Idiopathic Pulmonary Fibrosis*  
Challenges and Opportunities for the Clinician and Investigator  
Jeffrey J. Swigris, DO; Ware G. Kuschner, MD, FCCP; Jennifer L. Kelsey, PhD; and Michael K. Gould, MD, MS, FCCP

Idiopathic pulmonary fibrosis (IPF) is a relentlessly progressive and typically fatal interstitial lung disease. Besides its grave natural history and prognosis, three aspects of IPF challenge clinicians and investigators: (1) recent changes in the conceptual framework and definition of IPF complicate interpretation of prior clinical investigations; (2) while most patients with suspected IPF do not undergo open-lung biopsy, clinical definitions that do not include biopsy criteria have not been validated prospectively; and (3) available treatments have not been shown to be effective. To optimize clinical care and facilitate clinical investigation, a major goal of IPF research should be to develop validated sets of clinical diagnostic and prognostic criteria. Studies have shown the diagnostic value of high-resolution CT scans and identified important prognostic variables; many of these observations await prospective validation. While previous therapeutic studies have been limited by small sample sizes, lack of a placebo control group, and insufficient attention to patient-centered outcomes, the recent study of interferon γ-1b demonstrated the feasibility of a large-scale, multicenter clinical trial in IPF. In this article, we discuss how overcoming challenges in IPF research will enable future investigators to conduct well-designed observational studies and clinical trials, whose meaningful results will advance our understanding of IPF, its management, and its impact on patients’ lives. (CHEST 2005; 127:275–283)

Key words: interstitial; lung diseases; pulmonary fibrosis

Abbreviations: CC = clinician’s choice; ES = equipoise stratified; HRCT = high-resolution CT; IIP = idiopathic interstitial pneumonia; IPF = idiopathic pulmonary fibrosis; NSIP = nonspecific interstitial pneumonia; OR = odds ratio; PPV = positive predictive value; UIP = usual interstitial pneumonia

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease characterized by progressive parenchymal fibrosis and ventilatory restriction. Studies suggest that inflammation does not play a prominent pathophysiologic role, and that alveolar epithelial injury directly results in lung fibrosis, perhaps explaining why conventional therapy with corticosteroids and cytotoxic drugs is rarely effective.1 Prognosis is poor; reported median survival is < 3 years.

In this article, we review some of the challenges that IPF presents to clinicians and clinical researchers. First, we briefly describe historical changes in the nomenclature of the idiopathic interstitial pneumonias (IIPs). We show how these changes, includ-
ing those generated by the recognition of nonspecific interstitial pneumonia (NSIP), have altered understanding of IPF and complicated the interpretation of prior clinical IPF research. Subsequently, we outline specific challenges and discuss research opportunities in the areas of diagnosis, prognosis, and therapy, and suggest directions for future clinical investigations.

CHALLENGES RELATED TO NOMENCLATURE

A potentially confusing and ever-changing nomenclature makes it difficult to interpret prior studies and hinders effective communication about patients with IPF. IPF belongs to a group of related but distinct interstitial lung diseases (IIP). While most of the IIPs can present similarly, each has a unique pathologic pattern that forms the basis for their current classification.²

An international multidisciplinary consensus committee² has proposed this standardized classification system, which includes seven diseases: (1) IPF, (2) NSIP, (3) cryptogenic organizing pneumonia, (4) acute interstitial pneumonia, (5) respiratory bronchiolitis-associated interstitial lung disease, (6) desquamative interstitial pneumonia, and (7) lymphoid interstitial pneumonia. While agreeing that histologic patterns distinguish these diseases better than other diagnostic criteria, committee members stressed the importance of integrating all available clinical, radiologic, and pathologic information to achieve a correct final diagnosis.

