

**PILOT™ MISSION
STATEMENT**

PILOT™ is a national education initiative designed to provide physicians with a comprehensive continuing medical education program that focuses on the early and accurate diagnosis of idiopathic pulmonary fibrosis (IPF), while addressing educational objectives critical to optimizing disease intervention and management.

UPDATE ON EXPERIMENTAL THERAPIES AND CURRENT CLINICAL TRIALS
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Idiopathic pulmonary fibrosis (IPF) is a poorly understood disease with an equally poor outcome and an associated mean survival rate of only about 2.8 to 4 years.¹ There are no proven effective therapies for IPF and therefore the treatment of these patients remains controversial. In a consensus statement published in 2000, the American Thoracic Society (ATS) and European Respiratory Society (ERS) suggested combined therapy with steroids and either azathioprine or cyclophosphamide for patients who understand the benefits and risks of this treatment.² This combination therapy has commonly been referred to as "conventional therapy," despite the paucity of supportive data. Since the ATS/ERS statement, there has been little published literature to support the ongoing use of conventional therapy. There have been no further studies published attesting to the utility of azathioprine and steroids; however, 2 more recent studies have evaluated the combination of cyclophosphamide and corticosteroids and have confirmed no benefit to this form of therapy.^{3,4} The lack of response to these agents is not altogether surprising, considering that the characteristic pathologic features of IPF typically lack significant inflammation. Since other mechanisms have been identified that appear to be important in the genesis and propagation of the disease, new therapies targeting these pathways mandate further investigation and study.⁵ A number of such studies are currently planned or underway, or have been completed.

When assessing any therapeutic trial, there are 2 aspects to the data that need to be considered: first, how robust is the evidence and, second, what is the strength of the benefit. One of the issues raised by the first study of interferon gamma-1b (IFN γ -1b) is what constitutes an adequate surrogate of survival, and therefore a plausible endpoint by which to assess benefit. Furthermore, any benefit needs to be assessed in the context of "net benefit." This concept has particular relevance in relation to "conventional" therapy, where the side-effect profile might outweigh any salutary effects. It does appear that a decrease in the FVC of >10% is a useful surrogate for mortality. However, with spirometry recorded every 3 months, only 60% of patients met this criterion prior to their demise. Therefore, at this

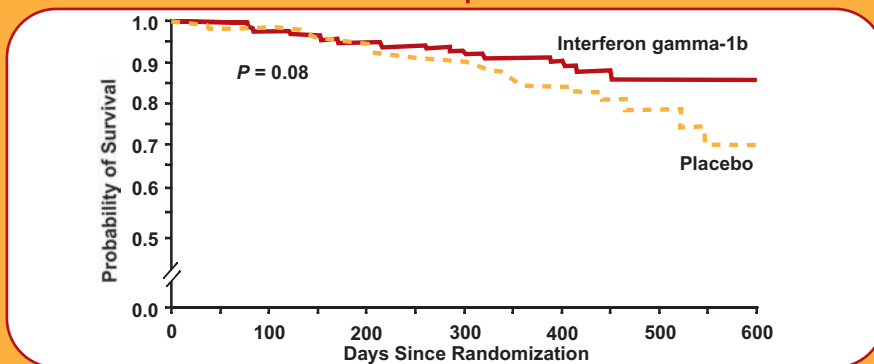
point in our understanding and monitoring of the disease, the best endpoint for IPF studies remains mortality.²

What is a practitioner to do with these difficult patients when there are no proven effective therapies? Foremost, a commitment is required by the pulmonary community to enroll patients into the available prospective therapeutic studies. This is essential to limit the period of empiric practice that currently exists due to the lack of quality evidence for effective therapies. How is such an approach tenable in this era of evidence-based medicine (EBM)? The latest paradigm of EBM includes a trimodal approach, where the clinical expert needs to account for each individual patient's clinical state and circumstance, draw on the available research evidence, and also factor in the patient's preference. This latter component should take precedence and therefore for those patients who wish to participate in the accrual of needed evidence or with no other available therapeutic recourse, enrollment in a study might be the most attractive of limited options. By the same token, for those patients who do not qualify or do not wish to be in a study, the available evidence

should be presented and a mutual decision made as to a course of action, which might range from no treatment to various forms of off-label therapies. Ideally, this discussion should happen only after the option of a treatment trial has been fully explored.

