Opinion

The development of anti-fibrotic therapy and idiopathic pulmonary fibrosis

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ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a lung condition that usually has a bad prognosis and progresses rapidly. The INPULSIS and ASCEND trial results, as well as the approval of nintedanib and pirfenidone, have heralded the start of a new era for IPF patients. But there are still uncertainties. Should these medications be taken sooner? How will they impact more serious illness? Do they have any after-effects after the trial period? The use of ant fibrotic drugs in IPF was the subject of a multidisciplinary meeting amongst doctors in pulmonology, radiology, and pathology, which produced this publication. According to our analysis of the available data, pirfenidone and nintedanib prevent functional deterioration in the early stages of disease. When given to individuals with advanced disease at the time of diagnosis, these medications also seem to have therapeutic advantages and remain beneficial over time. Further research is required, however the data also imply that ant fibrotic therapy should be continued even as the disease progresses. For preventing functional decline, halting disease progression, and enhancing quality of life, early diagnosis and treatment are essential.

Key Words: Idiopathic pulmonary fibrosis; Undernutrition; *Pleural disease;, Interventional pulmonology*

INTRODUCTION

The average period from diagnosis to death for people with idiopathic pulmonary fibrosis (IPF) is years. Men, smokers, and persons over the age of ten are more likely to experience it. Digital clubbing, nonproductive coughing, crackles on auscultation, and dyspnea with exertion are the symptoms that define the condition. When other known causes of typical interstitial pneumonia (UIP) have been ruled out, the condition is identified utilizing a specific combination of radiologic and/or histological characteristics of UIP. For suspected cases of IPF to be promptly referred to a multidisciplinary team with experience in interstitial lung disorders, general practitioners must be able to detect the signs of the condition. Accurate diagnosis is then dependent upon this evaluation by the multidisciplinary team. The result of a multidisciplinary meeting where physicians from the fields of pathology, radiology, and pulmonology met to discuss issues related to the use of ant fibrotic medications in the treatment of IPF. Early treatment approaches for IPF focused on reducing or suppressing the inflammatory component because the condition was once thought to be a chronic inflammatory disorder. Despite the scant data, the first worldwide guidelines on the diagnosis and management of IPF advocated corticosteroids and immunosuppressive/cytotoxic drugs (azathioprine or cyclophosphamide) as "standard treatment". However, the outcomes of his targeting of inflammatory pathways were underwhelming. Significant progress was made in our understanding of the pathobiology of IPF, and it was suggested that the disease may be caused by an abnormal healing response to repeated alveolar epithelial cell injury. There was insufficient data to support the continued use of immunomodulatory drugs and corticosteroids as conventional treatments for IPF. The findings of the IFIGENIA study, a clinical experiment that was double-blind and intended to look into the potential function of antioxidant pathways in IPF. In the trial, which compared prednisolone plus azathioprine to prednisolone plus azathioprine plus N-acetyl cysteine (NAC), patients receiving NAC in addition to prednisolone and azathioprine after weeks showed a significantly slower decline in forced vital capacity

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(FVC) and lung diffusion capacity for carbon monoxide (DLCO). Despite numerous methodological flaws in the experiment, this triple therapy became the new accepted course of treatment for IPF. Pirfenidone, a synthetic molecule that is orally accessible and has ant fibrotic, anti-inflammatory, and antioxidant properties, was being researched in clinical trials at the same time. Although the precise mode of action of pirfenidone in IPF is still unclear, its anti-inflammatory effects are thought to be caused by the suppression of tumor necrosis factor (TNF-), interleukin (IL), while its anti-fibrotic effects are thought to be primarily caused by inhibition of expression of transforming growth factor beta, a profibrotic cytokine, although other pathways have been proposed. Following the INPULSIS and ASCEND studies and the licensure of nintedanib and pirfenidone, a new era for IPF patients began. National and international recommendations on the diagnosis and management of IPF classified the two medications as effective in reducing functional decline and disease progression in IPF patients. The efficacy outcomes from the nintedanib and pirfenidone trials were comparable, but they also prompted logical concerns about how well the medications would work outside of the confines of clinical trials. The INPULSIS (nintedanib) and ASCEND (pirfenidone) studies used different inclusion criteria. In order to address a number of problems, trials, numerous post-marketing monitoring studies, and subgroup analyses looking at effects based on age or illness stage were conducted. Should these medications be administered sooner if they can stop the progression of IPF? What actions will they take in patients who have more advanced diseases? Will they have an aftereffect after the trial time? The timing of IPF treatment initiation is likely the topic of the greatest debate at the moment. We are aware that pirfenidone and nintedanib both reduce the progression of IPF progressive condition. It has been claimed that in a stable patient with a moderate condition, therapy should be delayed until functional deterioration starts. However, some individuals stay stable for several months. However, it is hard to forecast the rate or severity of a patient's illness progression or to foresee when an acute exacerbation will occur. Furthermore, even in individuals who do not exhibit obvious indicators of considerable functional decline, we cannot be certain that harmful subclinical alterations are not occurring. Similar rates of FVC loss in nintedanib-treated patients with % expected FVC was described in a recent post hoc subgroup analysis of pooled data from the INPULSIS trials. Similar findings were obtained from other pre-specified subgroup studies, with nintedanib consistently having a positive impact on FV patients. Clinically significant disease progression (decline in FVC, 6MWD, and dyspnea assessed by the University of California, San Diego Shortness of Breath Questionnaire) occurred at months in pirfenidone-treated patients with more preserved lung function, according to a post hoc analysis of pooled data from the CAPACITY and ASCEND trials. Whether lung function was categorized using the FVC or the GAP model, the pirfenidone treatment effect's magnitude was equivalent amongst the subgroups. The aforementioned data clearly support the recommendation to begin treatment as soon as IPF is diagnosed and emphasize the significance of early diagnosis by showing that patients diagnosed in the early stages of the disease experience significant functional deterioration. Additionally, they show that both nintedanib and pirfenidone have a positive effect on slowing progression in these early stages. The percent anticipated FVC is typically linked to serious illness. This was an exclusion criterion in both the pirfenidone and nintedanib studies, as was previously mentioned.