Committee members stated that identifying or excluding IPF should be the initial step in the diagnostic evaluation of a patient presenting with diffuse parenchymal lung disease, because of its markedly worse prognosis. If high-resolution CT (HRCT) of the chest does not reveal the typical findings of IPF, the committee advises performing a surgical lung biopsy, unless it is contraindicated. They stressed the importance of using precise terminology to distinguish clinical/radiologic/pathologic diagnoses (eg, IPF) from the corresponding patterns of lung injury (eg, usual interstitial pneumonia [UIP]).

Despite these efforts to implement uniform phraseology, new terms are already being created for IPF. For example, perhaps in an attempt to emphasize that a biopsy has been performed, various investigators have adopted the redundant term UIP/IPF (or IPF/UIP) for patients with IPF proven by biopsy. An essential feature of the current classification scheme is that, for a patient who has had a lung biopsy, an IPF diagnosis already implies the presence of a UIP pattern in at least one histologic specimen.³ The danger is that the term UIP/IPF will be applied to cases of IPF in which no biopsy has been performed, suggesting a degree of diagnostic certainty that may not be warranted.

For cases of lung fibrosis in which known causes have been excluded, we endorse IPF as the root term with other descriptors added in reference to how the diagnosis was made (Table 1). For example, if a patient with IPF has undergone lung biopsy, we use the term biopsy-proven IPF; for patients with IPF who have not undergone biopsy, we use the term clinical IPF. When speaking in general terms about patients with underlying conditions that explain their lung fibrosis, we prefer the term known-cause pulmonary fibrosis. When referring to the finding of a UIP pattern in the lung biopsy of such a patient, we recommend the term known-cause UIP pattern. The correlates of these terms in specific cases, as in rheumatoid arthritis, are rheumatoid arthritis-associated pulmonary fibrosis and rheumatoid arthritis-associated UIP pattern.

Unfortunately, prior classification schemes did not include the term IPF, prompting many people to inappropriately use the term UIP (which the schemes did include) to indicate a summary diagnosis. As a result, many patients suspected of having IPF, even those who did not undergo lung biopsy, were labeled inappropriately as having UIP. Also, many patients with diseases that explained the finding of UIP patterns on lung biopsy were wrongly labeled with IPF.

Thus, past studies of IPF should be interpreted with caution. Because of the confusing terminology and the imprecision of older classification systems, some participants in those studies had diseases other than IPF. Including subjects with these diseases (eg, connective tissue disease-associated pulmonary fibrosis or NSIP disease) resulted in overoptimistic conclusions about treatment response and prognosis, and almost certainly skewed the epidemiologic data for IPF.

Table 1—Terminology Regarding IPF and NSIP*  

<table>
<thead>
<tr>
<th>IIP Summary Diagnosis</th>
<th>Terminology Used in Reference to the Summary Diagnosis</th>
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<tbody>
<tr>
<td>IPF</td>
<td></td>
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<tr>
<td>Biopsy performed</td>
<td>UIP-pattern</td>
</tr>
<tr>
<td>No biopsy performed</td>
<td>N/A</td>
</tr>
<tr>
<td>NSIP (as an IIP, this implies an unknown cause)</td>
<td>NSIP-pattern NSIP disease</td>
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*N/A = not applicable.
Challenges Related to the Discovery of NSIP

One reason that classification schemes have become outdated is the discovery of NSIP. The presence of NSIP complicates the design of new studies and, like nomenclature, creates challenges to interpreting previous studies of patients with IPF. Katzenstein and Fiorelli described NSIP in 1994 as a “nonspecific” pattern of lung injury, consisting of varying degrees of inflammation and fibrosis that do not satisfy criteria for the histologic pattern of any other IIP. According to the most recent classification scheme, NSIP connotes both a pattern of lung injury as well as a particular IIP. To complicate matters, just as a UIP pattern is not specific for IPF, an NSIP pattern is not specific for NSIP (the disease).4

