REPORT

Evaluating New Treatment Options

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is the most prevalent type of idiopathic interstitial pneumonia, accounting for at least half of all diagnosed cases. Because it lacks a cure, the goal of treatment for IPF is to stabilize or reduce the rate of disease progression. Nonpharmacologic treatment options for IPF consist of long-term oxygen treatment, lung transplantation, and pulmonary rehabilitation. In the past, pharmacologic therapies for IPF included anticoagulants and anti-inflammatory or immunosuppressive agents. However, in late 2014, 2 therapies were approved by the US FDA for use in IPF: nintedanib and pirfenidone. While treatment of IPF was previously significantly impeded by a lack of effective agents and a paucity of clinical trial data on which to base guideline recommendations, these new agents provide notable breakthroughs in management of IPF, and continued research may break further, new fertile ground for management.

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Clinical Practice Guideline Changes

2011 ATS/ERS/JRS/ALAT Recommendations

Treatment of IPF combines nonpharmacologic and pharmacologic strategies, and goals of treatment focus on halting disease progression and preventing acute exacerbations, which are a potentially life-threatening complication in approximately 5% to 15% of patients.[1-5]

Over the past 2 decades, the landscape of pharmacologic therapy for IPF has changed dramatically.[2] A previous evidence-based clinical practice guideline for the treatment of IPF was published in 2011 by 4 sponsoring organizations: American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Society (ALAT). At that time, the committee involved in guideline preparation believed that the preponderance of evidence to date suggested that pharmacologic therapy for IPF was "without definitive, proven benefit." For that reason, the committee chose to make recommendations of varying strength against most pharmacologic agents for treatment. Strong recommendations were published against the use of multiple agents, including[1]:

- Corticosteroid monotherapy
- Colchicine
- Cyclosporine A
- Combined corticosteroid and immunomodulator therapy
- Interferon gamma 1b
- Bosentan
- Etanercept

In addition, weak recommendations were made against several agents, stating that they should not be used in a majority of patients with IPF, but may be a reasonable choice in the minority of patients[1]:

- Combined acetylcysteine, azathioprine, and prednisone
- Acetylcysteine monotherapy
- Anticoagulation
- Pirfenidone

This version of the guidelines strongly recommended long-term oxygen therapy in patients with IPF and clinically significant

resting hypoxemia, along with a strong recommendation for lung transplantation in appropriate patients.[1] The overall recommendations were based on the committee analysis that current evidence at that time demonstrated no proven pharmacologic therapy for IPF. Although a few studies suggested potential benefits from some pharmacologic agents, the recommendations for use of these agents were a "weak no." In the case of a well-informed patient with IPF who desires drug therapy, it was suggested that the choice of treatment be made from those that were weakly recommended against their use.[1]

2015 ATS/ERS/JRS/ALAT Recommendations

In 2015, a similar committee from the same 4 specialty organizations again met to assess new advanced data surrounding management of IPF and to provide an update to the 2011 clinical practice guideline. The purpose of reissuing the recommendations was to update the treatment guidelines with the reappraisal of previously assessed treatment options and new recommendations for novel agents. The goal of the guideline is for it to essentially be a reference of continually evolving recommendations, incorporating new evidence-based data once they become available. The intent is for the guideline committee to perform periodic reviews and updates to bring new evidence-based recommendations into clinical practice in as timely a manner as feasible.[6]

Strong recommendations against the use of the following drugs were again outlined in the new guideline, with notable changes from 2011[6]:

- Anticoagulation (warfarin)
- Imatinib, a selective tyrosine kinase inhibitor (TKI) against platelet-derived growth factor
- Combination prednisone, azathioprine, and *N*-acetylcysteine
- Selective endothelin receptor antagonist (ambrisentan)

Another new set of conditional recommendations was made for the use of the following agents for treatment of IPF[6]:

- Nintedanib, a TKI that targets multiple tyrosine kinases, including vascular endothelial growth factor, fibroblast growth factor, and platelet-derived growth factor receptors
- Pirfenidone, an oral antifibrotic agent with pleiotropic effects

Conditional recommendations were made against the following agents[6]:

