Editorial

Antifibrotic in interstitial lung diseases: When, where, and how long?

Interstitial lung disease (ILD), encompasses more than 100 heterogeneous groups of disorders that affect the lung parenchyma with an overlapping clinical, radiographic, and histopathologic presentation.[1] The most common ILD in our country is hypersensitivity pneumonitis, whereas worldwide it is idiopathic pulmonary fibrosis (IPF).[2] Antifibrotic drug, primarily used in treatment of idiopathic pulmonary fibrosis and both the drug Pirfenidone and Nintedanib got approval for it by FDA in 2014.[3,4] Recently, these drugs were also recommended for use in non-IPF fibrosing ILD. There are several questions related to the role of antifibrotics in ILD that are unanswered. Antifibrotic trial of IPF included mainly mild-to-moderate severity but whether it can be used in IPF patients with severe lung function impairment, normal lung function, or asymptomatic patients is not clear. How long it should be used? Where and when to use it in non-IPF ILD? This drug gained huge popularity in the last 2 years, with over-enthusiasm about its role in post-COVID lung fibrosis but do we have any evidence? Certain direct questions can help us understand the issue better.

Q1. Who would be the ideal patient of IPF for anti-fibrotic?

IPF is a chronic progressive fibrosing ILD, characterized radiologically and histologically by finding of usual interstitial pneumonia.[5] It is a gradually progressive disease associated with the worsening of dyspnea, and a decline in lung function; finally, the patient died within 3 to 5 years of the diagnosis.[6] As there is no cure for the disease, the goal of treatment is to retard the progression of the disease and acute exacerbation. The ideal patient for antifibrotic is an IPF patient with mild-to-moderate lung function (FVC >50% of predicted), which slows down the progression of the disease. This was based on the results of INPULSIS and ASCEND trials that showed an approximately 50% reduction in the rate of decline in the FVC after 1 year of treatment with nintedanib and pirfenidone, respectively.[7,8] A pooled analysis of Capacity 1-2 and ASCEND trial also demonstrated that the pirfenidone treatment for 1 year was associated with significant reductions in disease progression in patients with IPF.[9] Similarly, a pooled analysis of Tomorrow phase 2 and the INPULSIS trial showed that nintedanib effectively slows down the progression of the disease.[10]

Q2. Do we need to give antifibrotic in IPF with normal lung function (FVC >80%)?

Ideally, the treatment of IPF should be started as early as possible. Wait and watch behavior is not recommended considering the fatality of disease, unpredictable course of the disease, and poor 5-year median survival, which is even worse than that of several cancers.[11,12] An increasing number of IPF patients are diagnosed in the early stage due to increased use of HRCT chest when they have preserved lung function at rest and symptoms that become apparent only during exercise. In such patients, a clinician generally prefers to wait and watch rather than placing them on antifibrotics, considering the doubtful efficacy and possible side effects. One of the studies reported the proportion of IPF patients receiving antifibrotics in the USA and reason for not being prescribed by the physician. They found only 60% as receiving nintedanib or pirfenidone. The reason for patients with IPF not receiving antifibrotic therapy was that the physician believes that the disease is mild or stable, a lack of confidence in the diagnosis of IPF, access/reimbursement issues, and concerns over the adverse effects of antifibrotic drugs.[13] Another survey showed that pulmonologists have more concerns about adverse effects than disease progression.[14] A post-hoc analysis of the INPULSIS trials showed that patients with preserved lung function (FVC >90%) predicted at baseline experienced a similar decline in FVC over one 1 year as patients with less well-preserved lung function (FVC (<90%) (−224.6 vs. −223.6 mL/year).[15] A sub-group analysis of the CAPACITY and ASCEND trial also showed similar benefits in reducing the progression with pirfenidone in patients with FVC ≥80% or FVC <80%.[16] This post-hoc analysis indicates that the rate of decline in lung function is similar in both groups of IPF with preserved or reduced lung function and antifibrotic is effective in both groups. So, the antifibrotic should be started in IPF, irrespective of symptoms or lung function.

Q3. Whether antifibrotic effective in IPF with severe lung function impairment (FVC <50%)?

