The Questionable Efficacy of Pirfenidone in IPF

To the Editor:

Azuma and colleagues (1) report that pirfenidone treatment improves vital capacity and prevents acute exacerbations in patients with idiopathic pulmonary fibrosis (IPF) but fails to improve end-exercise hypoxemia in this population. Given the paucity of data from randomized, controlled trials in IPF, this investigation might have added important information regarding a promising therapy. Unfortunately, several serious design and methodologic issues limit the inferences that can be drawn from this study.

First, selection of the subjects was clearly biased. Randomization occurred before identification of an eligible population. By excluding the 27 subjects who were unable to complete the six minute exercise test (6MET) at baseline, the investigators lost the benefits of randomization, including prevention of confounding (2). Second, using an unvalidated test (the 6MET) as a primary outcome limited the assessment of the intervention. More troubling from a methodologic view, however, was the differential assessment of the 6MET. Every subject had a walking speed “tailored to their comfort,” ranging from 40 to 80 m/min, and was monitored for desaturation until a nadir SpO2 was reached. Clearly, the work required to reach a nadir while walking at a speed of 80 m/min is different from the work required to reach a nadir while walking at 40 m/min. Thus, even the trivial (but statistically significant) difference in lowest SpO2 attained in the subgroup treatment arm. Although the authors state that the study was stopped for safety, the study was actually stopped for “superiority” of pirfenidone based upon better outcomes (fewer acute exacerbations of IPF) in the treatment arm.

The clinical significance of acute exacerbations of IPF is unclear, as neither the incidence nor the impact of acute exacerbations upon the natural history of the disease is known. Thus, stopping the trial based upon five events of uncertain significance in the placebo arm is dubious. Since the Data and Safety Monitoring Board (DSMB) was integral to this decision, full disclosure regarding membership should be reported (3). Ultimately, despite the authors’ call for a “well designed phase III clinical trial,” stopping the trial early due to the “superiority” of pirfenidone will make further placebo-controlled trials difficult to justify.

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Stephen C. Mathai
Albert J. Polito
Johns Hopkins University
Baltimore, Maryland

References


Poor Choice of Primary Outcome in a Clinical Trial of Pirfenidone in Patients with IPF

To the Editor:

We were surprised that Azuma and colleagues chose to use the amplitude of oxyhemoglobin desaturation during a 6-min walk test (6MWT) as their primary endpoint in a recent placebo-controlled trial of pirfenidone in patients with IPF (1). This outcome has not been validated as an endpoint for therapeutic efficacy and has several additional limitations.

First, use of this endpoint required patients to complete a nonstandardized variant of the 6MWT on a treadmill set at a predetermined and individualized pace. Second, one might have predicted that it would be very difficult to detect worsening in the amplitude of desaturation during the course of the trial. A small but sustained drop in SpO2 from the mean baseline value of 87 to 84% would be enough to prevent completion of the test, because the protocol specified that the test be stopped when SpO2 fell below 80% or remained between 80 and 85% for 30 s.

In fact, the authors found that 25% of their study population was unable to complete the follow-up 6MWT. The decision to analyze separately patients that completed the 6MWT subverts the process of randomization, and the statistically significant differences they found do not seem to be clinically important.

Third, in the section describing their power calculations, the authors do not tell us what effect size they were hoping to detect, so we are left to wonder what constitutes a clinically important improvement in fall of SpO2. Given that pre-existing fibrosis is unlikely to respond to therapy and, as these authors found, anticipated efficacy will be in slowing, not reversing deterioration, it is hard to imagine a clinically relevant efficacy that would reliably be detected by the inherent limitations of this endpoint. Finally, Eaton and coworkers recently showed that amplitude of desaturation during 6MWT had poor reproducibility (SD/mean value = 42.5%) and correlated poorly with 6MWT distance (2).

Other outcomes in this study are more informative. The finding of a reduction in acute exacerbations is intriguing; and while in our opinion this result did not warrant early cessation of the trial, it is consistent with results of a published trial of γ interferon in IPF (3) and suggests that the efficacy of current therapies may lie in reducing exacerbations and mortality, rather than slowing the progressive decline in lung function characteristic of this disease.