- Phosphodiesterase-5 inhibitor (sildenafil)
- Dual endothelin receptor antagonists (macitentan, bosentan)

The key new features in the guideline were the conditional recommendations for the use of nintedanib and pirfenidone. In the case of nintedanib, the recommendation placed a high value on the potential benefit of this agent on essential patient outcomes, including disease progression as measured by rate of forced vital capacity (FVC) decline and mortality, along with a lesser value on the potential adverse effects (AEs) of therapy and the costs associated with nintedanib treatment. It was noted that unlike more selective TKIs, nintedanib appeared to offer some benefit in patient-important outcomes even though no significant effect on mortality was observed.[1,6]

Pirfenidone was addressed in the 2011 clinical practice guideline with a weak recommendation against its use. However, in the updated recommendations, it was noted that new evidence had become available since the prior edition that led to a new conditional recommendation in favor of treatment with pirfenidone. As with nintedanib, this new recommendation placed a high value on the potential benefit of this agent on patient-important outcomes, including disease progression as measured by rate of FVC decline, and a lesser value on related AEs and costs associated with pirfenidone use.[6]

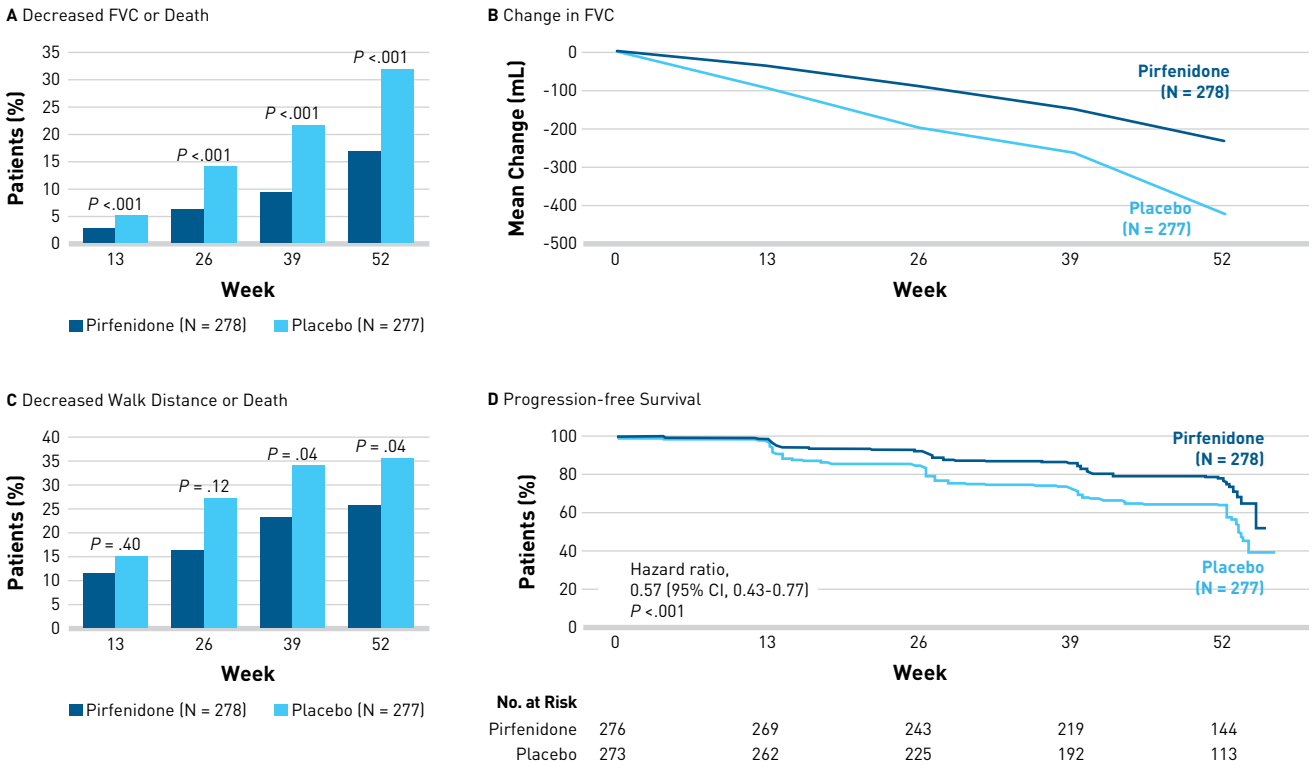
Update of Newly Approved Therapeutic Options: Pirfenidone

