Variables Predict Long-Term Lung Prognosis

BY BRUCE JANCIN
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KEYSTONE, COLO. — A major and welcome recent development in interstitial lung disease is the greatly improved ability to prognosticate long-term outcomes in affected patients, Dr. Stephen K. Frankel said at a meeting sponsored by the National Jewish Medical and Research Center.

"Patients will come in to you and ask, 'Doc, how long do I have to live?' The last 2-3 years have taught us how to follow-up patients longitudinally and predict who'll do well and poorly—who has 2-3 years to live and who has potentially 15 years ahead of them," explained Dr. Frankel, assistant director of the interstitial lung disease program at the center, located in Denver.

What works best, physicians have learned, is an approach that incorporates a handful of variables, including high-resolution CT findings, exercise capacity, serial measurements of forced vital capacity, and lung biopsy results.

"All of these are basically complementary and additive. So we tend to follow all of these together to determine long-term outcomes and prognoses," he continued. These variables include:

▶ **Forced vital capacity.** This is the most reproducible physiologic variable. It's not the baseline number that's key to predicting long-term course, it's the change in FVC over the first 6 or 12 months of follow-up, he explained.

A study conducted by Dr. Frankel's colleagues at National Jewish on 81 patients with idiopathic pulmonary fibrosis (IPF) showed that those with a stable FVC over the first 6 months had a 5-year survival of 45%. IPF is the most common form of idiopathic interstitial lung disease.

In contrast, patients with a 10% or greater decline in FVC percentage predicted had a 5-year survival of only about 20%, while those with a 10% or more improvement in FVC percentage predicted had a 5-year survival of 70% (Am. J. Respir. Crit. Care Med. 2003;168:538-42).

Investigators have developed a CT fibrosis scoring system in which a high score independently conferred a 2.7-fold increased mortality risk.

This observation was confirmed in a recent double-blind placebo-controlled clinical trial of interferon g-1b in 330 IPF patients, in which a 10% or greater decline in FVC percentage predicted was associated with a 2.4-fold increased mortality risk (Chest 2005;127:171-7).

▶ **High-resolution CT.** Patients with CT changes that suggest fibrosis and scarring—namely honeycombing and reticulation—have worse outcomes than those with the ground-glass attenuation that indicates inflammation, he said. National Jewish investigators have developed a CT fibrosis scoring system in which a high score independently conferred a 2.7-fold increased mortality risk in a study of 315 IPF patients (Am. J. Respir. Crit. Care Med. 2005;172:488-93).

▶ **Six-minute walk test.** A modified version of this functional capacity test proved predictive of survival 2 years later. The significant predictors were walk distance and velocity, end-exercise saturation, and change in saturation with exercise (Eur. Respir. J. 2005;25:96-103).

▶ **Disease exacerbations.** Patients with mild to moderate IPF who underwent hospitalization for respiratory disorders had a more rapid disease progression and higher IPF-related mortality, Dr. Frankel said. Frequent hospitalizations may be a red flag supporting early referral for a lung transplant (Ann. Intern. Med. 2005;142:963-7).

▶ **Histologic pattern on lung tissue biopsy.** Patients with the bland-looking fibrosis that is characteristic of usual interstitial pneumonia have a markedly worse prognosis than patients who have nonspecific interstitial pneumonia and other inflammatory processes. Indeed, individuals with the histologic diagnosis of usual interstitial pneumonia were at 25.5 times greater mortality risk than those with nonspecific interstitial pneumonia in a prospective study of 39 patients treated with high-dose prednisone (Eur. Respir. J. 2002;19:275-83).

In patients unable to undergo lung biopsy, high-resolution CT serves as a reasonable proxy, Dr. Frankel said. ■

Interstitial Lung Disease Therapeutics Finally Get Traction

BY BRUCE JANCIN
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KEYSTONE, COLO. — Interstitial lung disease, long a sinkhole of therapeutic nihilism, has recently seen its first-ever flurry of randomized clinical trials—and while they haven't produced any therapeutic breakthroughs, promising leads abound, Dr. Stephen Frankel said at a meeting sponsored by the National Jewish Medical and Research Center.

The quest for novel, safe, and effective treatments for idiopathic pulmonary fibrosis (IPF) and other forms of interstitial lung disease is proceeding on two fronts. Just last year, the National Institutes of Health established the Idiopathic Pulmonary Fibrosis Network, also known as IPF-Net. National Jewish is one of 12 participating centers. IPF-Net investigators anticipate launching their first two NIH-sponsored clinical trials later this year.

In addition, the pharmaceutical industry has, in the past several years, developed great interest in interstitial lung disease. Major randomized controlled trials have recently been completed involving interferon gamma-1b, bosentan, *N*-acetylcysteine, and cyclophosphamide, noted Dr. Frankel of the interstitial lung disease program at National Jewish in Denver.