Interferon gamma-1b (IFN γ -1b)

IFN γ -1b has recently advanced to the fore of so-called experimental therapies for the treatment of IPF. The first large randomized, double-blind, controlled study of this agent was based on a small pilot series and generated results that remain controversial.^{7,8} Three parameters constituted the primary endpoint of this study: first, a decrease in the FVC of >10%; second, an increase of the A-a gradient of >5 mm Hg; and third, death. This was a negative study based on these primary endpoints. However, most of the patients satisfied the primary endpoint by way of the physiologic parameters. Once these were abstracted and mortality alone was scrutinized, there did appear to be a trend towards a survival benefit in the IFN γ -1b group in the intent-to-treat analysis ($P = 0.08$) (Figure 1). This mortality benefit was more apparent in post-hoc subgroup analyses

**FIGURE 1.
KAPLAN-MEIER ESTIMATE OF OVERALL SURVIVAL AMONG
PATIENTS TREATED WITH IFN γ -1b OR PLACEBO**

No. at Risk

Interferon gamma-1b	162	158	154	144	83	29	4
Placebo	168	165	159	142	80	27	4

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{Continued from page 1}

of patients with milder disease. This study revealed previously unappreciated information on the natural history of IPF.⁹ It also provided the foundation for the follow-up study, which has been designed to further evaluate the apparent survival benefit. This study is currently underway through an international collaborative effort in the form of the INSPIRE study.¹⁰

N-acetylcysteine (NAC)

N-acetylcysteine is a precursor of glutathione that also scavenges reactive oxygen species, including hydrogen peroxide, hydroxyl radical, and hypochlorous acid. Excessive oxidant stress may contribute to parenchymal injury and interstitial fibrosis. Levels of glutathione, the major antioxidant in the lung, are reduced at the alveolar epithelial surface in IPF patients.¹³ Therefore, there appears to be good biologic plausibility to support the use of NAC in IPF.

N-acetylcysteine was recently studied through the Idiopathic Pulmonary Fibrosis International Group Exploring NAC I Annual (IFIGENIA) trial, a randomized, double-blind, controlled study conducted in 7 European countries. The results were presented at 2 international meetings and the manuscript is pending publication.¹¹ The IFIGENIA trial included 184 patients with IPF who were randomly assigned to conventional therapy with prednisone and azathioprine versus conventional therapy plus NAC 600 mg 3 times a day. Eligibility criteria included an age range of 18–75 years, disease of at least 3 months duration, dyspnea score ≥ 2 out of a maximal 20, forced vital capacity (FVC) $< 80\%$ of predicted (or TLC $< 90\%$ of predicted), and DL_{co} $< 80\%$ of predicted. The changes in FVC and DL_{co} at 6 and 12 months were evaluated as primary efficacy endpoints.

NAC administered in conjunction with immunosuppressive therapy was associated with a significantly lower rate of decline in the FVC and DL_{co} at 12 months as compared to placebo plus immunosuppressive therapy.¹¹ At 12 months, the

absolute differences between treatment groups for FVC and DL_{co} were 9% ($P = 0.02$) and 24% ($P = 0.003$), respectively. Despite the effects on pulmonary function, NAC did not significantly improve survival. Seven of 80 patients (8.8%) in the NAC group and 8 of 75 patients (10.7%) in the placebo group died during the course of the study. Moreover, NAC did not affect a variety of secondary efficacy endpoints, including dyspnea score and health status. It remains unclear whether the physiologic benefits observed in the study represent a true therapeutic effect or arguably, an attenuation of a potentially negative effect of prednisone/azathioprine on pulmonary function.¹² This study underscores the importance of a true placebo arm and endpoint selection. Although it is a positive study based on the prespecified endpoints, it is unclear if the difference in the global rate of decrement in lung function will ultimately translate to a benefit for individual patients. However, as opposed to “conventional” therapy, the side-effect profile of NAC is relatively benign and therefore the magnitude of its benefit need not be great in order to justify its use. Ideally, further studies with placebo controls will be necessary to confirm these findings and to clarify the role of NAC in the treatment of IPF.