Many patients of IPF are diagnosed in the later stage and have a severe lung impairment (FVC <50%). The effectivity of antifibrotics in such a patient is not clear as such patients were generally excluded from clinical trials of antifibrotics and mainly took IPF with mild to moderate lung dysfunction (FVC >50%).[7,8] Although we do not have RCTs that included severe IPF patients, recent evidence suggests that nintedanib has a similar

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effect on FVC decline in subjects with severe impairment in gas exchange (diffusing capacity for carbon monoxide (DLCO) ≤35% predicted) at baseline as seen in those with mild-to-moderate disease.[17] In another study INPULSIS-ON, which is an open-level extension study of phase 3 INPULSIS, patients with FVC <50% were also included. Post-hoc analysis of the available data concluded that patients with baseline FVC ≥50% and FVC <50% of predicted had a similar benefit to nintedanib in reducing the progression.[18] However, this finding should be taken cautionary as this was an open-extension trial associated with bias and a small sample size. Many physicians already started using antifibrotics in such patients as there is no restriction for its use; however, many have caution considering the efficacy and more side effects. Finally, antifibrotics should be used in such patients, and at the same time, counseling should be done for lung transplantation.

Q4. How long antifibrotic in IPF should be used?

Ideally, antifibrotics should not be stopped in IPF unless patients have unbearable side effects. It is even advised to continue in which the disease is progressive even after treatment (>10% fall in FVC in last 6 months) as still better than placebo. Nathan *et al*.[19] analyzed the data of three phase-3 clinical trials of pirfenidone and concluded that in patients who progressed during the treatment, continued treatment with pirfenidone resulted in a lower risk of subsequent FVC decline or death. INPULSIS-ON study suggested that nintedanib had sustained effects in reducing the decline in FVC even for more than 4 years.[20]

Q5. When and where to use antifibrotic in non-IPF-ILD?

Previously, IPF was only considered as a progressive fibrosing ILD but now it has been realized that many fibrosing ILDs other than IPF have also a progressive course similar to IPF, characterized by gradual worsening of symptoms, quality of life, decline in lung function, and early mortality given the terminology as progressive fibrosing ILD (PFILD).[21] Recently the ATS-ERS joint committee guidelines preferred to use the terminology progressive pulmonary fibrosis (PPF) rather than PFILD.[22] As PF-ILD may have self-sustaining fibrosis and lack of response to anti-inflammatory, immunosuppressive medications, similar to IPF, it seems plausible that the antifibrotic drugs could exert similar therapeutic effects under these conditions.[23] The first evidence for antifibrotic (nintedanib) in non-IPF ILD came after the sub-group analysis of the INPULSIS trial.[24] Researchers thought that some patients in INPULSIS trials actually had fibrotic lung diseases other than IPF because the diagnosis of IPF in the INPULSIS 1 and 2 trials was not ascertained by histopathology features of UIP in patients who did not have honeycombing. So, it is possible that up to 32% of patients enrolled in these trials may not have had true IPF and actually had PFILD. This study showed an almost similar reduction in FVC in confirmed IPF (−117 mL) compared to the probable IPF (probably PFILD) (−98.9 mL). Another case-control study showed that 20 of the 46 (43%, 95% CI 29-58) patients with IPF according to the 2011 guidelines had a subsequent diagnosis of chronic hypersensitivity pneumonitis with a detailed work-up of patients.[24] Both these studies hope that nintedanib may be effective in non-IPF fibrosing progressive ILD (PFILD). Later on, to confirm the effectivity of antifibrotics in non-IPF ILD, the INBUILT trial was designed.[25] This trial randomized 663 patients with fibrosing ILDs other than IPF to nintedanib or placebo for 52 weeks. The decline in FVC was significantly less in the nintedanib arm compared to the placebo arm (80.8 mL/year vs. 187.8 mL/year, a difference of 107 m, $P < 0.001$). Later on, the sub-group analysis of the INBUILT trial assessed the effects of nintedanib across five non-IPF ILD (chronic hypersensitivity pneumonitis (26%), autoimmune ILD (26%), idiopathic non-specific interstitial pneumonia (19%), unclassifiable idiopathic interstitial pneumonia (17%), and other ILDs (12%). It found that nintedanib was equally effective in reducing the progression across the five ILD subgroups, regardless of the underlying diagnosis.[26] Another question was that out of three progression criteria, which one is the best predictor for the efficacy of nintedanib. To address this question, a subgroup analysis of the INBUILT trial was performed and published in the European Respiratory Journal. They categorized all patients into three groups according to the criteria of progression: a relative decline in the FVC of at least 10% of the predicted value (group A), a relative decline in the FVC of 5% to less than 10% of the predicted value, and worsening of respiratory symptoms or an increased extent of fibrosis on high-resolution Computerized tomography (CT) (group B) or worsening of respiratory symptoms and an increased extent of fibrosis (group C). In the placebo group, the rate of decline in FVC over 52 weeks in the overall population was greater among subjects in Group A (−241.9 mL per year) than in Group B (−133.1 mL per year) or Group C (−115.3 mL per year) ($P = 0.0002$). This study concluded that the inclusion criteria used in the INBUILD trial, based on FVC decline or worsening of symptoms and extent of fibrosis on HRCT, were the most effective criteria at identifying patients with progressive fibrosing ILDs.[27] Although the criteria used by the INBUILT trial to define progression are the most accepted, several other studies used different cut-offs for FVC and period of assessment. The RELIEF trial took absolute FVC decline of ≥5% in the last 6 months,[28] whereas ATS-ERS extrapolated the progression criteria of IPF to PFILD and recommended physiologically as either the patient having an absolute decline in FVC of >5% or absolute decline in DLCO (corrected for Hb) of >10% within 1 year of follow-up.[22] ATS-ERS gives a conditional recommendation for nintedanib in the treatment of PPF in patients who have failed standard management for fibrotic ILD, other than IPF.[22]