Thus, information on the potential effects of ant-fibrotic medications in patients with advanced disease is limited, and generally, patients with this level of functional impairment are not included in the treatment indications listed by the health authorities. However, post-marketing monitoring studies have produced some intriguing evidence in this regard. Patients who began treatment with nintedanib bid with percent predicted FVC showed a similar absolute mean change in FVC from baseline to week as those with FVC at baseline in the open-label INPULSIS-ON extension trial, suggesting that nintedanib may have a similar therapeutic effect in advanced forms of the disease. Patients with moderate to severe disease showed a larger reduction in decline in percent projected FVC when they were stratified by FVC and GAP stage. Functional and symptomatic stability was seen in patients who started taking pirfenidone within the first year of the drug's approval for the treatment of IPF, independent of the severity of functional impairment. It was determined that the disease progressed in two-thirds of the patients. The RECAP trial, an expansion of the CAPACITY studies, compared patients with percent anticipated FVC with patients with FVC, and the findings were presented at the Respiratory Congress by Constable and colleagues. Long-term pirfenidone treatment produced a similar rate of FVC, despite the subgroup with more advanced illness having a greater treatment termination rate. The aforementioned statistics imply that nintedanib and pirfenidone both have a beneficial effect in patients who had advanced disease at diagnosis, despite the fact that there were only a limited number of patients. If the unfavorable benefit seen for nintedanib and pirfenidone in terms of reducing FVC decrease is maintained after months is another subject that post-marketing surveillance studies and extension trials have attempted to address. Results of a long-term safety evaluation of patients in the CAPACITY trials who received pirfenidone. Although safety was the main focus of the study, it was shown that pirfenidone treatment for up to years was not only well tolerated but also had a long-lasting beneficial therapeutic effect. This was demonstrated in oral communication at the ERS Congress where data from the RECAP extension were presented. A continuous reduction of more than in FVC and/or DLCO is considered a sign of disease progression in IPF. Following the start of treatment, lung function is typically assessed every six months. Once the disease has advanced, the treating physician(s) can decide whether to stop the medication and solely provide palliative care, stop the medication and move to an alternative therapy, add an alternative therapy, or keep the medication despite the functional impairment. However, none of these ideas are supported by enough evidence. Published the findings of a pooled analysis of participants from the CAPACITY and ASCEND trials, demonstrating that in the subgroup of patients who experienced a functional decline in FVC after months, those who continued to take pirfenidone had a lower risk of subsequently developing a serious adverse event. These findings imply that ant-fibrotic medication should be continued even when disease progression has been established. Reported that when a subgroup of individuals transitioned from pirfenidone to nintedanib, they had clinical and functional stability. Pirfenidone and nintedanib have also been suggested as a combined regimen since they are thought to work

synergistically in various fibrotic pathways. One safety and pharmacokinetics study found that nintedanib was well tolerated whether it was taken alone or in combination with pirfenidone. It also suggested that pirfenidone Coad ministration may reduce nintedanib bioavailability. Despite these results, additional information and research are required to direct treatment plans for patients whose diseases are progressing. In the TOMORROW and INPULSIS studies, diarrhea, nausea, and vomiting were the most frequently reported side events for nintedanib, and these occurrences were more common in the dosage group. Although some participants in the INPULSIS studies experienced diarrhea, only one patient stopped taking the medication because of it. Compared to the placebo group, more patients in the nintedanib group prematurely discontinued treatment due to total adverse events, according to a pooled analysis of data from the TOMORROW and INPULSIS trials. Patients in both groups almost universally experienced one or more severe adverse events. However, nintedanib-related side effects are often mild or moderate and manageable in the majority of individuals. We can infer that both pirfenidone and nintedanib, regardless of the disease stage determined by FVC or GAP, have a significant impact on FVC decline based on the data available from clinical trials and extension studies. Additionally, it was demonstrated by the RECAP and INPULSIS-ON extension trials that the impact persisted over time. Both nintedanib and pir- pirfenidone were found to increase survival, with a decrease in death from all causes and IPF-related causes. The data now available support the suggestion that treatment with nintedanib or pirfenidone should be taken into consideration when IPF is identified, regardless of disease stage, despite the relatively high incidence of adverse effects, which are primarily of a gastrointestinal nature. Early diagnosis and therapy are essential for preventing functional decline, minimizing symptoms, and enhancing the quality of life because IPF is a progressive long illness.