Etanercept

Etanercept is a recombinant fusion protein that binds with tumor necrosis factor alpha (TNF- α), a cytokine that has been shown to stimulate fibroblast proliferation and collagen synthesis via tumor growth factor beta (TGF- β) and PDGF pathways.¹⁴ Therefore, blocking TNF- α may be a useful therapeutic strategy in IPF. Etanercept was recently studied in a randomized, double-blind, placebo-controlled Phase 2 study of IPF patients. Eligibility for this study was defined by worsening dyspnea in conjunction with worsening oxygenation, a worsening chest radiograph, or lack of improvement in the FVC or DL_{co}. Entry criteria included a FVC $\geq 45\%$, a DL_{co} $\geq 25\%$, and a PaO₂ ≥ 55 mm Hg. The results of this study were presented at the American College of Chest Physicians meeting in Montreal in November 2005.¹⁵ A total of 87 patients were enrolled. There was

no significant difference in the rate of change of physiologic indices including the FVC, TLC, DL_{co}, A-a gradient, and 6 minute walk test (6MWT). However, in post-hoc analysis there was trend toward a difference in the combined exploratory endpoint of death or a decrease in the FVC of $>10\%$, in favor of the treatment group (33% versus 55%, $P = 0.052$). These results will need to be verified in a larger Phase 3 study.

Pirfenidone

Pirfenidone is a unique compound that inhibits TGF- β -induced collagen synthesis in lung fibroblasts and blocks the mitogenic effects of other profibrotic growth factors and cytokines.¹⁴ This agent has been studied previously in 2 open-label studies, and more recently in a large prospective double-blind trial from Japan in which 107 IPF patients were randomly assigned to receive either pirfenidone or placebo.¹⁵ After 6 months of treatment, pirfenidone showed a trend for improving the primary efficacy endpoint, which was the lowest oxygen saturation (SpO₂) measured by pulse oximetry during a 6MWT ($P = 0.07$). In addition, pirfenidone reduced episodes of acute exacerbation of IPF ($P = 0.003$) and improved the FVC ($P = 0.037$) relative to placebo. A Phase 3 study of pirfenidone is planned in the USA in 2006.

Imatinib mesylate

Imatinib mesylate is an inhibitor of the c-Abl tyrosine kinase that targets both platelet-derived growth factor and transforming growth factor-B through independent pathways. Both of these profibrotic cytokines are thought to play an integral role in the potentiation of lung fibrosis.¹⁶ The utility of this agent in the treatment of IPF is currently being explored in a randomized, double-blind, placebo-controlled Phase 2 trial. The primary endpoint will be IPF progression defined as a $\geq 10\%$ decline in FVC or death. Enrollment of approximately 120 patients for this study is now complete and follow up will continue for 2 years before the results will be analyzed.

Bosentan

Bosentan is a dual endothelin receptor antagonist that is approved for the treatment of pulmonary arterial hypertension. In addition to its vasoactive properties, endothelin-1 (ET-1) also stimulates fibroblast proliferation and collagen synthesis.¹⁸ Elevated levels were described in the BAL fluid from patients with IPF.¹⁹ Bosentan is being evaluated in a randomized, double-blind, placebo-controlled, multicenter study of patients with IPF. Eligible patients must have a FVC $\geq 50\%$, a DL_{co} $\geq 30\%$, and PaO₂ ≥ 55 mm Hg. The efficacy of bosentan will be evaluated based on the change from baseline in 6MWT. This study has been closed and results should be available soon.

Therapies for pulmonary arterial hypertension (PAH)

Although bosentan is being studied in IPF primarily for its antifibrotic properties, any benefit might be through its effects on the pulmonary vasculature.

TABLE 1.
POTENTIAL AGENTS FOR TREATMENT OF IPF

Drug	Mechanism	Status
IFN γ -1b	Antifibrotic and immunomodulatory cytokine	Phase 3 ongoing (INSPIRE)
N-acetylcysteine	Antioxidant	Pending publication (IFIGENIA)
Etanercept	TNF- α blocker	Phase 2 completed, results presented
Pirfenidone	Unknown	Phase 3 study planned 2006
Imatinib mesylate	c-Abl and PDGF receptor tyrosine kinase inhibitor	Phase 2 study closed, results awaited
Bosentan	Endothelin ET _A /ET _B receptor antagonist	Phase 2 study enrollment complete
Inhaled iloprost	Therapy for PAH	Phase 2 study currently recruiting (ACTIVE)