Pirfenidone has been also evaluated in a few trials for PFILD. One of the phase-2 trials in progressive

unclassifiable IIP for 24 weeks found a 69.4 mL less reduction in the pirfenidone arm compared to the placebo arm.[29] Another multicentre study showed the effect of pirfenidone in PFILD by reduction of progression in lung function decline, although the study was pre-terminated due to poor recruitment.[28]

Q6. Is there a benefit of antifibrotic and immunosuppressive combination in PFILD?

Immunosuppressive medications are not prescribed in the treatment of IPF considering an increased risk of mortality and other adverse consequences, without any clear benefit.[30] Based on these findings, immunosuppressive medications are used with great caution in patients with an IPF-like phenotype. There are several studies underway, evaluating these combination therapies for PFILD and expecting improvement. Post-hoc analyses of the INBUILD and SENSCIS trials by immunomodulator use at baseline have suggested that nintedanib can be used in combination with glucocorticoids[31] and mycophenolate[32] without affecting the efficacy of nintedanib on disease progression.

Q7. When and how long antifibrotic in Post-COVID pulmonary fibrosis?

Pulmonary fibrosis is a well-recognized long-term consequence of moderate and severe COVID-19.[33] Post-COVID-19 lung fibrosis has been given several names but the most accepted term is a post-COVID interstitial lung disease.[34] Several prospective cohort studies showed that the majority of these lung sequelae resolved without any use of antifibrotics.[35,36] There are a few similarities in lung fibrosis in COVID-19, IPF, and systemic sclerosis-related ILD.[37] Just the presence of fibrosis-like changes in the CT chest is not enough to put the patient on antifibrotics. Post-COVID pulmonary fibrosis is generally non-progressive and the majority get resolved on its own.[38] Although the expert group in one of the studies recommended antifibrotics in a patient with persistent symptoms, hypoxia, and fibrosis-like changes for 3 to 6 months.[34] Currently, a few trials of nintedanib and pirfenidone in post-COVID fibrosis are going on, which will provide insights into the efficacy of antifibrotics in preventing as well as treating fibrosis in moderate-to-severe COVID-19 patients. One study by Umemura *et al*.[39] assessed nintedanib in the acute phase; it enrolled 30 patients with severe COVID-19 for 28 days and showed a significantly shorter length of mechanical ventilation in the nintedanib group. At present, there is no evidence in favor or against antifibrotics in post-COVID pulmonary fibrosis.

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There are no conflicts of interest.

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