Many patients with an NSIP pattern of injury—either with an identifiable cause (which we refer to as known-cause NSIP pattern) or without (which we refer to as NSIP disease)—respond to corticosteroid therapy with stabilization or improvement (Table 1). Survival in many patients with an NSIP pattern, with a known cause or not, is markedly better than patients with IPF.5,6

Although NSIP was described in 1994, it was not until after 1998, when NSIP gained more universal acceptance as a distinct clinicopathologic entity, that these differences in survival were first noted. Prior to that (ie, pre-NSIP), a UIP pattern had been more broadly defined and encompassed a wide range of histologic features, including those that today define an NSIP pattern. When such a pattern had been seen in a biopsy in the pre-NSIP era, it would have likely been labeled UIP and the clinical diagnosis would have been IPF.

Bjoraker et al7 were first to highlight that many patients with IPF diagnosed in the past might have had histologic patterns consistent with NSIP rather than UIP. These investigators reviewed pathologic specimens from 104 patients with a diagnosis of IPF between 1976 and 1985. They discovered that 14% of these patients had biopsy findings that fulfilled criteria for NSIP, but were described originally as consistent with UIP. Five-year survival in these patients approached 70%, while 5-year survival was <30% in patients with IPF (Fig 1). Subsequent studies5,6,8,9 found NSIP patterns in 24 to 36% of patients’ specimens previously read as UIP patterns. These studies confirmed that NSIP is a distinct disease, and motivated the current narrow case definition of IPF predicated on histopathology. They also strongly suggest that most other previous studies of IPF probably enrolled heterogeneous populations, including a mix of patients with IPF, NSIP disease, and various other interstitial lung diseases.

Flaherty et al10 showed that a patient with a UIP pattern in one or more biopsy specimens might also have samples from the same lobe (or from a different lobe in the same lung) with injury patterns consistent with NSIP. However, a UIP pattern in one biopsy specimen, regardless of what pattern is found in any other, confers the same dismal prognosis as when a UIP pattern is found in all specimens.10

Katzenstein et al11 noted similar findings in a recent study of biopsy specimens and subsequent autopsy explants from 21 patients suspected to have IPF. Interestingly, “NSIP-like areas” were found in most specimens, including those with UIP patterns. These two studies emphasize the importance of obtaining biopsy samples from multiple lobes to ensure that the most accurate diagnosis is made, and to decrease the effects of sampling variability or error. They also provide a possible explanation for the less typical case in which a patient with a cellular NSIP pattern on biopsy does not respond to conventional therapy; in such patients, a UIP pattern may have been present but missed by the biopsy.

Most previous IPF studies require reappraisal in the context of what is now known about NSIP. For example, many patients in older studies who responded to therapy with stabilization or improvement likely had NSIP patterns (or some other injury pattern) and not UIP patterns of lung injury—and by implication, NSIP disease and not IPF. Thus, the actual percentage of patients with IPF who meaningfully improve with therapy is probably exceedingly low or nil. Updated and reliable epidemiologic data for IPF are needed in the post-NSIP era. For example, in a frequently cited population-based registry of interstitial lung diseases published in 1994 (ie, pre-NSIP), the prevalence of IPF was 13 to 20 cases per 100,000 people.12 These investigators faced hurdles often encountered when collecting epidemi-
ologic data: working with death certificates (since shown to be particularly inaccurate for patients with IPP), imprecise diagnostic coding, and recall bias. Additionally, as many as one half of the patients with an IPP diagnosis in this registry might actually have had some other diffuse pulmonary disease, like NSIP. For studies to generate meaningful data and useful conclusions about patients with IPP and the clinical behavior of the disease, investigators must either carefully exclude subjects with NSIP disease (and other non-IPP diagnoses) or analyze them separately from subjects with IPP.

