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Editorial

Antifibrotic drugs for idiopathic pulmonary fibrosis: What we should know?

Interstitial lung disease (ILD) is a group of heterogeneous diseases that results from the damage to the lung parenchyma due to inflammation and fibrosis of varied patterns[1]. ILD has been attributed to exposure to chemicals, medications, radiation or underlying connective tissue diseases (clinical or subclinical). However, a significant number of ILD cases remain idiopathic which are classified as idiopathic interstitial pneumonias (IIPs). The diagnosis and management of IIPs is considerably challenging. In an attempt to standardize the diagnosis of IIP, international respiratory societies have proposed guidelines for the diagnosis and classification of various IIPs which are followed globally[2,3]. Currently, all IIPs are classified into idiopathic pulmonary fibrosis (IPF), idiopathic non-specific interstitial pneumonitis (NSIP), respiratory bronchiolitis-ILD, desquamative interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial pneumonia and rare IIPs (idiopathic lymphoid interstitial pneumonia and idiopathic pleuroparenchymal fibroelastosis). Some IIPs remain unclassifiable despite all efforts[3].

IPF is the prototype of progressive fibrosing IIPs characterized by self-sustaining fibrosis, increasing pulmonary symptoms, deteriorating lung functions and early mortality[3,4]. Till date, there is no drug that can cure IPF. Many therapies including corticosteroids, azathioprine, N-acetyl cysteine, bosentan, interferon gamma and sildenafil have been tried but failed to show any benefit in IPF[5]. Currently, there are two antifibrotic drugs that have been approved for the treatment of IPF - pirfenidone and nintedanib[5,6]. However, both of these drugs have modest benefits and only halt/slow down the progression of IPF. Hence, the existing goal of treatment among these patients only includes halting the declining in lung functions, prevention of exacerbations, improvement in the quality of life and some survival benefits.

Pirfenidone

Pirfenidone is an oral drug with anti-inflammatory, antioxidative and antiproliferatory properties. It also reduces circulating tumour necrosis factor-alpha (TNF-α) levels[6]. However, the exact mechanistic pathways of antifibrotic action in IPF are not well elucidated. Benefits of pirfenidone on decline in forced vital capacity (FVC) in IPF have been demonstrated in CAPACITY-004, CAPACITY-006 and ASCEND trials[7,8]. Mean decline in FVC per cent predicted reported at 72 wk was lesser among patients treated with pirfenidone compared to the placebo, *i.e.*, −8.0 versus −12.4 per cent; *P*=0.001 in CAPACITY-004 and −9.0 versus −9.6 per cent; *P*=0.501 in CAPACITY-006 study[7]. ASCEND trial compared proportion of patients who had a 10-point decline in percent predicted FVC or mortality after 52 wk of pirfenidone as compared to placebo[8]. The results demonstrated that pirfenidone use reduced the decline in 10-points of per cent predicted FVC or mortality by 47.9 per cent as compared to the placebo (16.5 and 31.8%, respectively). Preliminary data also suggest that pirfenidone reduces the risk of exacerbation of IPF[9,10]. Based on these promising results, pirfenidone was approved in many countries for treatment of mild to moderate IPF[11]. The long-term outcomes (up to five years follow up) of the use of pirfenidone have also shown survival benefits[12,13] suggesting that it remains safe and well-tolerated in long-term basis also. The common adverse effects reported with pirfenidone were related to skin (rash and photosensitivity) and gastrointestinal tract.

Nintedanib

Nintedanib is an oral intracellular tyrosine kinase inhibitor that inhibits downstream signalling pathways of fibrogenesis[14]. It acts as a triple growth factor inhibitor *viz*., platelet-derived growth factor receptors, vascular endothelial growth factor receptors (VEGFRs) and fibroblast growth factors receptors

that are involved in the proliferation, migration and differentiation of fibroblast or myofibroblast in the IPF lungs. The drug also inhibits *Src* family of non-receptor tyrosine kinases including Src, Lck and Lyn[14]. Efficacy of nintedanib for treatment of IPF has been studied in TOMORROW, IMPULSIS 1 and 2 trials[15,16]. TOMORROW, a phase II trial, showed that 150 mg twice daily of nintedanib was associated with a reduction in the rate of decline in FVC by 68.4 per cent compared to placebo (60 and 190 ml, respectively; P=0.01)[15]. The other two trials also demonstrated a lesser annual decline in FVC among patients using nintedanib as compared to placebo. The results of IMPULSIS 1 showed a difference of 125.3 ml/yr (−114.7 and −239.9 ml/yr; P<0.001) while those of IMPULSIS 2 showed a difference of 93.7 ml/yr (−113.6 and −207.3 ml/yr; P<0.001) in the FVC between nintedanib and the placebo[16]. Pooled analysis of the trials revealed that nintedanib was associated with reduced progression of IPF, risk of exacerbations, mortality and improved health-related quality of life[17]. The data also suggest that nintedanib is a well-tolerated drug with diarrhoea as the most common adverse effect[16-18].