The prevalence of pulmonary hypertension in patients with IPF has been reported to range between 25% and 85% of patients and has been shown to have a significant impact on survival and functional status.^{20,21,22} In addition to bosentan, there are 4 other FDA-approved medications for the treatment of PAH. Of these, sildenafil and inhaled iloprost are being studied as potential therapies for IPF. Inhaled iloprost is being studied through the ACTIVE trial, with the 6MWT as the primary endpoint. The criteria of this study have been broadened to include patients with more severe disease, including patients with FVC's > 40% predicted. Sildenafil is being studied in a short-term, double-blind crossover study with the 6MWT once again providing the primary endpoint.²³

In conclusion, it is the dawn of a new era in the management of IPF patients with multiple trials of promising agents in various stages of implementation. Our current ability to effectively and uniformly treat patients with IPF is limited by a lack of consensus and conclusive evidence attesting to treatment efficacy. An integral aspect of evidence-based medicine is the accrual of the evidence and the opportunity to contribute to this process. Therefore, it is incumbent for all physicians in the field to continue to offer the option of enrollment in a trial to all patients with IPF. Only with such a concerted effort will all these studies be populated and results expedited to help guide future management of this devastating condition.

References

1. Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic fibrosis. *Am J Respir Crit Care Med.* 1998;157:199-203.

2. King TE Jr, Costabel U, Cordier J-F, DoPico GA, Du Bois RM, Lynch D, et al. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med.* 2000;161:646-664.
3. Zisman DA, Lynch JP, Toews GB, et al. Cyclophosphamide in the treatment of idiopathic pulmonary fibrosis. *Chest.* 2000;117:1619-1626.
4. Collard HR, Ryu JH, William W, Douglas WW, et al. Combined corticosteroid and cyclophosphamide therapy does not alter survival in idiopathic pulmonary fibrosis. *Chest.* 2004;125:2169-2174.
5. Selman M, King TE, Pardo A. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med.* 2001;134:136-151.
6. King TE Jr, Safran S, Starko KM, Brown KK, Noble PW, Raghu G, et al. Analyses of efficacy end points in a controlled trial of interferon γ -1b for idiopathic pulmonary fibrosis. *Chest.* 2005;127(1):171-177.
7. Ziesche R, Hofbauer E, Wittmann K, Petkov V, Block L-H. A preliminary study of long-term treatment with interferon gamma-1b and low-dose prednisolone in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 1999;341(17):1264-1269.
8. Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *N Engl J Med.* 2004;350(2):125-133.
9. Martinez FJ, Safran S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med.* 2005;142:963-967.
10. The INSPIRE trial: a study of interferon gamma-1b for idiopathic pulmonary fibrosis (IPF). Available at: <http://www.clinicaltrials.gov/ct/gui/show/NCT00075998>. Accessed April 13, 2005.
11. Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med.* 2005;353:2229-2242.
12. Hunninghake GW. Antioxidant therapy for idiopathic pulmonary fibrosis. *N Engl J Med.* 2005;353:2285-2287.

13. Kinnula VL, Fattman CL, Tan RJ, Oury TD. Oxidative stress in pulmonary fibrosis: a possible role for redox modulatory therapy. *Am J Respir Crit Care Med.* 2005;172:417-422.
14. Selman M, Thannickal VJ, Pardo A, Zisman DA, Martinez FJ, Lynch JP III. Idiopathic pulmonary fibrosis: pathogenesis and therapeutic approaches. *Drugs.* 2004;64(4):405-430.
15. Azuma A, Nukiwa T, Tsuboi E, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2005;171:1040-1047.
16. Daniels CE, Wilkes MC, Edens M, Kottom TJ, Murphy SJ, Limper AH, et al. Imatinib mesylate inhibits the profibrogenic activity of TGF- β and prevents bleomycin-mediated lung fibrosis. *J Clin Invest.* 2004;114(9):1308-1316.
17. IPF research. Available at: <http://www.coalitionforpf.org/IPFResearch/default.asp>. Accessed September 28, 2005.
18. Park S-H, Saleh D, Gaid A, Michel RP. Increased endothelin-1 in bleomycin-induced pulmonary fibrosis and the effect of an endothelin receptor antagonist. *Am J Respir Crit Care Med.* 1997;156:600-608.
19. Fagan KA, McMurtry IF, Rodman DM. Role of endothelin-1 in lung disease. *Respir Res.* 2001;2(2):90-101.
20. Shorr AF, Davies DB, Nathan SD. Outcomes for patients with sarcoidosis awaiting lung transplantation. *Chest.* 2002;122:233-238.
21. Lettieri CJ, Nathan SD, Barnett SD, et al. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest.* 2005;128:2393-2399.
22. Nadroos HF, Pellikka PA, Krowka MJ, et al. Pulmonary hypertension in patients with idiopathic pulmonary fibrosis. *Chest.* 2005;128:2393-2399.
23. Ghofrani HA, Wiedemann R, Rose F, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomized controlled trial. *Lancet.* 2002;360:895-900.