The CAPACITY Trials

While only preliminary data surrounding the CAPACITY trials were available when the 2011 clinical practice guideline was published, more complete results were assessed in the preparation of the 2015 guideline update.[6] The CAPACITY program of 2 trials was designed to confirm the results of a phase 2 study that suggested the novel antifibrotic pirfenidone reduced deterioration in lung function in patients with IPF. CAPACITY consisted of 2 concurrent trials (004 and 006) of patients with IPF aged 40 to 80 years, randomly assigned to receive either oral pirfenidone or placebo for a minimum of 72 weeks in a total of 110 centers in North America, Europe, and Australia. In study 004, patients were assigned in a 2:1:2 ratio to pirfenidone 2403 mg/day, pirfenidone 1197 mg/day, or placebo. In study 006, the assignment consisted of a 1:1 ratio of pirfenidone 2403 mg/day or placebo. The primary endpoint of the study was change in the percentage predicted FVC after 72 weeks, with analysis by intent to treat.[7]

In study 004, pirfenidone reduced decline in FVC, with a mean change at week 72 of −8.0% (SD 16.5%) in the 435 patients who received the 2403 mg dosage versus −12.4% (SD 18.5%) for the 174 patients in the placebo group. Mean percentage change in FVC in the 87 patients assigned to receive pirfenidone 1197 mg daily was intermediate to that of those in the higher-dosage pirfenidone cohort and the placebo cohort. In study 006, mean change in FVC at week 72 was −9.0% (SD 19.6%) for the 344 patients who received pirfenidone versus −9.6% (SD 19.1%) for those who were assigned placebo, and the difference in FVC between the 2 groups was not significant. However, this study demonstrated a consistent pirfenidone effect that remained apparent until week 48 ($P = .005$).[7] Patients from both

FIGURE 1. Primary and Secondary Outcomes of the ASCEND Trial[8]



Panel A shows the proportion of patients who had a decreased percentage of the predicted FVC (defined as a decline of at least 10 percentage points from baseline) or who died. Panel B shows the mean change from baseline in FVC. Panel C shows the proportion of patients who had a decreased walk distance (defined as a decline of 50 meters or more in the distance walked in 6 minutes) or who died. *P* values shown in Panels A, B, and C were calculated with the use of ranked analysis of covariance. Panel D shows the Kaplan-Meier distribution for the probability of progression-free survival. The *P* value was calculated with the use of the log-rank test.

From *N Engl J Med*. King TE Jr, Bradford WZ, Castro-Bernardini S, et al; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis [published correction appears in *N Engl J Med*. 2014;371(12):1172]. 370(22):2083-2092. Copyright 2014 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

studies who received high-dose pirfenidone reported higher rates of nausea, dyspepsia, vomiting, anorexia, photosensitivity, and rash compared with patients in the placebo group.[6,7]

The ASCEND Trial

The ASCEND trial was designed to confirm the beneficial effect of pirfenidone on disease progression as measured by decline in FVC seen in the previous phase 3 trials (CAPACITY 004 and a small previous trial of 275 patients conducted in Japan). In ASCEND, 555 patients were randomized to receive either 2403 mg of oral pirfenidone daily versus placebo for 52 weeks. The primary endpoint of the study was the change in FVC or death after 52 weeks.[8] However, it must be noted that the ASCEND trial had stricter patient exclusion criteria than did the CAPACITY studies, such as a forced expiratory volume in 1 second (FEV_1) to FVC ratio (FEV_1/FVC) below 0.8.[6,8] Results showed a relative reduction of 47.9% in the proportion of patients with an absolute decline of ≥10 percentage points in percent predicted FVC or who died. A relative increase of 132.5% in the proportion of patients with no decline in FVC was also demonstrated (P <.001). There was also a reduction in decline in 6-minute walk distance (P = .04) and improved progression-free survival in patients treated with pirfenidone (P <.001) (**Figure 1**[8]). Mortality or dyspnea scores did not differ between the 2 treatment cohorts, although patients who received pirfenidone experienced more treatment-related AEs, which was consistent with the previous trials.[7,8]