### Challenges Related to Diagnosis and Evaluation

**Surgical Biopsy: the Current “Gold Standard”**

In IPP clinical research, the first step should be to ensure that all study subjects have IPP. Many studies have used the finding of a UIP pattern in the appropriate clinical setting as the diagnostic reference test. Even though the characteristic features of a UIP pattern have been outlined in several important articles, it is often difficult for less experienced pathologists to make this histologic diagnosis. Sometimes even experts cannot agree on the presence of a UIP pattern. For example, in a multicenter study that examined the utility of lung biopsies for the diagnosis of IPP, expert pulmonary pathologists disagreed on whether a UIP pattern was present in 15% of cases.

The possibility that more than one injury pattern can exist even within a single lobe adds another layer of complexity to obtaining an accurate histologic diagnosis. While obtaining biopsy specimens from multiple lobes will reduce the likelihood of sampling error, it does not address the subjectivity of the current diagnostic “gold standard.” In spite of these challenges, for now the most accurate diagnosis of IPP is made on the basis of combined clinical, radiographic, and pathologic data.

**Clinical Diagnostic Criteria**

For many patients, the risks of biopsy are thought to outweigh the potential benefits. Thus, most patients with IPP have the disease diagnosed without biopsy, on the basis of clinical and radiographic criteria alone. A joint American Thoracic Society/European Respiratory Society consensus committee recently defined clinical criteria for making the diagnosis of IPP. These criteria were formulated on the basis of expert opinion and have been widely implemented, but they have yet to be systematically validated. The criteria are listed in the Table 2.

#### Table 2—Major and Minor Clinical Criteria for the Diagnosis of IPP

<table>
<thead>
<tr>
<th>Major criteria</th>
<th>Minor criteria</th>
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<tr>
<td>Exclusion of other known causes of interstitial lung disease, such as certain drug toxicities, environmental exposures, and connective tissue diseases</td>
<td>Age &gt; 50 yr</td>
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<tr>
<td>Abnormal pulmonary function studies that include evidence of restriction (reduced vital capacity often with an increased FEV1/FVC ratio) and impaired gas exchange (increased alveolar-arterial oxygen pressure difference with rest or exercise) or decreased diffusion capacity for carbon monoxide</td>
<td>Insidious onset of otherwise unexplained dyspnea on exertion</td>
</tr>
<tr>
<td>Bibasilar reticular abnormalities with minimal ground-glass opacities on HRCT scans</td>
<td>Duration of illness ≥ 3 mo</td>
</tr>
<tr>
<td>Transbronchial lung biopsy or BAL showing no features to support an alternative diagnosis</td>
<td>Bibasilar, inspiratory crackles (dry or “Velcro” type in quality)</td>
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</table>

In a study conducted at a center with recognized expertise in caring for patients with IPP, when implemented by an expert, the criteria had a sensitivity and specificity of 62% and 97%, respectively, for the diagnosis of IPP (which was based on the presence of a UIP pattern confirmed by one pathologist). Thus, in this study, the criteria usually excluded IPP when it was absent but missed nearly 40% of biopsy-proven cases.

In another study, a core of three expert pulmonologists assessed symptoms, pulmonary function tests, and HRCT scans in 91 incident cases of suspected IPP. Their diagnostic impression was 72% sensitive, 84% specific, 77% accurate, and had a positive predictive value (PPV) of 87% for biopsy-proven IPP. When they could diagnose IPP with confidence, their impressions carried a sensitivity of 79%, a specificity of 87%, and a PPV of 87% for biopsy-proven IPP. However, the expert investigators in these latter two studies could confidently make a clinical diagnosis of IPP in only about 50% of patients subsequently confirmed by biopsy to have IPP. It is not clear whether the criteria can be applied with similar accuracy by practicing pulmonologists. However, in a study of 26 patients who subsequently underwent lung biopsy, the American Thoracic Society/European Respiratory Society clinical criteria missed nearly 30% of patients with biopsy-proven IPP when applied by three board-certified pulmonologists.