EXERCISE TESTING FOR INTERSTITIAL LUNG DISEASE

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The most common symptom associated with interstitial lung disease (ILD) is dyspnea on exertion. This symptom is difficult to measure and, more importantly, varies with the degree of exercise performed. If disease progresses, the degree of exercise tolerance invariably worsens. Usually, the deterioration in exercise tolerance is slow and gradual. Therefore, patients will gradually limit their activities and often report that dyspnea is unchanged. Only when a critical activity of daily living becomes impaired will patients report their worsening dyspnea to a physician.

Activities of daily living vary for each patient. Stair climbing, particularly when necessary for entry to the home or bedroom, is one important activity that is sensitive to change. The gradual transition from noticing some dyspnea at the top of the stairs while continuing onward to a pause at stair top is often the first symptom. Sensitive measures of recovery

during the stair-top pause include the number of sigh breaths required for dyspnea relief or the actual time of pause. This symptom has been noted by generations of physicians as a preoperative screening tool and has an advantage of being free for the asking.

Another sensitive measure of exercise tolerance includes treadmill or bicycle testing. As pulmonary rehabilitation becomes more widely used for interstitial lung disease, larger numbers of patients are engaging in formal exercise sessions in the home or gym after completing formal pulmonary rehabilitation. The goal of rehabilitation is to improve exercise capacity as a major component of quality of life. Quality-of-life improvements and measures of exercise capacity begin to plateau by six weeks of rehabilitation in most patients. At this time, measurements of exercise capacity on the treadmill provide meaningful insight into disease severity.

Many formal measurements of exercise capacity have been proposed as outcome measures for clinical trials. Most physicians find that a formal cardiopulmonary exercise test measuring maximal oxygen consumption ($\dot{V}O_2$ max) is too time consuming for routine clinical care, requires the presence of a physician, and requires costly monitoring equipment. Therefore, more clinically useful and less time-consuming tests have been developed.

Functional walk tests are exercise tests that measure functional status or capacity, mainly in the ability to undertake physically demanding activities of daily living.¹ They are considered objective measures that provide a means of monitoring response to treatment.² Compared to traditional laboratory indexes of exercise capacity such as cycle, treadmill, and step ergometry, walk tests

{Continued from page 3}

require less technical expertise and equipment, making them inexpensive and easy to administer. More importantly, they employ an activity that individuals use on a daily basis.³

There are several types of clinical exercise tests available for objective evaluation of functional exercise capacity. One of the most popular is the 6-minute walk test (6MWT). This test evaluates comprehensive and integrated responses of all systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism.⁴ The 6MWT is a practical, simple test that requires a 100-foot hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. The test measures the distance that a patient can quickly walk on a flat, hard surface within a 6-minute time period.

The 6MWT is a timed submaximal-walking (not running) test that is currently performed in many idiopathic pulmonary fibrosis (IPF) clinical trials in progress today. Standards for the 6MWT have been published,⁴ although much of the clinical experience in interstitial lung disease has been obtained in the years since the standards publication.

The walk requires a long hall or circular course that is free of interference. Baseline oxygen saturation, heart rate, blood pressure, and dyspnea score is recorded and repeated at the end of the walk. The walk is described to the patient as a maximal distance test to encourage walking as fast as possible. However, after the walk has begun, no other encouragement is allowed. The rule disallowing encouragement during the test was established for patient safety, since patients will be less likely to slow or stop in response to symptoms if there is verbal encouragement occurring continuously. Stopping is permitted if necessary, and the number of stops is recorded. The primary outcome of distance walked in 6 minutes is recorded after the course is well measured and adequately marked. Some clinics use small cones at the ends of the hall to assure the distance is accurate. The symptom limiting exercise distance is recorded.