Further Analyses

Multiple other analyses have been performed on the efficacy and safety of pirfenidone in continued therapy using the data from these landmark clinical trials. One study by Nathan et al assessed a patient population who experienced meaningful disease progression during treatment with pirfenidone. This analysis focused on the rate of disease progression variability and examined the effect of continued treatment with pirfenidone in this treated patient population. This study assessed the patients from the CAPACITY and ASCEND trials, who suffered a ≥10% decline in FVC

in the first 6 months after randomization, and then compared the proportion of these patients in the treatment and placebo cohort who experienced a further 10% FVC decline or death in the next 6 months. After 6 months of therapy, 34 patients (5.5%) who received pirfenidone and 68 (10.9%) who received placebo experienced a ≥10% FVC decline (P <.001). But during the following 6 months, fewer patients in the pirfenidone cohort versus those who received placebo experienced a 10% FVC decline or death (5.9% vs 27.9%, respectively; P = .009). Interestingly, most of this difference was driven by mortality, with 1 death in the treatment cohort (2.9%) versus 14 (20.6%) in the placebo group. These findings suggest a potential benefit to continued pirfenidone treatment in patients who experience disease progression during therapy. An additional finding from this study was a weak negative correlation between FVC changes during consecutive 6-month intervals in patients who received placebo, indicating substantial variability. This high intersubject and intrasubject variability in the disease progression rate emphasized the inability to reliably assess therapeutic response simply based on serial trends in FVC.[9]

Another study performed a pooled analysis of CAPACITY and ASCEND data to assess all-cause mortality, treatment-emergent all-cause mortality, IPF-related mortality, and treatment-emergent IPF-related mortality at weeks 52, 72, and 120 in patients treated with either pirfenidone or placebo. The analysis demonstrated that the relative risk of death for all mortality outcomes studied was significantly lower in patients treated with pirfenidone versus those who received placebo in the pooled population (P = .0107). At the longest follow-up interval of 120 weeks, significant differences in the pooled analysis demonstrated a salutary effect for pirfenidone in terms of treatment-emergent all-cause mortality (P = .0420), IPF-related mortality (P = .0237), and treatment-emergent IPF-related mortality (P = .0132). A meta-analysis of the CAPACITY and ASCEND studies combined with those of 2 earlier Japanese trials of pirfenidone, Shionogi Phase 2 and Shionogi Phase 3, was also performed. This meta-analysis for all-cause mortality also demonstrated both a clinically relevant and significant risk reduction in the patients treated with pirfenidone versus those treated with placebo. This treatment benefit of pirfenidone therapy across multiple mortality outcome analyses provides additional evidence to support the use of pirfenidone in patients with IPF.[10]

Additional safety analyses of trial data have continued to demonstrate that long-term treatment with pirfenidone is safe and generally well tolerated. Lancaster et al assessed data from 1299 patients in the CAPACITY and ASCEND trials, along with data from 2 open-label RECAP studies (study 002 and 012), looking at safety outcomes during the period from administration of the first dose until 28 days after final study drug administration. A cumulative total exposure to pirfenidone of 3160 person-years was demonstrated across these trials. AEs found were generally mild to moderate in severity, with gastrointestinal (GI) events including nausea (37.6%), diarrhea (28.1%), dyspepsia (18.4%), and vomiting (15.9%). In addition, 25% of patients studied experienced a rash with pirfenidone treatment. Of note, alanine aminotransferase or aspartate aminotransferase elevations that were >3 times the upper limit of normal occurred in 3.1% of patients treated with pirfenidone; however, these elevations were generally transient and reversible with therapy dose modification or drug discontinuation, and were without significant clinical sequelae. Overall, this study followed patients prospectively for up to 9.9 years and found that long-term treatment with pirfenidone was safe and well tolerated in the treatment populations.[11] Another analysis by Anderson et al, using comprehensive data from randomized clinical trials (RCTs), meta-analyses, safety studies, and postmarketing studies, was performed to assess the safety and efficacy of pirfenidone. This analysis confirmed that the drug was well tolerated, with a majority of AEs related to GI or skin complaints. The study did note that pirfenidone has been associated with neurologic AEs, including dizziness, fatigue, anxiety, drowsiness, and insomnia.[12] This assessment noted that 1 meta-analysis of 6 clinical trials showed that pirfenidone had a significantly higher rate of neurologic AEs compared with placebo. However, it should be noted that among these neurologic AEs, only dizziness and fatigue actually occurred significantly more frequently in patients treated with pirfenidone.[12,13]