**HRCT Scans**

Like biopsy specimens from patients with a putative IPP diagnosis, HRCT is particularly subject to interpretive variability. When expert thoracic radiol-
ologists interpret HRCTs, sensitivity is 77%, specificity is 72%, and the PPV is 85% for biopsy-proven IPF. When they are confident in their diagnosis of IPF—like the expert pulmonologists (this only occurs approximately 50% of the time)—these radiologists diagnose IPF with a sensitivity of 87%, specificity of 95%, and a PPV of 96%.

Thus, HRCT findings consistent with IPF can overlap with findings more characteristic of other diagnoses, and atypical HRCT features are sometimes present in cases of IPF.23 IPF experts now recommend that surgical biopsy be reserved for patients whose HRCT findings are not typical for IPF.16 For this approach to be successful, HRCT readers must be able to determine the presence of typical findings such as mid- and lower lung zone-predominant, patchy, subpleural reticular opacities accompanied by traction bronchiectasis and honeycombing, and without significant ground-glass opacities.

It appears that physicians at referring centers are able to recognize the presence of lower lobe honeycombing. A recent study24 found that, as determined by clinicians at such centers, the presence of lower lobe honeycombing on HRCT scans of patients suspected of having IPF was very strongly associated with biopsy-proven IPF (odds ratio [OR], 11.45; p = 0.0004); however, this finding was not very specific (78%; 95% confidence interval, 62 to 90%). In the same study,24 a multivariable analysis of HRCT findings, as determined by a core of expert radiologists, revealed that the presence of honeycombing in the lower lobe (OR, 5.36; p = 0.007) or irregular lines in the upper lobe (OR, 6.28; p = 0.004) had the strongest associations with biopsy-proven IPF. However, when the radiologists observed these features together, the specificity was only 81% (95% confidence interval, 64 to 91%) for biopsy-proven IPF.

HRCT has become an invaluable tool for diagnosing IPF. What remains to be seen is under what circumstances HRCT can obviate the need for surgical lung biopsy in the diagnostic evaluation of patients suspected of having IPF. In the future, it is likely that the recommendation regarding which patients should undergo biopsy will be driven by specifically defined and objectively derived HRCT criteria, rather that the current more subjective stance that biopsy be utilized in patients with an HRCT that is “not typical” for IPF.

**CHALLENGES RELATED TO STUDIES OF PROGNOSIS**

Practical, validated prediction rules can provide concrete and reliable information about prognosis for patients and their family members. They facilitate communication between physicians and, in the case of IPF, such models can provide valuable information about the optimal timing of referral for lung transplantation. When used in drug trials, prognostic models serve three purposes: (1) permitting baseline comparisons between patients assigned to placebo and those assigned to active treatment; (2) assessing the effect of disease severity on various outcomes, including response to therapy and quality of life; and (3) alleviating lead-time bias, by permitting analyses stratified on the prognostic variable(s).25

The variability in the natural history of IPF poses challenges for patients and caretakers alike. Which patients will experience precipitous decline and early death, and which will outlive the median survival of 3 to 5 years has been a focus of research for some time. As is true in older studies of treatment, it is likely that most past IPF prognostic studies enrolled heterogeneous patient populations, and few included only patients with biopsy-proven IPF.10,14,26–29

Recently, a handful of studies30–32 have shed light on clinical variables that provide valuable prognostic information. Perhaps most intriguing, because of its simplicity and practicality, is the finding reported by Lama and colleagues31 that peripheral oxygen desaturation to <88% during a 6-min walk test with the patient breathing room air (and performed within 7 months of biopsy in patients with IPF) is an extremely strong predictor of mortality. Among the subjects with IPF, 4-year survival was 35% for “desaturators” and 69% for “nondesaturators.” Other studies have identified additional variables (eg, change in FVC from baseline to 6 months after lung biopsy40) and more complicated prognostic models32 that await external validation in different patient populations.