Many clinics use the 6MWT over other testing modalities for exercise because patients can alter their stride and stop when necessary, assuring that the test approximates activities of daily living. Studies with COPD patients have shown that exercise distance is greater on a 6MWT than when treadmill speed is varied over 6 minutes, presumably because of the ability to speed and slow more rapidly.⁵ The walk distance is the primary variable for clinical trials because of the close correlation with VO₂ max and small standard deviation on repeated testing.⁶

There are problems with using data from the 6MWT to influence ILD treatment decisions. First, there is a learning curve associated with optimizing 6MWT distance. The guidelines suggest that two tests are sufficient to achieve a maximal walk distance, although it is not clear over what duration that learning is retained.

There is a lack of consensus concerning what to do about the oxygen desaturation that is very common in advanced lung diseases, including ILD. While desaturation to less than 88% on a room air 6MWT is associated with worse prognosis in IPF,⁷ the test can still provide meaningful longitudinal data in patients with desaturation. Since oxygen administration will improve exercise distance and blunt desaturation, comparable tests require the same amount of inspired supplemental oxygen. Some clinics stop patients and abort the walk when O₂ desaturation less than 80% occurs. The walk distance is then recorded and will obviously be shorter as disease progresses. The difficulty with this practice is that patients can walk more slowly and improve dropping O₂ saturations; therefore, additional variables are introduced into the test. This variation in the lowest recorded O₂ saturation makes this measurement suboptimal for clinical trial design.⁸ Most clinics do not stop patients because of desaturation as long as the patient is asymptomatic without chest pain, dizziness, or diaphoresis.

An additional limitation of the 6MWT is that the test is not sensitive when disease is mild. Since patients cannot run, the limitation of walking imposes a barrier to measuring cardiopulmonary performance. Walk distances greater than 1800 feet (550 meters)

are often associated with low dyspnea scores, implying that a more formal cardiopulmonary exercise test that records VO₂ max might be a better measure of exercise performance and disease activity.

Lastly, some tests are limited by physical factors other than dyspnea. Although generalized fatigue may be a symptom attributable to cardiac output limited by cor pulmonale, tests that are limited by knee or hip pain—common in the elderly or those with connective tissue diseases—should not be used to infer the activity of lung disease.

While the United States Food and Drug Administration has given the 6MWT some credibility for pulmonary hypertension, researchers of other disease states who choose the 6MWT as a primary outcome variable will need to validate this test for ILD. These studies are in progress at a number of ILD centers. Transition of the 6MWT from a clinical trials test of interest to the practicing pulmonary office will also require some validation. In summary, the 6MWT is a sensitive test that integrates a large number of physiologic variables that influence the course of interstitial lung disease. Interest in its use will grow when drugs with proven activity for IPF are available.

References

1. Guyatt GH, Thompson PJ, Berman LB, et al. How should we measure function in patients with chronic heart and lung disease? *J Chronic Dis.* 1985;38:517-524.
2. Singh S. The use of field walking tests for assessment of functional capacity in patients with chronic airway obstruction. *Physiotherapy.* 1992;78:102-104.
3. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. *Chest.* 2001;119:256-270.
4. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med.* 2002;166:111-117.
5. Stevens D, Elpern E, Sharma K, et al. Comparison of hallway and treadmill six-minute walk tests. *Am J Respir Crit Care Med.* 1999;160:1540-1543.
6. Eaton T, Young P, Milne D, Wells AU. Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. *Am J Respir Crit Care Med.* 2005;171:1150-1157.
7. Lama VN, Flaherty KR, Toews GB, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med.* 2003;168:1084-1090.

PILOT™ RESOURCE HUB

RECENT AND ONGOING TRIALS FOR IPF

Trial	Target	N	Primary Endpoints
Phase 3			
Interferon gamma GIPF-001	Multiple	330	Progression-free survival time
Interferon gamma INSPIRE trial (ongoing)	Multiple	800	Survival time
N-acetylcysteine (NAC) IFIGENIA trial	Oxygen radicals	184	Change in FVC, DL _{CO}
Phase 2			
Pirfenidone (ongoing)	Multiple	450	Time to disease progression
Thalidomide	Multiple	19	Safety, feasibility, efficacy
Iloprost	Multiple	50	Safety, 6MWT
Phase 1			
FG-3019	CTGF	21	Safety, tolerability, PK

<http://www.clinicaltrials.gov>. Accessed November 2005.
<http://www.coalitionforipf.org>. Accessed November 2005.
National Heart, Lung, and Blood Institute Strategic Plan. FY 2005-2009.

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