Patient Pearls for Therapy

In the analysis by Anderson et al, the authors note that pirfenidone is approved for treatment of IPF without mention of disease severity, leaving actual prescribing to the discretion of clinicians as to whether or not to use it in patients with more advanced disease. While clinical trial data in this area are sparse, observational data suggest benefit of pirfenidone in patients with this level of disease. The analysis notes that the key to success with pirfenidone is to maintain patients on therapy. Therefore, patient counseling and management of expectations is critical, along with managing any associated AEs. A mutual decision between patient/caregiver and treating clinician, with an emphasis on AE profiles, dosing, frequency, drug interactions, and patient preference, is crucial for successful therapy and patient management.[12]

Update of Most Recently Approved Therapeutic Options: Nintedanib

Phase 2 Trial

Nintedanib was assessed in 3 RCTs that were published in 2 separate reports. The first of these was a 12-month, phase 2 trial evaluating the efficacy and safety of 4 doses of nintedanib (then called BIBF 1120), 50 mg once or twice daily, 100 mg twice daily, and 150 mg twice daily versus placebo in 432 patients with idiopathic pulmonary fibrosis. The primary endpoint was the annual rate of decline of FVC, with

secondary endpoints including acute exacerbations, quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ), and total lung capacity. Results demonstrated that FVC declined by 60 mL per year in the patients who received 150 mg of nintedanib twice daily compared with 190 mL per year in those who received placebo ($P = .06$ with the closed testing procedure for multiplicity correction; $P = .01$ with the hierarchical testing procedure), such that the percentage of patients with >10% FVC decline during the follow-up period was lower with the highest dose of nintedanib. This higher dosage also resulted in a lower incidence of acute exacerbations compared with placebo ($P = .02$), although patients treated with any dose of nintedanib had fewer IPF exacerbations. There was also a small decrease in the SGRQ score ($P = .007$, lower scores indicating better quality of life) versus an increase in SGRQ scores in the placebo cohort. AEs included GI symptoms, with more AEs and serious AEs in the treatment cohort, but these were not statistically significant. The conclusion was that the nintedanib 150-mg twice-daily dose was associated with a trend toward a reduction in the decline of lung function along with fewer acute disease exacerbations and preserved quality of life.[6,14]

The INPULSIS Trials

The INPULSIS trials (INPULSIS 1 and INPULSIS 2) were 2 replicate 52-week phase 3 RCTs to evaluate the efficacy and safety of the 150-mg twice-daily dose of nintedanib versus placebo. Similar to the earlier phase 2 trial, the primary endpoint was the annual rate of decline of FVC, with key secondary endpoints including the time to first acute exacerbation, and the change from baseline in the SGRQ, both assessed over the 52-week time period. Patients (N = 1066) were assigned to receive either nintedanib or placebo in a 3:2 ratio. Results from INPULSIS 1 showed that the annual rate of change in FVC was −114.7 mL in the patients who received nintedanib compared with a decline of −239.9 mL in patients in the placebo cohort ($P < .001$). In INPULSIS 2, the rate of FVC change was −113.6 mL with nintedanib versus −207.3 mL with placebo ($P < .001$). Fewer patients treated with nintedanib had a >10% decline in FVC over 52 weeks, although there was no significant benefit on mortality seen with nintedanib. In INPULSIS-1, there was no significant difference between the treatment and control cohorts in the time to first exacerbation ($P = .67$); however, in INPULSIS-2, there was a significant benefit seen with nintedanib versus placebo in time to first exacerbation ($P = .005$) (**Figure 2**[15]). AEs were reported more significantly in the treatment cohort, with diarrhea reported by 61.5% of patients treated with nintedanib versus 18.6% of those treated with placebo. However, most patients continued to receive nintedanib for the entire trial period. The authors concluded that the data from INPULSIS demonstrated that nintedanib reduced the decline in FVC in patients with IPF, consistent with a slowing of IPF disease progression.[6,15]