Conflict of Interest Statement: Neither of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Joseph Levitt
Stanford University Medical Center
Stanford, California

Michael K. Gould
VA Palo Alto Health Care System
and
Stanford University
Palo Alto, California

References


From the Authors:

Several of Mathai and Polito’s and Levitt and Gould’s concerns about our paper have already been addressed in the article itself and in the editorial that accompanied it (1, 2).

While we agree that the study would have revealed further insights regarding the safety and efficacy of pirfenidone had it not been aborted, the ethical issues raised by the Data Safety Monitoring Board’s (DSMB) recommendation for the early cessation of the trial should be appreciated. The patients and clinicians in Japan are sensitive to the diagnosis of acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) and are well aware of this clinical scenario ever since it was first described in Japanese patients with IPF (3). Clinicians are increasingly becoming aware of AE as a fatal complication in the clinical course of IPF. In fact, an acute clinical deterioration preceded death in 47% of patients who died with progressive IPF (4, 5). Thus, recognition of the occurrence of AE in patients with IPF has important implications and is clinically relevant. However, the criteria for definition of AE in IPF need to be established by an international consensus among experts. Since the efficacy of a treatment regimen for IPF in reducing the occurrence/frequency of AE and consequent improvement in survival is yet to be determined, we were cautious in reporting our findings as encouraging and never concluded that pirfenidone was “superior” as alleged. In our study, a modified version of the criteria for AE used by Kondoh and coworkers (3) was defined and prespecified. Thus the DSMB’s recommendation to stop the trial is far from “dubious.”

Mathai and Polito have misinterpreted the data regarding the randomization of the eligible population. Levitt and Gould were also concerned regarding this. An enrollment center determined and ascertained that all subjects enrolled in the study met the prespecified eligibility requirements before randomization occurred. The eligibility criteria did not depend on the subject’s ability to complete the 6-min exercise test (6MET). Thus, all eligible patients (including the 27 patients in question) were entered in this study, randomized, and analyzed as the full analysis set. Based on prespecifications, we amended our design at the beginning of the study and proactively decided to perform the analysis in this subset of patients. We have emphasized this in the article and the data for all of the eligible population have been presented as primary data.

The power calculation in determining the sample size was based on simulations; the sample size was prespecified to be 90 patients. This minimum number of patients provided statistical power of approximately 0.9 to detect assumed efficacy at the significance level of 0.025 and maintained the power greater than 0.8 assuming some patients may drop out.

A decrease in SpO2 during exertion is a characteristic clinical feature of IPF. In this regard, oxygen desaturation using SpO2 measurements during the 6-min walk test (6MWT) and a modified version, the timed walk test, have been associated with survival in the IPF population in two recent studies (6, 7). Our decision in choosing the primary endpoint was based on the encouraging, but unpublished, results of an ongoing study (8).

In this prospective study, end exercise SpO2 change in SpO2 during exercise, walk distance and walk velocity were strongly correlated with survival in patients with IPF followed for five years (7). While the recently published study by Eaton and coworkers (9) raises potential concerns in utilizing and assessing SpO2 measurements obtained during the routinely used 6MWT, a steady state exercise study (the 6MET) was used in the pirfenidone study. Hence, Eaton and coworkers’ results cannot be extrapolated to the findings with the 6MET used in our study.

Anticipating reproducibility problems in the 6MWT in the Japanese patients, we opted for the steady state 6MET (10). The protocol was followed per prespecifications. Since the speed chosen by the individual patient at baseline for the 6MET was kept the same during the follow-up 6MET, the physical burden associated with the 6MET was standardized for each patient. To investigate if the walking speed affected the lowest SpO2, we have evaluated the mean changes of the lowest SpO2 from baseline to the 6th and 9th month among the groups defined by the treadmill speed with one-way ANOVA. Equality was not rejected for the values observed at 6th and 9th month follow-up (p = 0.2114 and p = 0.4732, respectively). There was no significant difference in the distribution of the treadmill speed between pirfenidone and placebo groups (p value of the Wilcoxon rank-sum test was 0.9683). Nevertheless, the limitation of utilizing this endpoint has been acknowledged and discussed (1, 2). It must be emphasized that conventionally used measures of the functional status in patients with IPF were not omitted as they were assessed as secondary endpoints in this study.