**CHALLENGES RELATED TO STUDIES OF TREATMENT**

Recent pathologic and clinical data suggest inflammation does not play a prominent role in the pathophysiology of IPF. This observation, combined with evidence from in vitro studies demonstrating alveolar epithelial injury may directly induce fibrosis,33 provide impetus for the hypothesis that IPF is an “epithelial-fibroblastic disease.”31 Nevertheless, widely used management strategies for IPF have included anti-inflammatory and immunosuppressive medications in the form of glucocorticoids and cytotoxic agents. Corticosteroids and both azathioprine and cyclophosphamide (the most commonly used agents along with glucocorticoids)
work via immune modulating mechanism directed primarily against lymphocytes. In the context of the "epithelial-fibroblastic" paradigm, it is not surprising that response to these medications, even when broadly defined to include disease stabilization, is extremely uncommon. The actual response rates are unknown; however, there has been no convincing published evidence to suggest any therapy improves quality of life or survival. In fact, there are little data to support the use of any conventional drug regimens.34,35

It has been reported that 10 to 30% of patients with IPF respond to conventional therapeutic regimens.36 However, these data come from studies performed prior to, or without implementing the current case definition of IPF.15,37–40 Estimates from more recent retrospective observational studies,5–7 in which a UIP pattern was appropriately distinguished from other pathologic patterns, suggest true response rates are even lower, perhaps 0 to 10%.

Most prior IPF treatment trials are limited by small patient populations and suboptimal study designs (that lack randomization, placebo controls, or consistent treatment regimens). Most are observational case series, and many are retrospective. All lack sufficient rigor to make confident, definitive statements about how patients with IPF respond to conventional therapies. There have been very few randomized, prospective treatment trials, and none have compared active treatments with placebo.41–43 No randomized, prospective study has enrolled only patients with biopsy-proven IPF and UIP patterns of injury as presently defined. The hypothesis that patients with IPF respond favorably to conventional therapy has not been proved. Yet, two thirds of patients with IPF continue to receive a therapeutic regimen including either corticosteroids alone or corticosteroids in combination with a cytotoxic drug.17,20,44

**Future Trials**

What should be the design of future IPF therapeutic trials? Small, single-center trials enable testing of a wide range of novel therapeutic agents, and they sometimes generate hypotheses for future studies. Because patient numbers at any one center are small, such trials must be designed to look for large differences in the effects of treatment between groups (as opposed to large trials, which have greater statistical power and are able to look for smaller effects). For IPF, large, multicentered trials are probably most useful for studying new therapies that have shown promise in preliminary testing. Such trials should be double blind, randomized, and placebo controlled by design. When possible, multivariable statistical analyses should be used to adjust for observed differences between groups after randomization. Outcomes must be clinically important and include measures of morbidity, quality of life, and disease-specific and all-cause mortality rates.

**Study Populations**

A challenging question is how to define the study cohort. Enrolling a mix of clinical and biopsy-proven IPF cases will continue to raise the issue of population heterogeneity; as in prior studies, a certain percentage of patients with clinically diagnosed disease will have diseases other than IPF. However, including only patients with biopsy-proven IPF substantially reduces the number of potential study participants. In the general population, only 20 to 30% of patients suspected of having IPF undergo lung biopsy.45 With such a small number of patients outside the research setting undergoing biopsies, the ability to generalize results from a study in which all patients undergo biopsy would be limited to patients with biopsy-proven IPF. Such select populations also raise the issue of healthy patient bias; only patients young enough and well enough to undergo biopsy would be enrolled.

Most important, any future studies that enroll a mixed population of patients with both clinical and biopsy-proven IPF must analyze results from these two groups separately. Data from both groups could be combined only if the groups have comparable baseline characteristics and similar responses to the investigational agent(s).