Further Analyses

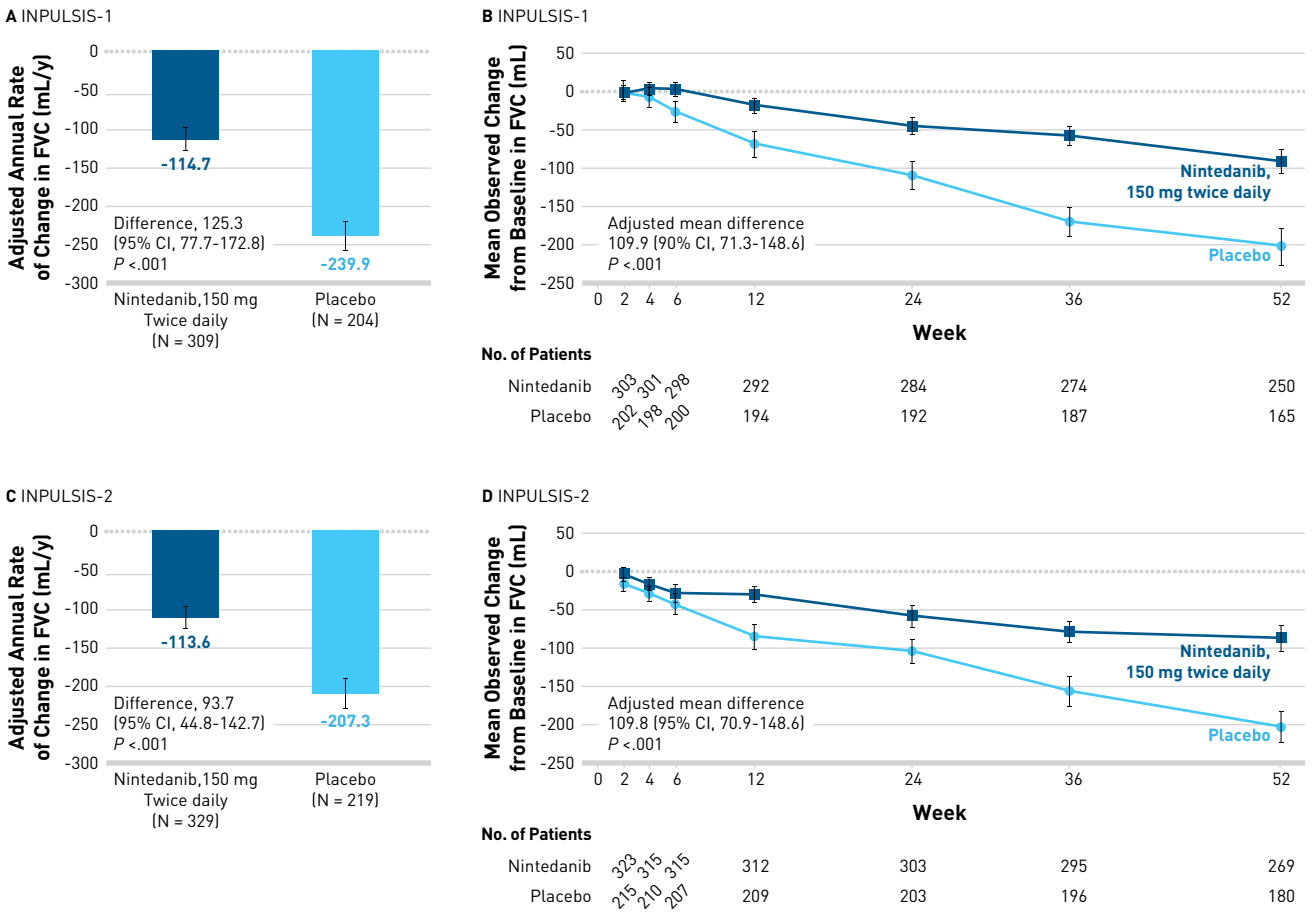
Patients who completed the INPULSIS trials could continue to receive nintedanib in an open-label extension trial, named INPULSIS-ON. Patients whose FVC was <50% of predicted were excluded from the INPULSIS 1 and 2 trials, but could participate in the extension trial. Patients in this trial received open-label nintedanib at either the 100-mg or the 150-mg twice-daily dosage, depending on previous dosing in INPULSIS, with dosing at the discretion of the investigator. An analysis of the first data in this patient population found that in patients with baseline FVC ≤50% predicted, the absolute mean change in FVC to week 48 of the extension trial was −62.3 mL versus a decline of −87.9 mL in those whose FVC was >50% predicted at baseline. No new safety signals were identified in INPULSIS-ON. Overall, the FVC decline in both baseline FVC groups in INPULSIS-ON was similar to that seen in patients treated with nintedanib in the original INPULSIS trials, suggesting a similar benefit on disease progression.[16]