The issue regarding the disclosure of the membership of the DSMB is an appropriate one. The following were the members of the DSMB:

1. Shigeru Tsukagoshi, M.D., Representative, Association for the Clinical Pharmacology and Drug Development, Tokyo.
2. Keiichi Nagao, M.D., Professor, Safety and Health Organization, Chiba University, Chiba.
3. Aiyoshi Kondo, M.D., Professor, Niigata Railway Health Check Center, Niigata.

It should be reiterated that this was a phase II clinical study and not a definitive, phase III clinical trial. The signals and lessons from this study have provided useful clinical information for better design and choice of appropriate endpoints for IPF clinical trials. The “call” for a well-designed phase III clinical trial is thus valid. The difficulty and feasibility of conducting a real placebo-controlled trial (i.e., a control population without any treatment) is independent of the results of this study and a subject for a different debate. A placebo-controlled phase III clinical trial using pirfenidone in Japanese patients is already well underway. It is hoped that the results of this ongoing study will clarify the concerns raised in the phase II study.

This letter is submitted on behalf of the Japanese IPF study group and my coinvestigators.

**Conflict of Interest Statement:** G.R. received $1,000 in 2002 from Shionogi, $500 in 2003 from Intermune as a consultant, and $2,500 in 2004 from Intermune as an Advisor for pirfenidone studies in idiopathic pulmonary fibrosis.

**References**

surveillance of beryllium-exposed workers. Detecting a disease in its early stages before large reductions occur in function is beneficial as identified by Cullen and coworkers, in a previous paper (5). The experience with DOE workers shows that LPT testing provides the benefit of early detection. Longer follow-up in the DOE group, as with the NJMRC cohort, is likely to yield an increase in those with significant physiologic impairment. Considering the recent confirmation of the risk to workers in industries using low percentage beryllium alloys (6), even workers with relatively low exposures should be tested.

Conflict of Interest Statement: T.K.T. is a medical consultant to the Dept. of Labor Energy Employees Occupational Illness Compensation Program and advises on medical aspects of workers’ beryllium claims. He was also paid as an expert on a panel evaluating the use of the beryllium lymphocyte proliferation test convened by Exponent and paid for by Brush Wellman, Inc. L.P., was the Chair of the Current Worker Beryllium Surveillance Program for Rocky Flats Workers. The program was managed by the Occupational and Environmental Health Program at National Jewish Medical Center. He received approximately $500–$1,000 per year for 3.5 years as the Panel Chair. He also received travel expenses, and food and lodging. He was a Visiting Professor and Lecturer at National Jewish Medical Center in 1999 and received $500.

TIM K. TAKARO
University of Washington
Seattle, Washington

LEW PEPPER
Boston University
Boston, Massachusetts

References

From the Authors:
We thank Drs. Takaro and Pepper for their letter and agree with their conclusions supporting medical surveillance using the BeLPT. The substantial number of cases of CBD and BeS that they report in the DOE cohort supports Dr. Cullen’s statement in his editorial accompanying our paper that “the blood BeLPT has now met the first of three critical challenges for a screening test; that those testing positive have a high likelihood of developing CBD” (1). Epidemiologic studies have shown that an average of 50% (range, 14–100%) of individuals with abnormal BeLPTs have CBD on initial clinical evaluation. Our study of surveillance-identified BeS addressed the clinical fate of the remainder: workers who had BeS without evidence of CBD. Those workers progress to CBD at a rate of 6 to 8% per year (2).