Pirfenidone versus nintedanib

The two antifibrotic drugs that have been approved for the treatment of IPF have different mechanisms of action. Under such circumstances, to identify the better one among these, remains contested. A network meta-analysis of 10 published phase II and III randomized controlled trials (4 nintedanib vs. placebo and 6 pirfenidone vs. placebo) comparing the change in FVC (decline in %predicted ≥10%), rate of exacerbations, mortality, treatment dropouts and adverse events suggested a favourable response of both the drugs for change in FVC (decline in %predicted ≥10%): pirfenidone odds ratio (OR)=0.54 [95% confidence interval (CI) 0.37, 0.80] and nintedanib OR=0.59 (95% CI 0.41, 0.84) with a number need to treat of nine (95% CI 7, 22) and nine (95% CI 6, 23), respectively[18]. There were no differences in the rate of exacerbations [OR 0.39 (95% CI 0.00, 15.53)], mortality [OR 0.93 (95% CI 0.38, 1.94)], treatment dropouts [OR 0.75 (95% CI 0.33, 1.27)] and serious adverse events [OR 1.02 (95% CI 0.62, 1.62)] between pirfenidone and nintedanib. Adverse event number need to harm was 12 (95% CI 7, 58) and 14 (95% CI 8, 61) for pirfenidone and nintedanib, respectively[18]. These results indicate that pirfenidone holds slight clinical advantage over nintedanib when it comes to safety and it may be imperative while considering lifelong therapy. There have been other network meta-analyses that have reported similar results[19-21], indicating only marginal differences in the outcomes between the two drugs. Hence, treatment economics may be an important aspect while prescribing antifibrotic drugs.

There have been attempts to compare the cost-effectiveness of both of these drugs[19-21]. One study reported that in the United Kingdom, where per day cost of both pirfenidone and nintedanib is equal (£71.5), either drug therapy for IPF was cost-effective as compared to placebo[22]. However, they found substantial uncertainty regarding overall cost effectiveness of comparisons between pirfenidone and nintedanib. A study from France reported nintedanib to be a more cost-effective therapy compared to pirfenidone and reduced exacerbation rates were cited as the main reason for such a conclusion[23]. Another study showed that pirfenidone (€99,477 per patient) was more cost effective than nintedanib (€104,610 per patient)[24]. Overall, these data suggest conflicting conclusions about the superiority of one drug over the other with respect to cost of treatment to the patient. It is noteworthy that these studies have evaluated the economics of these drugs in Europe or the USA where the cost of both these drugs is almost similar. However, in India, the monthly cost of the therapy for pirfenidone varies from ₹25,00 to 35,00 for a dose of 2.4 g/day; whereas nintedanib is available with a market price of ₹156,000 and 77,000 for one month for 150 and 100 mg capsules, respectively. Considering the average per-capita income for an Indian as approximately ₹142,000[25], nintedanib remains beyond reach of majority of Indian patients with IPF, unless it is reimbursed by insurance or some other means.

Which one to choose

At present, it is difficult to recommend one drug over the other as there is no head-to-head trial between pirfenidone and nintedanib. Meta-analyses and post hoc analyses indicate no difference in efficacy of these two drugs with respect to effect on lung functions, exacerbation rate and mortality[18]. Hence the selection of the drug is to be done on a case to case basis, factoring in both the patient's as well as physician's choice. Pirfenidone may be preferred over nintedanib among patients who are at the risk of bleeding such as those with bleeding diathesis or on anti-coagulants since nintedanib is a VEGFR blocker and associated

with an increased risk of bleeding. Nintedanib may be the first choice among patients with photosensitivity or other pre-existing dermatological diseases.

Combination of pirfenidone and nintedanib

Despite the use of antifibrotic drugs, either pirfenidone or nintedanib, the lung fibrosis continues to progress. Since both antifibrotic drugs have different mechanisms of action, there is an interest in use of combination of both antifibrotic drugs for the management of IPF. The available data suggested that use of a combination of both these drugs was not associated with any significant pharmacokinetic interactions, and the safety profile was similar to individual drug[26-28]. Preliminary observations also suggest that addition of pirfenidone to existing nintedanib therapy may lead to reduced rate of decline in FVC[28]. However, well-designed studies are required to assess the risk-benefit of the combination therapy.

Conclusions

Despite the availability of these two drugs, there is a long way to find an effective treatment that can significantly improve the long-term survival and quality of life among patients with IPF. Currently, there are many unanswered questions related to these drugs. Can these drugs be used sequentially? If yes, which one should be used first? What is the role of combination of these drugs? Further studies are required to elucidate the exact pathway based mechanistic role of these drugs. Furthermore, no data are available on the crosstalk between genetic predisposition, epigenetics and proteomics in addition to the effects of intrinsic and environmental factors associated with IPF that may be important covariates associated with response and progression of IPF. With more knowledge of these factors, we will be able to imply personalized therapy to combat this deadly disease.

***Conflicts of Interest*:** None.

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