In another study to assess whether patients with preserved lung volume would receive the same benefit from nintedanib as those with more impaired lung volume, the investigators performed a post hoc subgroup analysis of pooled data from the 2 INPULSIS trials using a baseline of ≤90% predicted vs >90% predicted FVC. This divided the patients studied into 2 groups, in which 274 patients had FVC >90% predicted and 787 patients had FVC ≤90% predicted. In patients treated with placebo in the original trials, the adjusted annual rate of decline in FVC was found to be consistent between both FVC cohorts; specifically, there was a decline of −224.6 mL/year for patients with FVC >90% predicted and −223.6 mL/year for those with FVC ≤90% predicted. Overall, the data analysis demonstrated no statistically significant difference between these subgroups in the effect of nintedanib on the annual rate of decline in FVC, change in SGRQ total score from baseline, or the time to first acute exacerbation. In patients whose baseline FVC was >90% predicted, the adjusted annual rate of decline in FVC with nintedanib was −91.5 mL/year (difference vs placebo: 133.1 mL/year) compared with −121.5 mL/year for those patients with baseline ≤90% predicted FVC mL/year (difference vs placebo: 102.1 mL/year). AEs associated with nintedanib treatment were similar in both subgroups. Overall, patients with IPF and FVC >90% predicted at baseline were found to have a similar rate of FVC decline and to receive the same benefits from nintedanib therapy as those with greater lung volume impairment, suggesting potential benefit and support to offering earlier treatment to patients with IPF.[17]

Patient Pearls for Therapy

Data pertaining to nintedanib, compared with other more selective TKIs, demonstrate benefit in terms of patient-important outcomes in IPF, although no overall mortality benefit was seen. Patients should be warned about the AEs associated with nintedanib, specifically diarrhea, to make an informed decision about therapy. Available

FIGURE 2. Annual Rate of Decline and Change from Baseline over Time in Forced Vital Capacity (FVC) in INPULSIS-1 and INPULSIS-2, According to Study Group[15]



Between-group differences (the FVC value in the nintedanib group vs the value in the placebo group) are shown for the adjusted rate of decline in FVC (Panels A and C) and the mean observed change from baseline at week 52 (Panels B and D). I bars indicate standard errors for the adjusted annual rale of decline in FVC and the observed change from baseline.

From *N Engl J Med*. Richeldi L, du Bois RM, Raghu G, et al; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis [erratum in *N Engl J Med*. 2015;373(8):782]. 370(22):2071-2082. Copyright 2014. Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

evidence does not outline optimal duration of therapy, and it remains to be seen how long the treatment effect endures with ongoing drug therapy.[6] As noted earlier, a mutual decision between patient/caregiver and treating clinician, with an emphasis on expected benefits, AE profiles, dosing, frequency, drug interactions, and patient preference, is crucial for successful therapy and patient management with either nintedanib or pirfenidone.[12]

Comparing the Agents, and Should All Patients With IPF Be Treated With Antifibrotics?