We agree with Drs. Takaro and Pepper that Cullen’s editorial is wrong to suggest that our subjects lack the “associated clinical manifestations of CBD.” They correctly point out that nine patients who progressed to CBD showed a significant decline in DLCO and V0max. Only 11 of the 17 patients who progressed to CBD had the opportunity for follow-up evaluations. It is
notable that all 11 showed some objective, physiologic decrements over the average 4.7-yr follow-up period, with one patient requiring corticosteroid treatment. These results address the second screening test “hurdle”: “showing that patients diagnosed with CBD clinically manifest disease." Drs. Takaro and Pepper inquired about the characteristics of workers diagnosed with CBD at baseline who were not part of this longitudinal study. We have been following more than 150 surveillance-identified patients with CBD and are currently analyzing longitudinal clinical data. This cohort will allow us to determine the progression of physiologic measures in CBD over time.

As Drs. Takaro and Pepper note, a separate publication by Cullen and colleagues (3) showed that treatment with corticosteroids is beneficial in CBD—a finding that is supported by other case series (4, 5), thus addressing the third hurdle for a screening test: “intervention made after a positive test has the potential to change the natural history.”

The letter from Drs. Takaro and Pepper supports the need for continued surveillance with the BeLPT for former and current workers, as well as to clinically follow those diagnosed with BeS and CBD. The case supporting the use of medical surveillance in secondary prevention and in aiding primary prevention strategies is clear.

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Lee S. Newman
Margaret M. Mroz
Ronald Balkissoon
Lisa A. Maier
National Jewish Medical and Research Center
Denver, Colorado

References

Blood Carbon Monoxide Will Increase from a Decline in Pulmonary Function Alone

To the Editor:

Yasuda and colleagues recently reported increased levels of carboxyhemoglobin (HbCO) in patients with COPD and suggested that the increase resulted from increased endogenous production of CO caused by "lung and systemic inflammation and production of reactive oxygen species” (1). No consideration was given to the effect of the major alterations of gas exchange in COPD on the HbCO level that would be expected without any change in the endogenous production in COPD. Yet, we know from the classical work of Coburn, Forster, and Kane (2) that a decrease in alveolar ventilation, a decrease in the carbon monoxide diffusing capacity (DLCO), or a decrease in the capillary oxygen tension would cause an increase in HbCO with no change in production. The patients in the current study had a significant increase in the arterial PCO2 (53.5 compared with 40.5 mm Hg in controls), compatible with a decrease in alveolar ventilation, and a significant decrease in arterial PO2 (64.4 compared with 90.2 mm Hg), compatible with a decrease in capillary O2 tension. DLCO measurements were not reported, but it is highly likely that DLCO would have been reduced in the patients studied. Thus, the patients of the present study would have had elevated HbCO levels as a result of the abnormal pulmonary function alone. It should be apparent that without actual measurements of the endogenous production, we cannot learn any more about inflammation from an increase in HbCO than we could about endogenous CO2 production from an increase in arterial PCO2. Either could become elevated without a change in endogenous production from a decrease in alveolar ventilation alone.

There are methods to measure the endogenous production of CO (3), and it has been reported that increased endogenous CO production occurs in patients with severe sepsis (4); but these methods were not applied in the current study. The authors used the arteriovenous HbCO concentration differences in an attempt to gain insight into CO production, but it is highly unlikely that these differences reflect endogenous production. The affinity of CO for hemoglobin is so great that there is a negligible arteriovenous difference (5). The apparent arteriovenous difference found in the current study is likely the result of a dependence of the spectrophotometrically measured HbCO on the difference in the oxygen tension between venous and arterial blood (6).

Conflict of Interest Statement: None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Solbert Permutt
David B. Pearse
Johns Hopkins University
Baltimore, Maryland

References

From the Authors:

