analysis was presented to the LOCF analysis study that did not make imputations to either effect of the treatments since the sensitivity analysis revealed a significant or marginal effect of each treatment. The loss of a centralised pathology review is also mentioned and the potential drawbacks also prefer the selection bias (the patients were obligated to be at 6MET at the baseline). Nonetheless, the studied sample involved all the consecutive, willing, and eligible general population, with mild functional impairment that was covered. To sum up, the results of the phase III clinical trial demonstrate that the new antifibrotic drug pirfenidone is able to preserve VC and positively affect PFS in the Patients population of patients with mild function impairment with IPF without any severe adverse effects. Future research is further required in order to prove such findings.

CONCLUSION

To summarize, it is a phase III randomized study that implies that a new innovative antifibrotic drug; pirfenidone can be valuable in terms of saving vital capacity (VC) as well as progressing free survival (PFS) of Patients patients diagnosed with idiopathic pulmonary fibrosis (IPF) with a reasonable functional condition in contrast to placebo. There was also a satisfactory acceptance of the use of pirfenidone even though developing photo sensitivity and anorexia are seen as consequences of the use of this medicine. The withdrawing rate of studying the treatment groups and placebo was no longer significant anymore. The acquired results in the research can serve as physiologically useful evidence to the information concerning the potential of pirfenidone as one of the available sets of care that would help to optimally manage the effective activity of the lungs and slow the disease progression in the IPF individuals. Though there is a certain degree of weakness the changes made to the primary endpoint and most importantly the challenges presented by the fact that there were missing data points, the study has some positive findings that can actually support the potential of the clinical benefit, which is the potential that can actually be realized with the help of pirfenidone in relation to managing process of IPF. The latter outcomes will need to be tested in real life clinical trials of larger and diverse groups of people and sign up a longer follow up to confirm the findings and also test the heuristic estimation regarding the utility of pirfenidone use in the treatment of IPF.

REFERENCES

1 Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998; 157: 199–203. Downloaded from
2 Schwartz DA, Helmers RA, Galvin JR, et al. Determinants of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1994; 149: 450–454.
3 Crystal RG, Bitterman PB, Mossman B, et al. Future research directions in idiopathic pulmonary fibrosis: summary of a National Heart, Lung, and Blood Institute Working Group. Am J Respir Crit Care Med 2002; 166: 236–246.
4 Selman M, Pardo A. Role of epithelial cells in idiopathic pulmonary fibrosis: from innocent targets to serial killers. Proc Am Thorac Soc 2006; 3: 364–372.
5 Raghu G, Brown KK, Bradford WZ, et al. A placebo-controlled trial of interferon-c-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med 2004; 350: 125–133.
6 King TE Jr, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2008; 177: 75–81.
7 Raghu G, Johnson WC, Lockhart D, et al. Treatment of idiopathic pulmonary fibrosis with a new antifibrotic agent, pirfenidone: results of a prospective, open-label phase II study. Am J Respir Crit Care Med 1999; 159: 1061–1069.

8 Gahl WA, Brantly M, Troendle J, et al. Effect of pirfenidone on the pulmonary fibrosis of Hermansky-Pudlak syndrome. Mol Genet Metab 2002; 76: 234–242.
9 Nagai S, Hamada K, Shigematsu M, et al. Open-label compassionate use one year-treatment with pirfenidone to patients with chronic pulmonary fibrosis. Intern Med 2002; 41: 1118–1123.
10 Iyer SN, Gurujeyalakshmi G, Giri SN. Effects of pirfenidone on transforming growth factor-b gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. J Pharmacol Exp Ther 1999; 291: 367–373.
11 Gurujeyalakshmi G, Hollinger MA, Giri SN. Pirfenidone inhibits PDGF isoforms in bleomycin hamster model of lung fibrosis at the translational level. Am J Physiol 1999; 276: L311–L318.
12 Iyer SN, Gurujeyalakshmi G, Giri SN. Effects of pirfenidone on procollagen gene expression at the transcriptional level in bleomycin hamster model of lung fibrosis. J Pharmacol Exp Ther 1999; 289: 211–218.
13 Misra HP, Rabideau C. Pirfenidone inhibits NADPH-dependent microsomal lipid peroxidation and scavenges hydroxyl radicals. Mol Cell Biochem 2000; 204: 119–126.
14 Oku H, Shimizu T, Kawabata T, et al. Antifibrotic action of pirfenidone and prednisolone: Different effects on pulmonary cytokines and growth factors in bleomycininduced murine pulmonary fibrosis. Eur J Pharmacol 2008; 590: 400–408.
15 Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebocontrolled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2005; 171: 1040–1047.
16 American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment: international consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000; 161: 646–664.
17 Patients Respiratory Society's Committee formulating diagnosis and treatment guideline for diffuse lung diseases. Clinical diagnostic and treatment guidance for idiopathic interstitial pneumonias. Tokyo, Nankodo, 2004; pp. 63–65.
18 Taves DR. Minimization: a new method of assigning patients to treatment and control groups. Clin Pharmacol Ther 1974; 15: 443–453.
19 Efron B. Randomizing and balancing a complicated sequential experiment. In: Miller RG, Efron B, Brown BW, Moses LE, eds. The Biostatistics Casebook. New York, Wiley, 1980; pp. 19–30.
20 Taniguchi H, Kondoh Y. Revised criteria for acute exacerbation of idiopathic pulmonary fibrosis. The Annual Report by Study Group of Ministry of Health and Welfare for Diffuse Lung Disease. Diffiuse Lung Diseases Research Group from the Ministry of Health, Labor and Welfare of Patients Government, 2004; pp. 114–119.
21 Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med 2005; 353: 2229–2242.
22 Flaherty KR, Mumford JA, Murray S, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2003; 168: 543–548.
23 King TE Jr, Safrin S, Starko KM, et al. Analyses of efficacy end points in a controlled trial of interferon-c1b for idiopathic pulmonary fibrosis. Chest 2005; 127: 171–177.
24 Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: The prognostic value of longitudinal functional trends. Am J Respir Crit Care Med 2003; 168: 531–537.
25 King TE Jr, Tooze JA, Schwarz MI, et al. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model.Am J Respir Crit Care Med 2001; 164: 1171–1181.