Both pirfenidone and nintedanib have been approved by the FDA for treatment of IPF, independent of disease severity. Currently, there is no definitive evidence to preferentially recommend either of these agents over the other.[12] One network meta-analysis of RCTs of pirfenidone, nintedanib, and *N*-acetylcysteine found that of the 3 treatments, only pirfenidone and nintedanib produced a statistically significant slowing in the rate of FVC decline as compared with placebo. An indirect comparison suggested that nintedanib is statistically significantly better than pirfenidone in slowing FVC decline, while mortality rates favored pirfenidone but were not statistically significant. However, of 1076 references in this analysis, 67 were pulled and only 11 studies were included, and limitations to indirect comparisons such as these must be considered.[18] In addition, clinical trials combining these agents are ongoing.[12,19]

A major question remains in IPF therapy: Should antifibrotic agents be administered to all patients with IPF, including those

TABLE. Major Inclusion and Exclusion Criteria of Nintedanib and Pirfenidone Phase 3 Trials[20]

Study	CAPACITY	ASCEND	INPULSIS
Drug	Pirfenidone	Pirfenidone	Nintedanib
Year	2011	2014	2014
Duration	72 wk	52 wk	52 wk
Major inclusion criteria	• Age 40-80 y • Diagnosis within 2 y • IPF diagnosis per study protocol (SLBx required for age <50 y) • FVC ≥50% predicted • DLCO 35%-90% predicted • 6MWT distance ≥150 m	• Age 40-80 y • Diagnosis within 6-48 mo of enrollment • Definite or possible UIP • FVC 50%-90% predicted • DLCO 30%-90% predicted • FEV_1/FVC >0.8 • 6MWT distance ≥150 m	• Age ≥40 y • Diagnosis within 5 y • IPF diagnosis per study protocol • FVC ≥50% predicted • DLCO 30%-79% predicted
Major exclusion criteria	• Obstructive lung disease • Active CTD • On lung transplantation waiting list	• Bronchodilator response • Recent/active smoking • COPD/asthma history • Expected to receive a lung transplant within 1 y • Unstable angina/recent MI • CHF hospitalization • Active CTD	• Unstable angina/recent MI • Abnormal LFTs • Therapeutic anticoagulation • High-dose antiplatelet therapy • Likely to undergo lung transplantation during study

6MWT = 6-min walk test; CHF = congestive heart failure; CTD = connective tissue disease; DLCO = diffusing capacity of the lung for carbon monoxide; IPF = idiopathic pulmorary fibrosis; LFTs = liver function tests; MI = myocardial infarction; SLBx = surgical lung biopsy; UIP = usual interstitial pneumonia.
Reprinted from *Chest*. 150/2, King CS, Nathan SD., POINT: should all patients with idiopathic pulmonary fibrosis, even those with more than moderate impairment, be treated with nintedanib or pirfenidone? Yes. Pages 273-275, Copyright 2016, with permission from Elsevier.

with more than moderate pulmonary impairment? As noted earlier, clinical trials for these novel agents tended to exclude patients with more severe FVC impairment (Table[20]).[20]

The effect of nintedanib and pirfenidone is to slow disease progression in IPF, reducing the rate of decline in FVC.[6,8,15,20] For those patients with more severe disease, it remains biologically plausible for these drugs to have the same effect on FVC.[20] Subgroup analyses of the major trials suggest that both agents had similar salutary effects in patients with both milder or more severe disease.[20-22] Because there is no gradient of disease severity in the studies, it could be inferred that similar treatment effects may be seen in those with disease severity that differs from that seen within the limits of the major RCTs. The actual labeling for these agents states simply "*...approved for the treatment of IPF,*" without mention of disease severity. This could be interpreted as a tacit endorsement to use them beyond the inclusionary and exclusionary criteria of the clinical trial in well-informed patients with well-established IPF as part of individualized, shared decision-making management.[20] An algorithm for patient evaluation and potential therapy has recently been proposed.[23]

Conclusion

There has been a sea of change in the management landscape of patients with IPF since the approval of the 2 antifibrotic agents. Their availability has raised the bar for an earlier and accurate diagnosis so that the option of therapy can be addressed with patients before significant loss of lung function, which invariably punctuates the course of this deadly disease. While neither drug is a cure, the availability of both represents hope for patients in terms of modulating the disease course. Their successful clinical development also establishes that the disease can be modified, with the further hope for other, more effective therapies in the future. ■

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