We thank Drs. Permutt and Pearse for their letter on our article demonstrating that increased arterial carboxyhemoglobin (HbCO) concentrations may relate to severity in patients with chronic obstructive pulmonary disease (COPD) because of lung and systemic inflammation and production of reactive oxygen species (ROS) (1). Although we could not measure DlCO in all patients with COPD and did not mention this in our study (1), DlCO predicted (%) in 12 of 58 patients with COPD under stable conditions was significantly lower than that (mean ± standard error, 53 ± 12 vs. 82 ± 6%, p < 0.0001, Student’s t test) in 9 of 61 control
subjects. Therefore, as suggested by Drs. Permutt and Pearse, and by Dr. Montuschi and coworkers (2), increased arterial blood HbCO concentrations in patients with COPD may partially reflect decreased carbon monoxide (CO) clearance due to the presence of significant airflow obstruction and limited alveolar ventilation (3). On the other hand, many articles have demonstrated that an increase in oxidative stress in the lung plays a key role in pathogenesis of COPD (4–6). Furthermore, systemic inflammation and production of ROS in the extrapulmonary organs, including muscles, have been reported in patients with COPD (7, 8). We measured the levels of serum lipid peroxide (LPO), a byproduct of oxidized unsaturated fatty acid in the presence of ROS, and found that the LPO levels in 58 patients with COPD during exacerbations (5.6 ± 0.4 nmol/ml) were significantly higher than those in patients with COPD at the stable conditions (2.3 ± 0.3 nmol/ml, p < 0.0001, Student’s t test), and those in 61 control subjects (1.4 ± 0.1 nmol/ml, p < 0.0001, Student’s t test). Furthermore, arterial blood LPO levels significantly correlated with arterial blood HbCO concentrations in patients with COPD (1). The difference between LPO levels during exacerbations and under stable conditions (5.8 patients with COPD (3.3 ± 0.2 nmol/ml) was also correlated with the difference of arterial HbCO concentrations between exacerbations and under stable conditions (0.28 ± 0.03%, r = 0.73, p < 0.0001, linear regression analysis), although we did not mention this in our article (1). HO-1, an inducible form of heme oxygenase, catalyzes heme to biliverdine and endogenously produces CO (9). These findings suggest that increased arterial HbCO concentrations might relate to the production of ROS, which increase HO-1.

Proinflammatory cytokines, such as tumor necrosis factor-α, interleukin-1β, and nitric oxide (NO), also increase HO-1 production (9). Montuschi and coworkers (2) reported increased levels of NO and CO in exhaled air of patients with COPD, and the increased levels of exhaled CO in patients with COPD in our article are consistent with their report. Furthermore, increased numbers of HO-1–positive inflammatory cells have been demonstrated in induced sputum samples in patients with COPD at the onset of acute exacerbations compared with the numbers after remission (6). These findings suggest that the increase in arterial blood HbCO concentrations may be also due to endogenous CO production in COPD (2). The production of endogenous CO might be associated with upregulated HO-1 and NO production (2, 6) in the lungs through inflammation and production of ROS (4, 5), and in extrapulmonary organs through systemic oxidative stress (7, 8).

Drs. Permutt and Pearse also mentioned the use of the arteriovenous (a-v) HbCO concentration difference to detect the site of endogenous CO production, and the high affinity of CO to hemoglobin. We agree that blood oxygen tension and fetal HbCO affect spectrophotometrically measured HbCO concentrations (10), as they mentioned. However, as we demonstrated in a previous study (11), a-v HbCO differences were observed in patients with inflammatory lung diseases, including bronchial asthma and pneumonia. On the other hand, significant a-v HbCO differences were not observed in patients with COPD, which is also an inflammatory lung disease (1). These findings suggest that mechanisms other than the differences in the oxygen tension between venous and arterial blood (12) might be also associated with a-v HbCO differences in patients with inflammatory pulmonary diseases. The increased systemic oxidative stress (7, 8) in patients with COPD might mask the a-v HbCO differences in such patients (1). Further study is needed to clarify the relationship between endogenous CO production and a-v HbCO differences.

Increased arterial HbCO concentrations in patients with COPD might be caused not only by hypoventilation, including decreased alveolar ventilation, but also by endogeneous production of CO through the upregulation of HO-1 associated with oxidative stress and NO.

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HIROYASU YASUDA
MUTSUO YAMAYA
KATSUOSHI NAKAYAMA
HIDE TADA SASAKI
Tohoku University School of Medicine
Sendai, Japan

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