**Control Groups**

Long trials using placebo controls are not ethical when there is an existing therapy that positively impacts morbidity or survival.46 For IPF, the efficacy of any therapy has not been established.17 Still, no therapeutic trial in patients with IPF, including the recent interferon-γ trial,47 has included an inactive (true) placebo control group.41,42

The reluctance to use a placebo-control design stems from a number of concerns. First, patients and physicians may feel compelled to "do something," and might not want to risk randomization to placebo in a trial. Second, even in patients who receive no obvious benefit from conventional therapy, there is anecdotal evidence suggesting that some patients rapidly deteriorate once this therapy is withdrawn. Therefore, many clinicians might be reluctant to discontinue all therapies in order to make a patient eligible for a placebo-controlled trial. However, there are no data to support the use of active control subjects in studies of IPF.
An alternative approach would be to use an “add-on” design,46 in which patients would receive identical standard regimens in addition to either placebo or the new agent. Such a design is not without its drawbacks. Given the low probability of benefit and high likelihood of toxicity, some patients might be unwilling to receive standard therapy. More important, even if the study results are positive, such a design does not address effectiveness of the new agent as monotherapy—rather, only as an added treatment to standard regimens.

Other interesting design options include clinician’s choice (CC) and equipoise-stratified (ES) randomization. In the CC strategy, several different treatment options are available to patients in each of the two treatment groups. For example, a trial48 for atrial fibrillation compared a rate-control group vs a rhythm-conversion group. Using the CC, each patient is randomly assigned to a group, but the specific therapy within that group is determined by the clinician. The main requirement is that at least one treatment option in each group is acceptable to the patient (and the clinician). In ES randomization, investigators enroll patients who determine (with the help of their clinician) the study treatments that are acceptable and “of rough parity.”49 This collection of treatment options is called the patient’s equipoise stratum. Patients are randomly assigned to one option within his or her own equipoise stratum. The ES design is complex and requires statistical expertise to implement; however, it offers the advantages of the CC and completely randomized study designs, but it avoids their specific pitfalls. A more detailed discussion is beyond the scope of this article, but we refer readers to the paper by Lavori and colleagues49 for a thorough review of these interesting design options.

Outcomes

Important IPF trial outcomes, besides survival, include measures of pulmonary function, functional status, and health-related quality of life. While virtually all studies of IPF have measured pulmonary function, measures of functional status deserve greater emphasis. Instruments such as the New York Heart Association classification are simple, informative, and easy to recall. Such stratifying information could be adopted into both the everyday care of patients with IPF and into future trials as a stratification tool and outcome measure.

More emphasis on patient-assessed outcome measures (eg, health-related quality of life) is also needed. Only a handful of studies have assessed the impact of this deadly disease, or its therapy, on patients’ feelings, ability to cope, and general attitudes.50–52 For patients with IPF, the psychometric properties (eg, internal consistency and test-retest reliability coefficients) and important performance characteristics (eg, floor and ceiling effect levels and sensitivities to change in status over time) of existing instruments are unknown. Such information could help investigators choose the most appropriate instrument to use in their studies.

Finally, identifying a valid and reliable biomarker that is sensitive to the presence of disease and its progression over time would alleviate the need for diagnostic biopsy, decrease reliance on highly variable clinical tests measuring disease severity, reduce prognostic uncertainty, and be a significant contribution to IPF clinical research and patient care.

Conclusions

IPF is a debilitating and typically fatal form of IIP. Treatments are commonly offered for IPF, but no regimen has been proven effective. The updated nomenclature of IIP and new conceptual framework, including the recent discovery and addition of NSIP, have reshaped perspectives on IPF. However, caution must be exercised when interpreting past IPF clinical studies because of evolution in the disease case definition. Future IPF clinical research should utilize precise nomenclature in reference to the IIP, and IPF in particular. Important advances have been made in clinically and radiographically characterizing IPF and in identifying prognostic variables. Goals of research should include validation of clinically useful diagnostic criteria and prognostic models. Promising new treatments should be tested in randomized, controlled trials that enroll well-defined patient populations and measure clinically relevant outcomes.

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