Here are the highlights:

▶ **Interferon gamma-1b.** The 300-patient Gamma Interferon for Pulmonary Fibrosis (GIPF 001) trial showed no significant difference between thrice-weekly interferon gamma-1b (Actimmune) and placebo in the primary combined end point of progression-free survival. However, secondary analysis suggested that the probability of survival at 600 days of follow-up was roughly 40% greater in the interferon group. Moreover, upon excluding patients with severe disease at baseline, the survival difference favoring interferon grew to nearly 80%.

On the basis of this encouraging mortality difference in GIPF 001, interferon gamma-1b's manufacturer, InterMune Inc., has funded the ongoing phase III International Study of Survival Outcomes in Idiopathic Pulmonary Fibrosis With Interferon Gamma-1b Early Intervention (INSPIRE) trial. The last of nearly 800 patients with IPF was recently randomized to interferon or placebo in the double-blind study, in which the primary end point is survival time.

▶ **Bosentan.** The rationale for studying bosentan (Tracleer) in fibrotic lung disease is that the drug targets endothelin, a key player in angiogenesis—and dysregulated angiogenesis is believed to be important in the development of fibrosis. Bosentan is already of proven efficacy in the treatment of primary pulmonary hypertension.

Actelion Pharmaceuticals Ltd. has funded two major Bosentan Use in Interstitial Lung Disease trials. BUILD-1, conducted in IPF patients, showed that the combined rate of death or disease progression was 22% with bosentan, compared with 36% with placebo—a 38% relative risk reduction—although there was no significant difference in the primary end point of 6-minute timed walk distance. Actelion plans to launch the phase III BUILD-3 trial in IPF patients next year. The study will focus on survival and disease progression.

BUILD-2 was a randomized trial of bosentan in scleroderma-associated interstitial lung disease. It was a true negative trial, with no benefit in survival, disease progression, 6-minute walk distance, or any other end point. No further studies of bosentan in scleroderma lung disease are planned.

▶ ***N*-acetylcysteine.** This supplement found in health food stores slowed IPF progression, compared with placebo in a randomized trial involving 155 patients who received azathioprine and prednisone as background therapy. The beneficial effect of *N*-acetylcysteine was reflected in vital capacity and the single-breath carbon monoxide diffusing capacity test (N. Engl. J. Med. 2005;353:2229-41).

However, a problem with the study was that the rate of decline in the placebo arm was faster than that seen in other studies in which azathioprine and prednisone were not used.

"The question becomes, do azathioprine and prednisone actually cause harm and *N*-acetylcysteine is preventing this harm? There's no way at this point to answer this question," Dr. Frankel said. "However, what one can say is that *N*-acetylcysteine is a well-tolerated over-the-counter agent and it's hard to argue against its use. Whether one wants to give it in conjunction with azathioprine and steroids requires a more detailed conversation with the patient," Dr. Frankel said.

▶ **Cyclophosphamide.** Use of this toxic drug resulted in a statistically significant but modest slowing of the rate of physiologic decline in lung function, compared with placebo in the 156-patient Scleroderma Lung Study. Forced vital capacity declined by 2.6% in 1 year in the placebo arm, compared with 0.3% with cyclophosphamide. The drug also resulted in improved skin thickness scores and dyspnea index. However, the price was a 19% incidence of leukopenia and 11% rate of hemorrhagic cystitis.

The Scleroderma Lung Study generated considerable excitement because cyclophosphamide now becomes the first therapy ever shown to affect scleroderma lung disease. Whether the modest benefit is worth the risks, however, is a matter for in-depth discussion between patient, pulmonologist, primary care physician, and rheumatologist, he continued.

Dr. Frankel noted that, in addition to the above completed randomized trials, major studies are either ongoing or planned for other novel potential therapies for interstitial lung disease. Among the agents under scrutiny are etanercept (Enbrel), inhaled iloprost (Ventavis), imatinib mesylate (Gleevec), antitransforming growth factor-β, and anticonnective tissue growth factor.

In addition, National Jewish will participate in a phase III U.S. clinical trial of pirfenidone this spring. Pirfenidone, owned by InterMune, is a novel antifibrotic agent, until now studied mostly outside the United States.

In response to an audience question, Dr. Frankel said that although he has no experience with imatinib in IPF, investigators participating in the ongoing clinical trial tell him they think they're seeing a dramatic effect. The data haven't been unblinded yet, but results should be available in about a year.

But even if imatinib and the other investigational therapies ultimately prove ineffective, the fact remains that contemporary therapy for interstitial lung disease is more promising than most physicians think.

"It's common to see a lot of nihilism about interstitial lung diseases such that patients are assumed to have a very poor prognosis and not respond to therapy. However, that's not necessarily true anymore. Entities such as hypersensitivity pneumonitis and primary connective tissue diseases are eminently treatable," Dr. Frankel said. ■